CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208399Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208,399/ IND 117,307 resubmission
Priority or Standard	Standard
Submit Date(s)	25 April 2017
Received Date(s)	25 April 2017
PDUFA Goal Date	25 October 2017
Division / Office	Division of Gastroenterology and Inborn Errors Products Office of Drug Evaluation (ODE) III
Reviewer Name(s)	Aisha P. Johnson, MD, MPH, MBA
Review Completion Date	20 September 2017
Established Name	Rolapitant Injectable Emulsion
(Proposed) Trade Name	Varubi® IV
Therapeutic Class	NK-1 inhibitor
Applicant	Tesaro, Inc
Formulation(s)	Emulsion for intravenous use, 185 mg (166.5 mg (b) (4) 92.5 mL (1.8 mg/mL).
Dosing Regimen	166.5 mg (b) (4) administered as an IV infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1
Indication(s)	VARUBI is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
Intended Population(s)	Adult Patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, the current 505(b)(1) Application of rolapitant injectable emulsion for intravenous administration should receive an approval action. The current Application is a re-submission. The initial NDA submission received a complete response action on 11 January 2017 due to a lack of an adequate bridge between th marketed formulation manufactured at (b) (4) in (b) (4) facility and the formulation utilized in the clinical trials (manufactured at in (b) (4)

1.2 Risk Benefit Assessment

Given the totality of the information submitted in support of this Application, the benefits associated with the use of rolapitant injectable emulsion currently outweigh the possible risks associated with the use of the therapy in patients receiving emetogenic chemotherapy.

The complete response letter described the following deficiencies:

A. Inadequate in vitro release method for drug product quality control purposes
B. Inadequate bridge between the to-be-marketed formulation manufactured at the (b) (4) manufacturing facility and the formulation utilized in the clinical trials (manufactured at the (b) (4) facility)
C. Deficiencies in the (b) (4) manufacturing facilities

The previous submission was not found to have any clinical deficiencies (i.e., rolapitant injectable emulsion was found to be safe and efficacious for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy in adults). The current submission contained a safety update which did not reveal any new safety signals or other areas of concern.

The current re-submission adequately addresses each of the deficiencies outlined in the complete response letter including the development of an adequate in vitro release method and adequate data to bridge the to-be-marketed formulation manufactured at (b) (4) in (b) (4) and the formulation utilized in the clinical trials manufactured at (b) (4) in (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant submitted plans for a pediatric program for rolapitant IV. The Division issued correspondence confirming agreement with the sponsor's initial Pediatric Study Program (iPSP). The sponsor requested a deferral for studies in patient's 0 to <17 years of age in accordance with the provisions of Section 505B (a)(3)(A)(i) of the Federal Food, Drug and Cosmetic Act (FDCA), "The drug or biological product is ready for approval for use in adults before pediatric studies are complete".

The following PMRs are being issued:

- A Phase 3, Multicenter, Randomized, Double Blind, Placebo Controlled Study of the Safety, Efficacy, and Pharmacokinetics of rolapitant injectable emulsion for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in pediatric patients ages 0-17 years old
- An in vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 28 days after a single dose administration of Varubi (rolapitant) intravenously and document when inhibition resolved.
- Confirmatory intravenous GLP toxicology study in juvenile rats ((b) (4)
- A GLP segmented dosing toxicology study in juvenile rats.
- In vitro studies to evaluate the inhibitory potential of Varubi (rolapitant) on MATE1 and OATP1B1 transporters and the IC50 values for each transporter

The phase 3 pediatric study cannot be started until the juvenile toxicology study data has been submitted to the FDA and reviewed.

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in rolapitant injectable emulsion (rolapitant hydrochloride) is a substance P/neurokinin 1 (NK1) receptor antagonist, chemically described as (5S,8S)-8-[[(1R)-1-[3,5-Bis(trifluoromethyl)phenyl]ethoxy]-methyl]-8-phenyl-1,7-diazaspiro[4.5]decan-2-one hydrochloride.

The solubility of rolapitant hydrochloride in aqueous solution is pH-dependent and is more soluble at lower pH. Rolapitant hydrochloride injectable is formulated in an oil-in-water emulsion. Each sterile vial for intravenous use contains 166.5 mg rolapitant (b) (4) (or 185 mg of rolapitant hydrochloride) and the following inactive ingredients: polyoxyl 15 hydroxystearate (44 mg/mL), medium chain triglycerides (11 mg/mL), soybean oil (6.6 mg/mL), sodium chloride (6.2 (b) (4) mg/mL) dibasic sodium phosphate, anhydrous (2.8 (b) (4) mg/mL), and may contain hydrochloric acid and/or sodium hydroxide to adjust pH.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1. Currently approved Drugs for Nausea and Vomiting in Adults

Drug	Dosage Form	Indications					
		PONV		CINV		Other NV	
		Prevention	Treatment	Prevention		Prevention	Treatment
				HEC	MEC		
5-HT3 Receptor Antagonists							
Zofran (ondansetron)	IV	√		√*	√*		
	Oral	√		√	√*	Radio-therapy	
Anzemet (dolasetron)	IV	√	√				
	Oral				√*		
Kytril (granisetron)	IV	√	√	√*	√*		
	Oral	√	√	√*	√*		
Sustol (granisetron)	SC						
Sancuso (granisetron)	Trans-dermal			√	√		
Aloxi (palonosetron)	IV	√	√	√*,†	√*,†,#		
	Oral				√*,†,#		
NK1 Receptor Antagonists							
Emend (aprepitant)	Oral	√		√*,†,#	√*		
Emend (fosaprepitant)	IV			√*,†,#	√*		
Varubi (rolapitant)	Oral			√*,#	√*		
5-HT3 and NK-1 Antagonist							
Akynzeo (palonosetron and netupitant)	Oral			√*,†,#	√*,†,#		
D2-Receptor Antagonists							
Droperidol	IV, IM	√					
Metoclopramide	IV	√		√ (not specified)			
Prochlorperazine	Oral						"severe"
	IV						"severe"
	Suppository						"severe"
H1 Receptor Antagonists							
Phenergan (promethazine)	Oral		√			Motion Sickness	Motion Sickness
		√ (certain types of anesthesia & surgery)					
	Suppository		√			Motion Sickness	Motion Sickness
		√ (certain types of anesthesia & surgery)					
	IV, IM	√ (certain types of anesthesia & surgery)					Motion Sickness
Antivert (meclizine)	Oral					Motion Sickness	Motion Sickness
Diphenhydramine	IV						Motion Sickness
Anticholinergics							
Transderm Scop (scopolamine)	Trans-dermal	√				Motion Sickness	
Cannabinoid							
Marinol (dronabinol)	Oral			√ (not specified) [refractory]			
Other							
Tigan (trimtho-benzamide HCl)	IM		√				Gastro-enteritis
	Oral		√				Gastro-enteritis

CINV: Chemotherapy-Induced Nausea and Vomiting; PONV: Post-operative Nausea and Vomiting
NV: Nausea and Vomiting; HEC: Highly Emetogenic Chemotherapy; MEC: Moderately Emetogenic Chemotherapy
*initial and repeat courses
†acute
#delayed
Source: Drugs@FDA
Table created by Anil K. Rajpal, MD, MPH

2.3 Availability of Proposed Active Ingredient in the United States

Rolapitant hydrochloride is available as the currently marketed oral product Varubi.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently two other substance P/neurokinin 1 (NK1) receptor antagonist products on the market in the U.S.—Emend and Akynzeo.

EMEND is available in two formulations- oral (aperepitant) and solution for injection (fosaprepitant).

Contraindications

Aprepitant (excerpt from 05/2017 label)

EMEND is contraindicated in patients:

- *who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions have been reported [see Adverse Reactions (6.2)].*
- *taking pimozide. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of this drug which is a CYP3A4 substrate, potentially causing serious or life-threatening reactions, such as QT prolongation, a known adverse reaction of pimozide [see Warnings and Precautions (5.1)].*

Fosaprepitant (excerpt from 08/2017 label)

EMEND is contraindicated in patients:

- *who are hypersensitive to any component of the product. Hypersensitivity reactions including anaphylactic reactions, flushing, erythema, and dyspnea have been reported [see Warnings and Precautions (5.2), Adverse Reactions (6.2)].*
- *taking pimozide. Inhibition of CYP3A4 by aprepitant, the active moiety, could result in elevated plasma concentrations of this drug, which is a CYP3A4 substrate, potentially causing serious or life threatening reactions, such as QT prolongation, a known adverse reaction of pimozide [see Warnings and Precautions (5.1)].*

Warnings and Precautions

Aprepitant

5.1 Clinically Significant CYP3A4 Drug Interactions
5.2 Decrease in INR with Concomitant Warfarin
5.3 Risk of Reduced Efficacy of Hormonal Contraceptives

Fosaprepitant

5.1 Clinically Significant CYP3A4 Drug Interactions
5.2 Hypersensitivity Reactions

5.3 Decrease in INR with Concomitant Warfarin
5.4 Risk of Reduced Efficacy of Hormonal Contraceptives

Akynzeo is a fixed combination of netupitant, a substance P/neurokinin1 receptor antagonist, and palonosetron, a 5-HT3 receptor antagonist.

Contraindications
None (from 12/2016 label)

Warnings and Precautions
The Akynzeo label has no warnings and precautions related to the netupitant part of the fixed dose combination product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Selected Regulatory Action(s)
25 May 2017	Re-submission of NDA 208,399
22 March 2017	Type A meeting (End of Review) ▪ FDA agreed with Applicant's proposed parameters for the IVDR method development for rolapitant injectable emulsion and gave specific CMC advice on a variety of drug substance and drug issues
11 January 2017	Complete Response Letter issued for NDA 208,399 ▪ See Section 1.4 above for details of deficiencies

2.6 Other Relevant Background Information

None known, except as discussed in other parts of the review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well organized and easily navigable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all studies were performed in accordance with the Monitoring Plan and the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements of the countries in which they were conducted.

3.3 Financial Disclosures

No clinical studies were reviewed as part of the current re-submission.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The deficiencies leading to a complete response action were due to lack of a validated in vitro release method that could be used for quality control. Given this deficiency, a bio-waiver could not be granted and in vitro comparability could not be established between the new (b) (4) and original (b) (4) drug product manufacturing facilities. These d are adequately addressed in the current application and the Office of Pharmaceutical Quality (OPQ) is recommending an approval action. See the OPQ reviews in DARRTS.

4.2 Clinical Microbiology

No issues identified.

4.3 Preclinical Pharmacology/Toxicology

No nonclinical studies were submitted as part of the current Application. The nonclinical program for rolapitant injectable emulsion was found to be adequate for approval during the previous review cycle.

4.4 Clinical Pharmacology

As part of the first submission, the Applicant submitted a study report for a drug-drug interaction study (PR-11-5021-C). The DDI study included an assessment on the effect of rolapitant IV and its metabolite on CYP2D6 substrates. The study showed a

maximum 2.7-fold increase in Cmax and 3.2-fold increase in AUC observed two weeks after the co-administration of rolapitant and dextromethorphan. By Day 28, 4 weeks after co-administration, the magnitude of CYP2D6 inhibition was similar to that on Day 1. Based on the results of the DDI study, the clinical pharmacology reviewer originally recommended contraindicating concurrent use of rolapitant injectable emulsion with all CYP2D6 substrates.

FDA Proposed Labeling and Rationale (sent to Sponsor at end of original review cycle)

> **4. CONTRAINDICATIONS**
> VARUBI is contraindicated in patients taking CYP2D6 substrates, including receiving thioridazine and pimozide, a CYP2D6 substrate. A significant increase in plasma concentrations of co-administration of VARUBI with thioridazine or pimozide may result in QT prolongation and Torsades de Pointes [see Warnings and Precautions (5.1)].

FDA Rationale:

1. The effect of CYP2D6 inhibition from single dose of IV rolapitant lasts at least 4 weeks and there is no data indicating when this inhibitory effect will diminish. We expect similar duration for the CYP2D6 inhibition from oral administration.
2. The magnitude of CYP2D6 inhibition is unknown when rolapitant is given every two weeks

As part of the current Application, Tesaro, Inc provided an alternate proposal. The Applicant currently proposes to contraindicate only CYP2D6 substrates with a narrow therapeutic index and QT prolongation and Torsades de Pointes potential (i.e., thioridazine and pimozide).

Applicant's Proposed Labeling and Rationale (submitted as part of the current Application)

> **4. CONTRAINDICATIONS**
> (b) (4)

Applicant's Rationale:

1. Magnitude of CYP2D6 inhibition is not a factor following dosing every 14 days due to minimal accumulation (<10%) of rolapitant predicted over 6 cycles.
2. Review of the clinical trial data by pooling from the four safety and efficacy oral clinical trials supports safe use. The TESAEs and TEAEs occurred with

similar frequency when grouped by concomitant CYP2D6 substrate use vs non-use.

3. Review of the clinical trial data by pooling from the 4 safety and efficacy oral clinical trials supports safe use. The TESAEs and TEAEs occurred with similar frequency when grouped by concomitant CYP2D6 substrate use vs non-use.

Clinical Reviewer's Comment:
During the current review cycle, the clinical pharmacology team decided that a complete contraindication of all CYP2D6 substrates was not appropriate based on a theoretical risk of increased plasma concentration of these drugs. Therefore, the clinical pharmacology team changed their recommendation to agree with the Applicant's proposal to contraindicate only the narrow therapeutic index CYP2D6 substrates—thioridazine and pimozide.

Given that the CYP2D6 inhibition was not completely reversed by the end of the 28-day study, the Applicant will be required to perform an in vivo drug interaction study with a sensitive substrate of CYP2D6 to study the duration of CYP2D6 inhibition beyond 28 days after a single dose administration of VARUBI (rolapitant) intravenously and document when inhibition is resolved. Given that the currently labeled minimum dosing interval for rolapitant is 14 days, the results of this study will be important.

Our review of the clinical data from the oral rolapitant program did not reveal any safety signals associated with concomitant CYP2D6 use. However, these studies were not powered to show a difference in adverse events. The clinical team deferred to the clinical pharmacology team for the decision regarding concomitant use of CYP2D6 substrates as the known rolapitant safety data (oral rolapitant program) do not provide sufficient evidence to recommend for or against a complete contraindication. See Section 7 for specific safety data.

4.4.1 Mechanism of Action

Rolapitant is a neurokinin-1 (NK-1) receptor antagonist. These receptors are broadly distributed in central and peripheral nervous systems. Studies have shown that rolapitant binds to the NK-1 receptor with high affinity and has little or no activity for the other NK receptors. The endogenous activator of the NK-1 receptor is the neuropeptide, Substance P.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

No new clinical studies were submitted as part of the current Application.

5.2 Review Strategy

For this clinical review, the safety results for the four phase 1 studies submitted in support of the current Application will be presented. See the full clinical pharmacology review for other details regarding these studies.

5.3 Discussion of Individual Studies/Clinical Trials

No clinical trials were submitted as part of the current Application.

6 Review of Efficacy

No efficacy evaluation was conducted in support of the current Application

6.1 Indication

The Sponsor has proposed the following indication statement for rolapitant IV:

(b) (4)

Mo Comment:
The proposed indication for rolapitant IV is (b) (4) *for the currently marketed oral rolapitant product.*

7 Review of Safety

No new clinical trials were submitted as part of the current Application.

The Complete Response letter specified that the Applicant should submit a safety update as part of the resubmission. There were no investigational studies initiated, on-

going or completed during the period following submission of the original NDA. Therefore, to fulfill this requirement, the Applicant submitted the 4th and 5th quarterly Periodic Adverse Drug Experience Reports (PADERs) for rolapitant oral (NDA 206,500, approved September 2017). There have been no ongoing rolapitant clinical trials since the submission of the first submission of NDA 208,399.

4th Quarterly PADER
Reporting period 02 June 2016 to 01 September 2016

During this reporting period, there were (b) (4) individual doses of rolapitant oral shipped patient accounts. The Applicant estimates that this is likely an overestimate of the number of patients exposed to rolapitant oral as it is likely that not all patients received the planned medication. There were sixteen (16) 15-Day Alert reports submitted during this period. There were thirteen (13) cases with fatal outcome. For each of these cases, the Applicant reported that despite their efforts only limited information is available which precluded a meaningful assessment of these cases. A review of the non-15 day adverse events reported did not reveal any unexpected AEs in the population of patients receiving chemotherapy.

5th Quarterly PADER
Reporting period 02 September 2016 to 01 December 2016

During this reporting period, there were (b) (4) individual doses of rolapitant oral shipped patient accounts. The Applicant estimates that this is likely an overestimate of the number of patients exposed to rolapitant oral as it is likely that not all patients received the planned medication. There were twenty-four (24) 15-Day Alert reports submitted for twenty-two (22) distinct cases during this period. There were sixteen (16) cases with fatal outcome. For each of these cases, the Applicant reported that despite their efforts only limited information is available which precluded a meaningful assessment of these cases. A review of the non-15 day adverse events reported did not reveal any unexpected AEs in the population of patients receiving chemotherapy.

MO Comment: Follow-up reports in subsequent PADERs should be reviewed to get a clearer picture of the circumstances regarding each of the deaths reported. Overall, the known safely profile of rolapitant appears to adequately represented in currently approved (for rolapitant oral) and currently proposed (for rolapitant injectable emulsion) labeling.

7.1 Methods

N/A

7.2 Adequacy of Safety Assessments

N/A

7.3 Major Safety Results

N/A

7.4 Supportive Safety Results

N/A

7.5 Other Safety Explorations

For this Application, a brief review of the oral rolapitant safety data was conducted. This review focused on comparing the adverse event profile of patients taking concomitant CYP2D6 substrates with the AE profile of patients not receiving these products. See Section 4.4 Clinical Pharmacology above for a discussion on the DDI Study results and the rationale for performing this safety analysis.

For this review, the safety data from patients in oral rolapitant Pooling Group 1 was reviewed. This group was the primary safety set for the oral rolapitant program and included all patients from the adequate, well-controlled, double-blind, randomized, parallel comparison studies conducted in patients at risk for CINV in oral rolapitant studies P04351, P04832, P04833, and P04834. For further details, see the Clinical Review for NDA 206,500 in DARRTS (Aisha P Johnson, September 2015).

In the oral rolapitant program, patients who concomitantly used CYP2D6 substrates reported TEAEs (including SAEs) at a higher rate than those patients not using CYP2D6 substrates concomitantly. However, no trend was seen between patients randomized to rolapitant vs control. See Table 2 and Table 3 below.

Table 2. Serious Adverse Events by Concomitant use of CYP2D6, Rolapitant Oral Pooling Group 1

	Overall CINV			
	Concomitant Use of CYP2D6		No Concomitant Use of CYP2D6	
Subjects with ≥ 1 Incidence	Control n/N (n%)	Rolapitant n/N (n%)	Control n/N (n%)	Rolapitant n/N (n%)
Cycle 1	96/720 (13.3)	101/800 (12.6)	30/581 (5.2)	32/767 (4.2)
Cycle 2	37/487 (7.6)	57/577 (9.9)	17/511 (3.3)	25/621 (4.0)
Cycle 3	31/399 (7.8)	30/477 (6.3)	11/435 (2.5)	21/506 (4.2)
Cycle 4	16/342 (4.7)	28/363 (7.7)	8/353 (2.3)	10/418 (2.4)
Cycle 5	10/158 (6.3)	11/205 (5.4)	7/207 (3.4)	7/234 (3.0)
Cycle 6	12/134 (9.0)	9/169 (5.3)	1/180 (0.6)	3/198 (1.5)

Source: ISS Appendix Table 95B
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Table 3. Treatment Emergent Adverse Events by Concomitant use of CYP2D6, Rolapitant Oral Pooling Group 1

	Overall CINV			
	Concomitant Use of CYP2D6		No Concomitant Use of CYP2D6	
Subjects with ≥ 1 Incidence	Control n/N (n%)	Rolapitant n/N (n%)	Control n/N (n%)	Rolapitant n/N (n%)
Cycle 1	548/720 (76.1)	619/800 (77.4)	292/581 (50.3)	402/767 (52.4)
Cycle 2	327/487 (67.1)	394/577 (68.3)	238/511 (46.6)	287/621 (46.2)
Cycle 3	252/399	296/477	164/435	202/506

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Clinical Reviewer Comment:
The data from oral rolapitant Pooling Group 1 show that patients with no concomitant use of CYP2D6 substrates have lower overall rates of TESAEs and TEAEs than those patients with concomitant use of CYP2D6 substrates. This trend was seen across all 6 chemotherapy cycles studied. This trend also held whether or not patients received oral rolapitant. See Tables 2 and 3 above. The reason for the higher rate of TESAEs and TEAEs for patients with concomitant use of CYP2D6 substrates is unclear. It is possible that the use of these substrates was associated with being a sicker patient with a relatively higher level of comorbidity resulting in a higher rate of AEs regardless of exposure to rolapitant. Of note, the most commonly administered CYP2D6 substrates in the rolapitant 200 mg group were ondansetron, metoclopramide, and ranitidine.

The rate of TESAEs and TEAEs within the group of patients with concomitant use of CYP2D6 substrates was generally similar between those with and without exposure to rolapitant. However, none of the studies included in Pooling Group 1 was powered to show a difference in AE rates based on exposure to rolapitant. Therefore, the safety results included in the tables above do not, alone, provide adequate data to fully understand the risk of adverse events associated the concomitant use of rolapitant and CYP2D6 substrates.

7.6 Additional Safety Evaluations

N/A

7.7 Additional Submissions / Safety Issues

N/A

8 Postmarket Experience

N/A

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

See the final approved label for final labeling recommendations.

9.3 Advisory Committee Meeting

N/A

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/s/

AISHA P JOHNSON
09/20/2017

ANIL K RAJPAL
09/20/2017

Summary Review for Regulatory Action

Date	9 January 2017
From	Shari L. Targum, M.D., M.P.H.
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	208399
Applicant Name	Tesaro Inc
Date of Submission	11 March 2016
PDUFA Goal Date	11 January 2016
Proprietary Name / **Established (USAN) Name**	Varubi/rolapitant
Dosage Forms / Strength	Injectable emulsion/166.5 mg/92.5 mL (1.8 mg/ml) in a single-dose vial
Proposed Indication(s)	1. In combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy.
Action/Recommended Action for NME:	*Complete Response*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Aisha P. Johnson, MD
Pharmacology Toxicology Review	Tamal K. Chakraborti
CMC Review/Biopharmaceutics Review	Hitesh N. Shroff, Ph.D./Tien-Mien (Albert) Chen, Ph.D.
Microbiology Review	Eric K. Adeeku, Ph.D.
Clinical Pharmacology Review	Elizabeth Y Shang, Ph.D., R. Ph.
DDMAC/OPDP	Adewale Adeleye, Pharm.D., M.B.A.
CDTL Review	Hitesh N. Shroff, Ph.D.
OSE/DMEPA	Sherly Abraham, R.Ph./Matthew Barlow, R.N., B.S.N.
CSS	Alicja Lerner, M.D., Ph.D.
Division of Medical Policy Programs	Nyedra W. Booker, Pharm.D., M.P.H.
Division of Pediatric and Maternal Health	Erica Radden, M.D., Jane Liedtka, M.D.

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication/OPDP=Office of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
CDTL=Cross-Discipline Team Leader

Signatory Authority Review Template

1. Introduction

This memo conveys the Division's recommendation to issue a Complete Response letter for NDA 208399 because of process deficiencies in the originally proposed (b) (4) manufacturing site; inadequate development and validation of the proposed in vitro drug release methods; and lack of a bridge between the "to be marketed" emulsion from a new (b) (4) site (added during the review cycle), and the emulsion used in the human pharmacokinetic (PK) studies.

2. Background

Rolapitant is a substance P/neurokinin 1 (NK1) receptor antagonist developed as an antiemetic for cancer chemotherapeutic agents, which stimulate emesis via serotonin and substance P release and activation of 5-HT3 and NK1 receptors.

Rolapitant oral tablets (VARUBI, NDA 206500) are approved (9/1/2015) in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. The recommended oral dosage regimen is 180 mg, administered approximately 1-2 hours prior to the initiation of each chemotherapy cycle, but at no less than 2 week intervals.

In NDA 208399, the applicant has proposed to market a new emulsion dosage form, with globule size in the nanometer scale, for intravenous (IV) infusion, for the same indication as the oral tablets; this is a 505(b) (1) application, using the oral rolapitant tablets as the reference product. The proposed dosage of the nano-emulsion is 166.5 mg intravenous infusion over 30 minutes within 2 hours prior to initiation of chemotherapy (on Day 1).

To support approval, the applicant conducted a pivotal relative bioavailability (BA) study (PR-11-5016-C) to establish a bridge between the proposed emulsion new dosage form and the approved oral tablet. The systemic exposures ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}120h}$) to rolapitant and its major active metabolite were comparable in this study. Because the Cmax from rolapitant IV administration was 1.9-fold that of oral rolapitant, the applicant conducted an additional phase 1 study in healthy subjects using doses higher than the proposed therapeutic dose, to support the safety of high peak plasma concentrations following 30-minute intravenous administration.

The NDA submission listed (b) (4) in (b) (4) as the manufacturing and testing facilities. (b) (4) provided the applicant with redacted copies of the

Form 483[1] after the latest Agency inspections and on (b) (4) published statements of Non-compliance with GMP for these facilities, based on their (b) (4) inspection. The injectable emulsion batches used in the human PK studies, including the pivotal BA/BE study, were manufactured by the (b) (4) site that failed to meet the process inspection.

During the initial filing letter from the Agency (24 May 2016), the applicant was notified that an in vitro release method needed to be developed, along with release acceptance criteria, for the proposed drug product, rolapitant in an emulsion dosage form, for drug product quality control purposes (i.e., drug performance and drug quality tests) in order to assess the in vitro release kinetics of rolapitant over time from the proposed drug product and for assessing the future changes in, e.g., composition/formulation, manufacturing site, process, etc. of the drug product.

In a July 2016 amendment to the NDA, the applicant added a second manufacturing facility in (b) (4) along with corresponding analytical testing sites for release of drug product.

In 15 November 2016 and 18 October 2016 communications to the applicant, the Agency stated that an adequate bridge had not been established between the oral rolapitant reference table and the to-be-marketed IV emulsion to be manufactured at the proposed (b) (4) (b) (4) site. The applicant's in vitro release data from (b) (4) in the rolapitant injectable emulsion drug product will not be considered sufficient to support the manufacturing site change from the (b) (4) ite (b) (4) to the proposed (b) (4) site. Because the clinical safety information for higher Cmax was collected using the emulsion manufactured at the (b) (4) site, the applicant was informed of the need to bridge (e.g., a relative BA study) between the IV emulsion manufactured at the (b) (4) site and the proposed (b) (4) tes.

3. CMC/Device/Biopharmaceutics

The Office of Pharmaceutical Quality (OPQ) recommended against approval because of the unresolved drug product manufacturing facility and biopharmaceutics issues.

The CMC reviewer concluded that the manufacturing, testing and release of the drug substance and the alternate drug product manufacturing, testing and release facilities located in (b) (4) were acceptable. At this time, the Office of Process and Facilities has made a final overall "Unacceptable" recommendation for (b) (4) the original drug product manufacturing facility, because of deficiencies related to (b) (4) processing.

[1] During an inspection, ORA investigators may observe conditions they deem to be objectionable. These observations, are listed on an FDA Form 483 when, in an investigator's judgment, the observed conditions or practices indicate that an FDA-regulated product may be in violation of FDA's requirements (www fda.gov).

The applicant initially proposed (b) (4), instead of an in vitro release method, as a quality control method. Since the applicant has not provided a validated in vitro drug release method, a bio-waiver cannot be granted and in vitro comparability cannot be established between the new and original drug product manufacturing facilities.

4. Nonclinical Pharmacology/Toxicology

There are no outstanding pharmacology/toxicology issues that preclude approval.

5. Clinical Pharmacology

The clinical pharmacology/biopharmaceutics reviewers recommended against approval of this application because of deficiencies at the (b) (4) site and lack of data demonstrating comparability of product manufactured at a proposed (b) (4) site.

The proposed IV emulsion has a complex dosage form, and the measured plasma concentrations represent total concentrations of rolapitant, or the sum of unbound, protein-bound and rolapitant (b) (4).

The applicant submitted four Phase 1 studies in healthy subjects, including single and multiple-dose dose escalation studies, one pivotal BA study, and a drug-drug interaction study.

Following a single IV administration of 185 mg rolapitant injectable emulsion to healthy subjects, the Cmax was reached at the end of infusion (30 minutes), mean Cmax was 1986 ng/mL (%CV: 39%) and the mean terminal half-life was 161 hours. The systemic exposures (Cmax and AUC) increased in a dose-proportional manner when the IV dose increased from 20 mg to 200 mg and from 225 mg to 300 mg. Rolapitant is metabolized by CYP3A to form a major active metabolite (SH720881, M19). The systemic exposures of parent to the active metabolite were comparable between IV and oral administration, suggesting that rolapitant is released (b) (4) into plasma to a comparable degree as that after the approved tablet.

Because of the Cmax following IV rolapitant administration was 1.9-fold that of oral rolapitant, the applicant submitted clinical safety data in subjects that received supratherapeutic doses of IV rolapitant.

Because of the change in manufacturing site, the applicant will need to demonstrate comparability between the IV batches manufactured at the new site (b) (4) and those batches manufactured at the (b) (4) site, with comparable physicochemical characteristics and in vitro dissolution profiles. If the applicant is unable to demonstrate comparability via adequate in vitro dissolution data, a new BE study will be needed to support the site change.

According to the biopharmaceutics reviewer, the in vitro release test is inadequate and cannot be used to support the biowaiver for an in vivo BE study to support the manufacturing site change.

6. Clinical Microbiology

There are no outstanding clinical microbiology or sterility issues that preclude approval.

7. Clinical/Statistical-Efficacy

No efficacy evaluation was conducted to support the current application. This application relied on the prior evidence of effectiveness for oral rolapitant.

8. Safety

I concur with the clinical reviewer that the use of IV rolapitant for the proposed indication appears to represent an acceptable risk.

Intravenous rolapitant was evaluated in 350 healthy adult subjects in four phase 1 studies. Of these subjects, 125 received a supratherapeutic dose (> 185 mg, maximum dose 300 mg IV rolapitant). The numbers of exposed subjects appears to be adequate. The most common reason for premature discontinuation was pump malfunction (Table 5, clinical review). The most common observed adverse events were headache, dizziness and infusion-related reaction (Table 12, clinical review); no serious adverse events were reported in this healthy subject population.

9. Advisory Committee Meeting

This application was not discussed at an Advisory committee meeting.

10. Pediatrics

This application triggers the requirement for a pediatric assessment under the Pediatric Research and Equity Act (PREA), since the proposed drug product is a new dosage form of rolapitant.

The Agency previously issued an agreed initial Pediatric Study Plan (iPSP) where the applicant requested a deferral of studies in pediatric patients (birth to 17 years) (IND 117307, 16 December 2015).

Final labeling and postmarketing requirements will be deferred until the next review cycle.

11. Other Relevant Regulatory Issues

There are no new data indicating increased abuse potential and rolapitant will not be a scheduled substance.

There are no financial disclosure issues.

12. Labeling

The proposed proprietary name, Varubi, is acceptable.

The Division of Medical Policy Programs, Office of Prescription Drug Promotion and Division of Medication Error Prevention and Analysis have deferred review of proposed prescribing information and labeling to a subsequent review cycle.

13. Decision/Action/Risk Benefit Assessment

I concur with the product quality, clinical pharmacology, biopharmaceutics and clinical reviewers that this application should receive a Complete Response action. The combination of inspection deficiencies at the (b) (4) drug product manufacturing site; lack of an adequate, validated in vitro drug release method; and unresolved need for a bridging BA/BE study comparing the "to be marketed" drug product manufactured at the (b) (4) site to the IV rolapitant product used in the human PK trials remain unresolved review issues that collectively impact approvability of this application.

If a validated drug product in vitro release method was sufficient to support a manufacturing site change, an additional bridging study in humans might not have been necessary to establish bioequivalence; however, this is not the case. Therefore, I concur with the clinical pharmacology reviewers that a relative bioavailability study will be needed, using the drug product manufactured at the (b) (4) facility, in order to establish bioequivalence between drug products manufactured at the (b) (4) and (b) (4) manufacturing sites.

Alternatively, th (b) (4) facilities could resolve their inspection issues and allow (b) (4) to assume its original role as the primary manufacturing facility for the drug product. However, this resolution has not yet taken place.

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/s/

SHARI L TARGUM
01/11/2017

Cross-Discipline Team Leader Review

Date	December 17, 2016
From	Hitesh Shroff, Ph.D., CMC Lead (Acting) CDER/ONDP II/Branch V
Subject	Cross-Discipline Team Leader Review
NDA #	NDA 208399
Applicant	Tesaro Inc., Waltham, MA
Date of Submission	March 11, 2016
PDUFA Goal Date	January 11, 2017
Proprietary Name / Established (USAN) names	Varubi (rolapitant) injectable emulsion
Dosage forms / Strength	166.5 mg/92.5 mL (1.8 mg/mL) of rolapitant in a single-dose vial
Proposed Indication(s)	VARUBI is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.
Recommended:	Complete Response

1. Introduction

Varubi (rolapitant) injectable emulsion is supplied as a sterile, translucent white homogenous emulsion in a stoppered single use vial. Each vial delivers 166.5 mg/92.5 mL (1.8 mg/mL) rolapitant (equivalent to 185 mg of rolapitant hydrochloride). The drug product also contains the following inactive ingredients: polyoxyl 15 hydroxystearate medium chain triglycerides, soybean oil, sodium chloride, dibasic sodium phosphate, anhydrous, water for injection, hydrochloric acid and/or sodium hydroxide to adjust pH to 7.0 to 8.0. The drug product packaged in plastic vials will be manufactured at (b) (4) The drug product packaged in glass vials will be manufactured a (b) (4)

This NDA has been filed as a 505(b)(2) application, using Varubi (rolapitant) tablets, 90 mg, which is also manufactured by Tesaro, Inc. as the reference listed drug. The applicant relied on the efficacy and safety findings of Varubi tablets for Chemotherapy Induced Nausea and Vomiting (CINV). A relative bioavailability (BA) study to establish a bridge between the proposed new injectable emulsion formulation and tablets was performed using only the drug product manufactured at (b) (4) The referenced NDA 206500 for Varubi tablets was approved on 09/01/2015.

2. Background

Varubi (rolapitant) injectable emulsion is indicated in combination with other antiemetic agents in adults for prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. The recommended dosage for Varubi injectable emulsion is 180 mg administered as an IV infusion over 30 minutes approximately 1 to 2 hours prior to the start of chemotherapy.

Rolapitant is a neurokinin-1 (NK-1) receptor antagonist. The neurokinin receptors are G protein coupled receptors found in central nervous system and peripheral nervous system. Rolapitant has high affinity for NK-1 receptor; however, it does not have significant affinity for NK-2, NK-3 or other receptors, transporters, enzymes and ion channels. The endogenous activator of the NK-1 receptor is the neuropeptide, Substance P.

3. CMC

Drug substance: The active pharmaceutical ingredient, rolapitant hydrochloride, is a white to off-white powder. It has three chiral centers with absolute configuration (S, S, R). It also contains a spirocyclic lactam ring. The proposed structure was confirmed by the spectroscopic methods such as NMR, IR, MS and UV. The drug substance only contains (b) (4) (b) (4) (b) (4) The drug substance was reviewed by Dr. Debasis Ghosh and was determined to be adequate for the NDA 208399.

Drug Product: The drug product is a sterile injectable emulsion supplied in clear (b) (4) plastic or glass vial with a rubber stopper. Each vial delivers 92.5 mL of the drug product. The drug product manufacturing process involves (b) (4) (b) (4) (b) (4) The drug product manufacturing process was reviewed and judged to be acceptable by Dr. Yuesheng Ye. The microbiology reviewer, Dr. Eric Adeeku, concluded that the applicant has demonstrated adequate sterility assurance for the manufacturing process.

The drug product specification includes tests and acceptance limits for the critical product quality attributes for identity, strength, purity and quality such as appearance, identity, assay, impurities, pH, particulate matter and globule size. Based on the satisfactory stability testing of three registration batches 12-month expiration dating period is granted when stored at room temperature in plastic or glass vials. The drug product quality was reviewed by Dr. Hitesh Shroff and deemed adequate.

The applicant has submitted a claim of categorical exclusion. The categorical exclusion cited at 21 CFR 25.31(b) is appropriate for the estimated amount of drug to be produced for direct use. A statement of no extraordinary circumstances has been submitted. The claim of categorical exclusion is acceptable.

In the amendment dated July 29, 2016 Tesaro included (b) (4) (b) (4) (b) (4) as an alternate drug product manufacturing, testing, packaging, release and testing site. In support of the application Tesaro provided CMC information for three drug product batches including acceptable batch analysis data to demonstrate that the drug product manufactured at the original site (b) (4) is comparable to the drug product manufactured at the alternate site, (b) (4) Thus from CMC perspective the drug products manufactured at both sides are comparable in quality.

Facilities: The drug substance manufacturing, testing and release facilities are acceptable. The alternate drug product manufacturing, testing and release facilities located in (b) (4) are also acceptable. However, the original drug product manufacturing facility, (b) (4) is not acceptable due to deficiencies related (b) (4) processing at this site. According the facilities reviewer, Dr. Vidya Pai, satisfactory resolution and on-site confirmation of corrective actions to inspectional deficiencies related to (b) (4) processing at (b) (4) facility is needed followed by an acceptable preapproval inspectional outcome for this application. As a result The Office of Process and Facilities (OPF) has made a final overall "Unacceptable" recommendation for the facilities involved in this application as of this review.

Biopharmaceutics: Tesaro initially proposed (b) (4) instead of an in-vitro release method as a quality control method. An in-vitro drug release method is needed to assess the bio-waiver between two drug product manufacturing sites. According to the biopharmaceutics reviewer, Dr. Hansong Chen, without a validated in-vitro drug release method, a bio-waiver cannot be granted and this NDA is not recommended for approval from biopharmaceutics perspective.

Overall OPQ Recommendation: This NDA is not recommended for approval from OPQ perspective because the Office of Process and Facilities (OPF) has made a final overall "Unacceptable" recommendation for the facilities involved in this application as of this review. Biopharmaceutics issues regarding in-vitro release method have not been adequately resolved. The label/labeling issues have not been completely resolved as of this review.

4. Nonclinical Pharmacology/Toxicology

The pharmacology/toxicology reviewer, Dr. Tamal Chakraborti, found no approvability issues with this NDA from nonclinical standpoint.

The applicant has conducted 13-week intravenous (infusion) toxicity studies in rats, 28-day and 13-week intravenous (infusion) toxicity studies in cynomolgus monkeys in support of intravenous administration of rolapitant injectable emulsion. The central nervous system appeared to be the primary target organ. Treatment related convulsions and tremors were observed in these studies. Vehicle related effects (clinical pathology and histopathology changes in the liver) were also observed in these studies. In addition, infusion site reactions were observed, which included abscess formation and/or inflammation. The NOAEL could not be determined for the 13-week rat study due to mortality observed at all placebo and rolapitant dose levels. The NOAEL in the 13-week study in cynomolgus monkeys was 10 mg/kg/day. Some of the histopathological findings (diffuse vacuolation of the adrenal cortex and brown pigmentation of adrenal glands and Kupffer cells in the liver) in monkey studies appeared to be related to the vehicle. Please refer to pharmacology review of NDA 206500 dated March 19, 2015 by Tracy L. Behrsing, PhD for other nonclinical studies with rolapitant including reproductive toxicity, genotoxicity, and carcinogenicity.

The proposed labeling appeared to be acceptable from nonclinical pharm/tox perspective. However, human dose multiple values were revised based on the recommended intravenous human dose of 166.5 mg (~167 mg/day or approximately 2.8 mg/k/day) of Varubi injectable emulsion.

5. Clinical Pharmacology

Tesaro relied on the efficacy and safety findings of their previously approved Varubi tablets for CINV. Tesaro conducted a relative bioavailability (BA) study to establish a bridge between the proposed injectable emulsion formulation and the approved tablets for efficacy. The BA study demonstrated that the systemic exposure ($AUC_{0\text{-}inf}$ and $AUC_{0\text{-}120h}$) to rolapitant and its major active metabolite were comparable and met the bioequivalence criteria. The Cmax from rolapitant IV administration was 1.9-fold that of the oral rolapitant tablets. The Cmax for the major active metabolite after administration of rolapitant tablet and the proposed emulsion met the bioequivalence criteria. The applicant also conducted a Phase I study in healthy subjects using doses higher than the proposed therapeutic dose to support the safety of high peak plasma concentrations following IV administration. Tesaro has demonstrated bioequivalence between the oral tablets and the IV product manufactured at (b) (4)

During the review cycle Tesaro proposed (b) (4) (b) (4) site as an alternative drug product manufacturing site. Tesaro has not performed a bridging study (BA/BE) to establish that the products manufactured at (b) (4) (b) (4) and (b) (4) are bioequivalent. Thus, a biowaiver for the drug product manufactured at (b) (4) (b) (4) is not granted from clinical pharmacology perspective. If the applicant is unable to demonstrate comparability between the drug products manufactured at both sites with acceptable in-vitro drug release data then an in vivo BE study is needed to support the site change.

According to the clinical pharmacology reviewers, Drs. Elizabeth Shang and Insook Kim, this NDA is not recommended for approval due to a lack of BA/BE studies for the manufacturing site change and pending labeling.

6. Clinical Microbiology

Not Applicable

7. Clinical

The safety, efficacy and tolerability of Varubi injectable emulsion were assessed in four Phase 1 studies in healthy subjects. In these studies rolapitant was found to be relatively safe and well tolerated. As a part of the IV development program 305 healthy subjects aged 18 to 55 years were enrolled. Of these subjects, 180 subjects received ≤185 mg and 125 subjects received >185 mg of rolapitant. There were no serious adverse events or deaths reported in these studies. The following is the summary of the Phase I studies.

Rolapitant IV Clinical Development Program

Study	Description	Study Specifics	Study Conclusion
PR-11-5016-C	Pivotal BE Study	BE study of 200 mg single oral dose of rolapitant and a 185 mg single IV dose of rolapitant administered over a 30 minute infusion	BE criterion based on AUC was met
PR-11-5012-C	Safety, tolerability and PK study of single ascending and multiple ascending doses of rolapitant IV	SAD doses of 20, 50, 100,150, 185, and 200 mg MAD doses x 10 days of 20, 40 and 60 mg of rolapitant IV	Safety and tolerability acceptable
PR-11-5022-C	Safety, tolerability and PK study of supratherapeutic single ascending doses of rolapitant IV	SAD of 225 to 300 mg of rolapitant IV	Safety and tolerability acceptable
PR-11-5021-C	DDI study that assessed administration of 185 mg rolapitant IV (infused over 30 minutes) on the PK of P-gp substrate (digoxin) a breast cancer resistance protein (BCRP) substrate sulfasalazine), and multiple CYP probe substrates (midazolam, omeprazole, warfarin, caffeine, and dextromethorphan)		The results from the IV DDI study suggest that no dosage adjustment is required when rolapitant IV is coadministered with P-gp, BCRP, CYP3A4, CYP2C9, CYP2C19, and CYP1A2 substrates, but dosage adjustment or caution are warranted when rolapitant IV is coadministered with CYP2D6 substrates with a narrow therapeutic index

In the opinion of the clinical reviewer, Dr. Aisha Johnson, this NDA should receive a Complete Response Action because a lack of BA/BE studies supporting drug product manufacturing site change. See the OPQ and clinical pharmacology reviews for further details. If an adequate bridge between manufacturing sites is established then this applicant would represent an acceptable risk and a recommendation could be made for approval from the clinical standpoint.

8. Safety

According the clinical reviewer, Dr. Aisha Johnson, in general the use of rolapitant injectable emulsion for the proposed indication of the prevention of CINV in the delayed (b) (4) appears to represent an acceptable risk. During four Phase I studies no unexpected safety signals were observed and there were no serious events or deaths reported.

9. Advisory Committee Meeting --

Not Applicable

10. Pediatrics

The Applicant submitted plans for a pediatric program for rolapitant IV. The Division issued correspondence confirming agreement with sponsor's initial Pediatric Study Program (iPSP). The sponsor requested a deferral for studies in patient's 0 to <18 years of age in accordance with the

provisions of Section 505B(a)(3)(A)(i) of the Federal Food, Drug and Cosmetic Act (FDCA), "The drug or biological product is ready for approval for use in adults before pediatric studies are complete".

11. Other Relevant Regulatory Issues

There are no relevant regulatory issues with this application. Tesaro referenced the following three patents of rolapitant emulsion from OPKO Health, Inc., FL

US Patent No. 7,049,320 – Expiry Date: Dec 08, 2023
US Patent No. 8,796,299 – Expiry Date: Dec 17, 2022
US Patent No. 9,101,615 – Expiry Date: Jul 14, 2032

12. Labeling

The Division of Medication Error Prevention and Analysis (DMEPA) reviewer, Dr. Sherly Abraham, and the Division of Medical Policy program (DMPP) reviewer, Dr. Nyedra Booker, have deferred the review of the labels and labeling until next review cycle. From the Division of Pediatric and Maternal Health the reviewer, Dr. Jane Liedtka, concluded that there is no new information available regarding rolapitant and pregnancy, lactation and effects on fertility. The labeling language for Section 8 will be updated to the currently recommended language for PLLR compliant labeling. The Division of Pediatric and Maternal Health (DPMH) reviewer, Dr. Erica Radden, concluded that the proposed labeling for Pediatric Use subsection is appropriate based on 21 CFR 210.57(c)(9)(iv), however, due to a CR action from DGIEP post-marketing requirements and final approved labeling will not be issued during this review cycle.

According the Dr. Alicja Lerner, the reviewer from Controlled Substance Staff concluded that rolapitant is a not a scheduled substance under the Controlled Substance Act (CSA) and recommended that Tesaro should continue to monitor for abuse, euphoria, hallucinations, dependence, withdrawal, overdose, diversion, misuse and any inappropriate use of the tablet and other approved formulations.

13. Recommendations/Risk Benefit Assessment

This NDA is not recommended for approval from OPQ perspective because the Office of Process and Facilities (OPF) has made a final overall "Unacceptable" recommendation for the facilities involved in this application. Biopharmaceutics issues regarding (b) (4) for assessing the drug product quality have not been adequately resolved. In absence of a validated (b) (4) (b) (4) required BA/BE studies were not performed in support of the drug product manufacturing site change as recommended by clinical pharmacology. The label/labeling issues have not been completely resolved.

Hitesh N. Shroff -S

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Hitesh Shroff, Ph.D.,
CDER/ONDP II/Branch V
December 21, 2016

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/s/

HITESH N SHROFF
12/21/2016

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208,399/ IND 117,307
Priority or Standard	Standard
Submit Date(s)	11 March 2016
Received Date(s)	11 March 2016
PDUFA Goal Date	11 January 2016
Division / Office	Division of Gastroenterology and Inborn Errors Products Office of Drug Evaluation (ODE) III
Reviewer Name(s)	Aisha P. Johnson, MD, MPH, MBA
Review Completion Date	01 December 2016
Established Name	Rolapitant Injectable Emulsion
(Proposed) Trade Name	Varubi® IV
Therapeutic Class	NK-1 inhibitor
Applicant	Tesaro, Inc
Formulation(s)	Emulsion for intravenous use, 185 mg (166.5 mg [redacted] (b) (4) 92.5 mL (1.8 mg/mL).
Dosing Regimen	166.5 mg [redacted] (b) (4)) administered as an IV infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1
Indication(s)	VARUBI is indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy
Intended Population(s)	Adult Patients

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

In the opinion of this reviewer, the current 505(b)(2) rolapitant IV Application should receive a Complete Response Action.

Oral rolapitant is currently approved for marketing in the United States for use in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy.

The proposed indication for rolapitant IV is the same as the currently approved indication for oral rolapitant.

1.2 Risk Benefit Assessment

Given the totality of the information submitted in support of this Application, the possible risks associated with the use of rolapitant IV currently outweigh the benefits of the therapy.

The pivotal study for the current 505(b)(2) rolapitant IV Application was a phase 1 bioequivalence (BE) study designed to compare 185 mg rolapitant (166.5 mg (b) (4) IV administered over 30 minutes to a single dose of 200 mg rolapitant (180 mg) oral administered as the same capsule formulation (4 x 50 mg) used in the phase 3 rolapitant oral clinical studies. The 185 mg IV dose (test) was considered to have met BE criteria based on AUC relative to the 200 mg rolapitant oral dose (reference). At the rolapitant IV dose of 185 mg, mean rolapitant Cmax was approximately 1.7- to 1.9-fold the Cmax of the oral formulation at 200 mg (~1700 to 1900 ng/mL for rolapitant IV and 1000 ng/mL for rolapitant oral, respectively). Therefore, it was necessary to evaluate clinical safety data of subjects exposed to rolapitant IV 185 mg to support the safety of the proposed rolapitant IV dose.

The clinical safety data for rolapitant IV was provided by the four phase 1 studies submitted as part of the current application. The rolapitant IV emulsion formulation used for these studies was manufactured at a site in (b) (4) (b) (4) Due to issues with the (b) (4) t the manufacturing site to a site in (b) (4) To support this change, the Applicant conducted a comparative in vitro release study and provided preliminary in vitro release data from (b) (4) of the rolapitant injectable emulsion drug product. However, CMC team determined during the

review cycle that these data were not sufficient to support the manufacturing site change from the (b) (4) site to the proposed (b) (4) site. To address this deficiency, the FDA informed the Applicant during the review cycle that a relative BA/BE study would be needed. See the CMC, clinical pharmacology and biopharmacology reviews for additional details.

Without an adequate bridge between the to-be-marketed rolapitant for injection emulsion formulation from the (b) (4) facility and the rolapitant injection for emulsion used in the phase 1 clinical studies, the clinical safety data cannot be relied upon to support the higher Cmax.

As part of the current Application, the safety of rolapitant IV was assessed in four phase 1 studies in healthy subjects. In these studies, rolapitant IV was found to be relatively safe and well-tolerated. These studies covered rolapitant IV dose groups of <185 mg, 185 mg, and >185 mg. During these studies, 305 subjects received rolapitant IV ≥185 mg IV. In these studies, no unexpected safety signal was observed. There were no serious adverse events or deaths reported in these studies.

If an adequate bridge between manufacturing facilities were to be established, this application would represent an acceptable risk and a recommendation would be made for approval from the clinical standpoint. See Section 7.5.5 for recommended labeling regarding drug-drug interactions.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None.

1.4 Recommendations for Postmarket Requirements and Commitments

The Applicant submitted plans for a pediatric program for rolapitant IV. The Division issued correspondence confirming agreement with sponsor's initial Pediatric Study Program (iPSP). The sponsor requested a deferral for studies in patient's 0 to <18 years of age in accordance with the provisions of Section 505B (a)(3)(A)(i) of the Federal Food, Drug and Cosmetic Act (FDCA), "The drug or biological product is ready for approval for use in adults before pediatric studies are complete".

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in rolapitant injectable emulsion (rolapitant hydrochloride) is a substance P/neurokinin 1 (NK1) receptor antagonist, chemically described as (5S,8S)-

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

The solubility of rolapitant hydrochloride in aqueous solution is pH-dependent and is more soluble at lower pH. Rolapitant hydrochloride is formulated in an oil-in-water emulsion. Each sterile vial for intravenous use contains 166.5 mg rolapitant (b) (4) (or 185 mg of rolapitant hydrochloride) and the following inactive ingredients: polyoxyl 15 hydroxystearate (44 mg/mL), medium chain triglycerides (11 mg/mL), soybean oil (6.6 mg/mL), sodium chloride (6.23 mg/mL) dibasic sodium phosphate, anhydrous (2.84 mg/mL), and may contain hydrochloric acid and/or sodium hydroxide to adjust pH.

2.2 Tables of Currently Available Treatments for Proposed Indications

Ondansetron	5-HT3 antagonist
Palenosetron	5-HT3 antagonist
Granisetron	5-HT3 antagonist
Dolasetron	5-HT3 antagonist
Aprepitant/fosaprepitant	NK-1 antagonist
palonosetron and netupitant	5-HT3 and NK-1 antagonist

2.3 Availability of Proposed Active Ingredient in the United States

Rolapitant hydrochloride is available as the currently marketed product Varubi.

2.4 Important Safety Issues With Consideration to Related Drugs

There are currently two NK-1 products on the market in the U.S.—Emend and Akynzeo.

Emend is available in two formulations- oral (aperepitant) and solution for injection (fosaprepitant). Akynzeo is a fixed combination of netupitant, a substance P/neurokinin1 receptor antagonist, and palonosetron, a 5-HT3 receptor antagonist.

Contraindications

Aprepitant (excerpt from 08/2014 label)

EMEND is contraindicated in patients who are hypersensitive to any component of the product. EMEND is a dose-dependent inhibitor of cytochrome P450 isoenzyme 3A4 (CYP3A4). EMEND should not be used concurrently with pimozide, terfenadine, astemizole, or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions [see Drug Interactions (7.1)]

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Fosaprepitant (excerpt from 10/2014 label)

4.1 Hypersensitivity

EMEND for Injection is contraindicated in patient s who are hypersensitive to EMEND for Injection, aprepitant, polysorbate 80 or any other components of the product. Known

hypersensitivity reactions include: flushing, erythema, dyspnea, and anaphylactic reactions [see Adverse Reactions (6.2)]

4.2 Concomitant Use with Pimozide or Cisapride. Aprepitant, when administered orally, is a moderate cytochrome P450 isoenzyme 3A4 (CYP3A4) inhibitor following the 3-day antiemetic dosing regimen for CINV. Since fosaprepitant is rapidly converted to aprepitant, do not use fosaprepitant concurrently with pimozide or cisapride. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these drugs, potentially causing serious or life-threatening reactions [see Drug Interactions (7.1)]

Akynzeo has no contraindications in the current version of the label (04/2015).

Warnings and Precautions

Aprepitant

5.1 CYP3A4 Interactions
5.2 Coadministration with Warfarin (a CYP2C9 substrate)
5.3 Coadministration with Hormonal Contraceptives
5.4 Patients with Severe Hepatic Impairment
5.5 Chronic Continuous Use

Fosaprepitant

5.1 CYP3A4 Interactions
5.2 Hypersensitivity Reactions
5.3 Coadministration with Warfarin (a CYP2C9 substrate)
5.4 Coadministration with Hormonal Contraceptives
5.5 Chronic Continuous Use

The Akynzeo label has no Warnings and precautions related to the netupitant part of the fixed dose combination product.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Selected Regulatory Action(s)
26 January 2016	Pre-NDA meeting (Applicant canceled meeting after receiving preliminary repsonses) ▪ FDA agreed that for the 4-month safety update, the Applicant could provide a quarterly PADER for Varubi along with a final nonclinical study report given that there are no on-going clinical trials or patient exposure of rolapitant IV nor are any expected to be initiated during the NDA review.
01 September 2015	Oral rolapitant approved (NDA 206,500)
25 February 2015	Type C meeting. ▪ FDA expressed concerns over accumulation of drug and accumulation of toxicity in repeat dosing of drug because of the long half-life and higher Cmax (than oral rolapitant) of the drug. FDA stated that additional safety studies could be completed in healthy subjects.
14 July 2014	Type C, Written Reponses Only ▪ The Division counseled the Applicant that even if BE criteria are

	achieved for AUC between the IV and the oral formulations, additional clinical studies would be needed to support the higher Cmax of the IV formulation.

2.6 Other Relevant Background Information

None known, except as discussed in other parts of the review.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was of reasonable quality. The electronic application was well organized and easily navigable.

3.2 Compliance with Good Clinical Practices

According to the Applicant, all studies were performed in accordance with the Monitoring Plan and the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the International Conference on Harmonization (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements of the countries in which they were conducted.

3.3 Financial Disclosures

Covered Clinical Study (Name and/or Number): PR-11-5016, PR-11-5022, PR-11-5021, PR-11-5012

Was a list of clinical investigators provided:	**Yes** ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1		
Number of investigators who are sponsor employees (including both full-time and part-time employees): **0**		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): **0**		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): **n/a**		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: ____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐ **n/a**	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐ **n/a**	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐ **n/a**	No ☐ (Request explanation from applicant)

None of the reported financial disclosures affect the approvability of the application.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

See the complete CMC review in DARRTS.

4.2 Clinical Microbiology

N/A

4.3 Preclinical Pharmacology/Toxicology

A comprehensive toxicology program was undertaken to support the oral administration of rolapitant in humans. These studies included single-dose toxicity studies in rats and monkeys, up to 6-month (rat) and 9-month (monkey) repeat dose toxicity studies in rats and monkeys, genotoxicity studies, two year carcinogenicity studies in rats and mice, developmental and reproductive studies in rats and rabbits, abuse potential liability studies in monkeys, and safety studies on the rolapitant major metabolite SCH 720881. Convulsions were observed in monkeys administered 60 and 100 mg/kg.

Toxicology studies in two species (rat and cynomolgus monkey) were conducted with IV rolapitant with a treatment duration of up to 13 weeks. Similar to the oral rolapitant nonclinical studies, the central nervous system (CNS) appeared to be the primary target organ in both species. Treatment related clinical signs included convulsions and tremors, which were consistent with the findings of the oral toxicology studies.

For further discussion of these studies and their results, see the pharmacology/toxicology review in DARRTS by Tamal Chakraborti, PhD.

No convulsions were seen in the healthy subject clinical studies submitted in support of the current Application.

4.4 Clinical Pharmacology

The rolapitant IV program included 4 phase 1 clinical studies conducted in healthy subjects. These studies included a pivotal BE study, a single- and multiple- dose PK study, a drug-drug interaction study, and a PK study of supratherapeutic doses of rolapitant IV. See Section 5 for further descriptions of the clinical studies submitted in support of the current Application.

Rolapitant IV was found to be highly, and slowly eliminated. Following single rolapitant IV dose administration of 20 to 200 mg (hydrochloride (b) (4)), the mean t½ ranged from 138 to 205 hours and was independent of dose. In the pivotal BE study, mean rolapitant t½ was 161 hours at the IV dose of 185 mg, which is consistent with the t½ of the oral formulation (167 hours at the therapeutic dose of 200 mg).

At the IV dose of 185 mg, mean rolapitant Cmax was about 1.7- to 1.9-fold the Cmax of the oral formulation at 200 mg (~1700 to 1900 ng/mL for rolapitant IV and 1000 ng/mL for rolapitant oral, respectively).

4.4.1 Mechanism of Action

Rolapitant is a neurokinin-1 (NK-1) receptor antagonist. These receptors are broadly distributed in central and peripheral nervous systems. Studies have shown that rolapitant binds to the NK-1 receptor with high affinity and has little or no activity for the other NK receptors. The endogenous activator of the NK-1 receptor is the neuropeptide, Substance P.

4.4.2 Pharmacodynamics

No significant efficacy or safety issues related to pharmacodynamics were identified.

4.4.3 Pharmacokinetics

For clinical pharmacology details of rolapitant, see the final label and the clinical pharmacology review in DARRTS by Dr. Elizabeth Shang.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1. Primary Evidence of Efficacy, Rolapitant IV Clinical Development Program

Study	Description	Study Specifics	Study Conclusion
PR-11-5016-C	Pivotal BE Study	BE study of 200 mg single oral dose of rolapitant and a 185 mg single IV dose of rolapitant administered over a 30 minute infusion	BE criterion based on AUC was met
PR-11-5012-C	Safety, tolerability and PK study of single ascending and multiple ascending doses of rolapitant IV	SAD doses of 20, 50, 100,150, 185, and 200 mg MAD doses x 10 days of 20, 40 and 60 mg of rolapitant IV	Safety and tolerability acceptable
PR-11-5022-C	Safety, tolerability and PK study of supratherapeutic single ascending doses of rolapitant IV	SAD of 225 to 300 mg of rolapitant IV	Safety and tolerability acceptable
PR-11-5021-C	DDI study that assessed administration of 185 mg rolapitant IV (infused over 30 minutes) on the PK of P-gp substrate (digoxin) a breast cancer resistance protein (BCRP) substrate sulfasalazine), and multiple CYP probe substrates (midazolam, omeprazole, warfarin, caffeine, and dextromethorphan)	.	The results from the IV DDI study suggest that no dosage adjustment is required when rolapitant IV is coadministered with P-gp, BCRP, CYP3A4, CYP2C9, CYP2C19, and CYP1A2 substrates, but dosage adjustment or caution are warranted when rolapitant IV is coadministered with CYP2D6 substrates with a narrow therapeutic index

As part of the IV development program, 350 subjects were enrolled in studies that evaluated rolapitant IV. Of these subjects, 180 received the proposed dose of 185 mg and 125 subjects received >185 mg.

5.2 Review Strategy

For this clinical review, the safety results for the four phase 1 studies submitted in support of the current Application will be presented. See the full clinical pharmacology review for other details regarding these studies.

5.3 Discussion of Individual Studies/Clinical Trials

Study Summaries

Study PR-11-5016-C (Pivotal BE study oral/IV)
This study was a phase 1, open-label, randomized, single-dose, single-center, parallel-group study designed to assess the BE of a single infusion of 185 mg rolapitant IV administered over 30 minutes versus a single dose of 200 mg rolapitant oral administered as a capsule formulation (4 × 50 mg). Dosing was administered under fasting conditions. The 4 × 50 mg capsule formulation was the same 200 mg dose administered in Phase 3 oral rolapitant clinical studies. Given rolapitant's long half-life (~180 hours), the study used a parallel study design instead of a cross over design.

The 185 mg IV dose (test treatment) was considered to have met BE criteria relative to the 200 mg rolapitant oral dose (reference treatment) based on AUC comparison. Rolapitant IV exhibited a higher mean Cmax 1900 ng/mL versus ~1,000 ng/mL.

See the full clinical pharmacology review for BE study results.

Study PR-11-5012-C
This study was a 2-part, phase 1, open–label, single-center, study of rolapitant IV infusion designed to assess the safety, tolerability, and PK of single ascending doses (SAD) of rolapitant IV ranging from 20 to 200 mg (Part 1) and multiple ascending doses (MAD) of rolapitant IV ranging from 20 mg to 60 mg administered daily for 10 days (Part 2). Doses were administered over 30-minutes with the exception of 45-minute infusions for the 200 mg dose in the SAD portion of the study.

Samples for PK analyses were obtained prior to the infusions and up to 504 hours after the start of the infusion in Part 1 and up to 288 hours after the start of the infusion on Day 10 in Part 2. A 7-day observation period between cohorts allowed for evaluation of the safety of treatment before the next higher dose level was administered.

Study PR-11-5022-C
This study was a 2-part, open-label, single-dose, single-center study of ascending doses of supratherapeutic doses of rolapitant IV (225 mg, 250 mg, 275 mg, and 300 mg

dose levels) administered as a 30 minute infusion (Part 1) followed by an expansion phase to further evaluate the safety of rolapitant IV in healthy subjects at the higher Cmax observed with the supratherapeutic dose of 300 mg (Part 2).

Samples for PK analyses were obtained prior to the infusions and up to 504 hours after the start of the infusion in Part 1 and up to 288 hours after the start of the infusion on Day 10 in Part 2. A 7-day observation period between cohorts allowed for evaluation of the safety of treatment before the next higher dose level was administered.

All PK data were summarized descriptively; no formal statistical hypothesis testing was conducted.

Study PR-11-5021-C (DDI Study)
This study was an open-label, single-center, 3-part DDI study of orally administered P-gp substrate, BCRP substrate, and multiple CYP probe substrates (midazolam, omeprazole, S-warfarin, caffeine, and dextromethorphan [Cooperstown Cocktail]) in the presence and absence of a single dose of rolapitant IV (30-minute infusion) at the proposed dose of 185 mg in healthy male and female subjects.

MO Comment:
It was important to characterize the potential DDIs associated with the higher Cmax following rolapitant IV dosing (185 mg) compared with rolapitant 200 mg oral.

Key Inclusion Criteria

In each of the Phase 1 rolapitant IV studies subjects eligible to participate were healthy, non-smoking, male or female subjects aged 18 to 55 years with body mass index between 18.5 and 32 kg/m2 and a weight of ≥ 50 kg.

Study Visits and Procedures

All four of the studies submitted in support of this Application were conducted at Parexel's Early Phase Clinical Unit, Baltimore, MD. The study visits and related safety assessments are summarized in the tables below.

Table 2. Safety Evaluations conducted in Rolapitant IV Clinical Studies

Study	Adverse Events	Vital Signs	Physical Examination	ECG	Clinical Laboratory Tests	Concomitant Medications
PR-11-5012-C (SAD/MAD)						
SAD	Scr through 30 days postRx	Scr, D-1, D1[a], D2, D3, D4, D6, D8, D11, D14, D17, D20, D22	Scr, D-1, D22	Scr, D1, D4, D22	Scr, D1, D2, D4, D22	30 days prior to Rx through D22
MAD	Scr through 30 days postRx	Scr, D-1, D1[a], D2[a], D3[a], D4[a], D5[a], D6[a], D7[a], D8[a], D9[a], D10[a], D11, D12, D13, D15, D17, D22	Scr, D-1, D22	Scr, D-1, D1, D2, D3, D4, D5, D6, D7, D8, D9, D10, D13, D22	Scr, D1, D3, D6, D10, D13, D22	30 days prior to Rx through D22
PR-11-5016-C (BE)	Scr through D39	Scr, D-1, D1 (4h, 8h, 12h postRx), D2, D3, D4, D14, D22, D39	Scr, D-1, D39	Scr, D-1, D1 (preRx and 0.5h postRx), D4, D39	Scr, D-1, D1, D4, D14, D22, D39	Scr through D39
PR-11-5021-C (DDI)						
Digoxin	Scr through D35	Scr, D-1, D1[b], D2, D3, D4, D5	Scr, D-1, D2, D5 (P2 only)	Scr, D1 (P1[c], P2[d]), D5 (P1, P2)	Scr, D-1 (P1, P2), D5 (P2)	Scr through D5
Sulfasalazine	Scr through D44	Scr, D-1, D1[b], D2, D3[b], D4-D12, D13[b], D14	Scr, D-1, D2, D13, D14	Scr, D1[e], D3[d], D13[e], D14[f]	Scr, D-1, D14	Scr through D14
Cooperstown cocktail (midazolam, omeprazole, S-warfarin, caffeine, dextromethorphan)	Scr through D68	Scr, D-1, D1[b], D2-6, D7[b], D8-13, D14[b], D15-20, D21[b], D22-27, D28[b], D29-34, D35[b], D36-38	Scr, D-1, D6, D13, D20, D27, D34, D38	Scr, D1[e], D7[d], D14[e], D21[e], D28[e], D35[e], D38	Scr, D-1, D38	Scr through D38
PR-11-5022-C (SAD)	Scr through D30	Scr, D-1, D1[a], D2, D3, D4, D6, D8, D11, D14, D17, D20, D22	Scr, D-1, D22	Scr, D-1, D1[g], D4, D22	Scr, D-1, D1[h], D2, D4[h], D22[h]	Scr through D30

Abbreviations: BE, bioequivalence; D, day; DDI, drug-drug interaction; MAD, multiple-ascending dose; P, period; Rx, dose; SAD, single-ascending dose; Scr, screening
[a] Obtained preRx, 4h, 8h, and 12h postRx/end of infusion.
[b] Obtained preRx, 1h, 2h, and 4h postRx.
[c] Obtained preRx, 1h, 2h, 6h, and 24h postRx.
[d] Obtained preRx, prior to the end of rolapitant infusion, 0.25h, 0.5h, 0.75h, 1h, 2h, 6h, and 24h postRx.
[e] Obtained preRx, 1h, 2h, 4h, 6h, and 24h postRx.
[f] Obtained only as an early termination assessment.
[g] Obtained preRx, 0.25h, 0.5h, 0.75h, 4h, 8h, and 12h post Rx.
[h] On Day 1, serum chemistry and hematology collected preRx and 0.5h postRx. Serum cardiac troponin I analysis performed on D1, D4, and D22.

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6 Review of Efficacy

Efficacy Summary

No efficacy evaluation was conducted in support of the current Application

6.1 Indication

The Sponsor has proposed the following indication statement for rolapitant IV:

> BRAND NAME is a substance P/neurokinin-1 (NK-1) receptor antagonist indicated in adults for use in combination with other antiemetic agents for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy.

Mo Comment:
The proposed indication for rolapitant IV is identical to the indication for the currently marketed oral rolapitant product.

6.1.1 Methods

N/A

6.1.2 Demographics

See Safety section for demographic summary of the safety population.

6.1.3 Patient Disposition

See Safety Section for patient disposition summary of the safety population.

6.1.4 Analysis of Primary Endpoint(s)

N/A

6.1.5 Analysis of Secondary Endpoints(s)

N/A

6.1.6 Other Endpoints

N/A

6.1.7 Subpopulations

N/A

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

N/A

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

N/A

6.1.10 Additional Efficacy Issues/Analyses

N/A

7 Review of Safety

Safety Summary

In general, the use of rolapitant IV for the proposed indication of the prevention of CINV in the delayed (b) (4) appears to represent an acceptable risk. See the Risk Benefit Assessment Section 1.2.

7.1 Methods

Adverse events and medical histories in rolapitant IV Studies PR-11-5016-C and PR-11-5022-C were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.1. Study PR-11-5012-C was originally coded using MedDRA version 16.0. A coding evaluation revealed that the SOC and PT levels would not change if transposed to version 17.1.

All safety analyses were performed on the Safety Population. The safety population included all subjects who were randomized to any treatment group and received at least one dose of study drug. Only treatment-emergent adverse events (TEAEs) were tabulated. A TEAE was defined as any AE which started or worsened after receipt of the study drug treatment (Study Day 1).

Adverse events with missing information were considered TEAEs. Adverse events with missing relationship to study drug were included in the "related" category.

All four studies included only healthy adult subjects and were conducted at Parexel's Early Phase Clinical Unit in Baltimore, Maryland.

The safety data as summarized in current rolapitant oral labeling and discussed more completely in the oral rolapitant clinical review (NDA 206, 500) provide supportive safety data.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Overall, rolapitant IV was evaluated in 350 healthy subjects in four phase 1 studies—PR-11-5016-C, PR-11-5012-C, PR-11-5022-C, and PR-11-5021-C. Of these subjects, 180 received the proposed dose of 185 mg and 125 subjects received >185 mg. In addition, as part of Study PR-5016-C (single dose BE study), 67 patients received rolapitant oral (200 mg) to serve as a comparator group. See Table 3, below.

7.1.2 Categorization of Adverse Events

Adverse events were categorized using the Common Terminology Criteria for Adverse Events (CTCAE) grading system.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

For the primary safety evaluation, an integrated analysis of healthy subjects who received single dose rolapitant IV as monotherapy comprised the IV ISS Pooled Analysis Group. This group was chosen for pooling to avoid the possible confounding effects of multiple doses or concomitant therapies. Subjects who received multiple dose IV rolapitant as part of Study PR-11-5012-C and subjects who participated in the DDI study (PR-11-5021-C) are not included in the pooled analysis set and their safety are presented separately.

Table 3. Studies and Study Cohorts Included in IVSS Pooled Analysis Group

Study (Type)	Study Design	Study Treatment	Inclusion in IV ISS Pooled Analysis Group
PR-11-5012-C (SAD/MAD)	Open label, 2 parts: single ascending dose (Part 1) and multiple ascending dose (Part 2)	Part 1: Rolapitant IV SAD 20, 50, 100, 150, 185, and 200 mg; 30-minute infusion 200 mg; 45-minute IV infusion Part 2[a]: Rolapitant IV MAD: 30-minute infusion × 10 days 20, 40, 60 mg	All subjects from Part 1.
PR-11-5016-C (BE)	Open label, randomized, parallel group comparison	Rolapitant IV: 185 mg; 30-minute infusion Rolapitant oral: 200 mg	All subjects (oral subjects presented separately)
PR-11-5022-C (SAD with expansion)	Open label, 2 parts, single ascending dose (Part 1) with expansion (Part 2)	Part 1: Rolapitant IV SAD: 225, 250, 275, 300 mg 30-minute infusion Part 2: Rolapitant IV Expansion: Single dose 300 mg 30-minute infusion	All subjects

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Abbreviations: BE, bioequivalence; ISS, integrated summary of safety; IV, intravenous; MAD, multiple ascending dose; SAD, single ascending dose
[a] Data from subjects in Part 2 MAD are presented separately.

7.2 Adequacy of Safety Assessments

The safety assessments performed were adequate. Safety variables included adverse events (AEs), clinical laboratory evaluations (hematology, clinical chemistry, and urinalysis), vital signs, and physical examination parameters. Patients who were given at least one dose of the study medication were included in the safety analysis populations described in Section 7.1.

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety Population Exposure

IV ISS Population

As part of the four phase 1 studies submitted in support of the current Application, 350 patients received rolapitant IV. In addition, 67 patients received oral rolapitant as part of a comparator group. Doses of rolapitant IV up to 300 mg and as multiple doses up to 60 mg for 10 days were studied.

Table 4. Rolapitant IV Studies by Dose Group

Study		Rolapitant Oral 200 mg	Rolapitant IV			
			<185 mg	185 mg	>185 mg	Total IV
IV ISS Pooled Analysis Group						
PR-11-5012-C	Part 1, Single-dose	0	25	7	25	57
PR-11-5016-C	Single-dose, BE	67	0	71	0	71
PR-11-5022-C	Single-dose	0	0	0	100	100
Subtotal		**67**	**25**	**78**	**125**	**228**
Individual Rolapitant IV Studies or Cohorts Not Included in IV ISS Pooled Analysis Group						
PR-11-5012-C	Part 2, Multiple-dose[a]	0	20	0	0	20
PR-11-5021-C	Single-dose DDI	0	0	102	0	102
Subtotal		**0**	**20**	**102**[b]	**0**	**122**[b]
TOTAL		**67**	**45**	**180**	**125**	**350**

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Abbreviations: BE, bioequivalence; DDI, drug-drug interaction; ISS, integrated summary of safety; IV, intravenous
[a] 20 mg, 40 mg or 60 mg for 10 days
Source: CSR PR-11-5012-C, CSR PR-11-5016-C; CSR PR-11-5021-C; and CSR PR-11-5022-C

Most subjects in the rolapitant IV ISS Population completed the study with only 12.7% of subjects in this group discontinuing the study prematurely. See Table 5, below.

Table 5. Subject Disposition, Rolapitant IV ISS Population

Disposition:	Healthy Subjects [n (%)]				
	200 mg Oral Rolapitant (N = 67)	< 185 mg IV Rolapitant (N = 25)	185 mg IV Rolapitant (N = 78)	> 185 mg IV Rolapitant (N = 125)	All Rolapitant IV[a] (N = 228)
Number in IV ISS Pooled Analysis Group	67 (100.0)	25 (100.0)	78 (100.0)	125 (100.0)	228 (100.0)
Number Prematurely Discontinued from Study	4 (6.0)	1 (4.0)	9 (11.5)	19 (15.2)	29 (12.7)
Reason for Discontinuation					
Adverse Event	2 (3.0)	1 (4.0)	0	2 (1.6)	3 (1.3)
Lost To Follow-Up	0	0	0	2 (1.6)	2 (0.9)
Protocol Violation	1 (1.5)	0	1 (1.3)	0	1 (0.4)
Withdrew Consent	0	0	0	1 (0.8)	1 (0.4)
Other[b]	1 (1.5)	0	8 (10.3)	14 (11.2)	22 (9.6)

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Abbreviations: IV, intravenous; ISS, integrated safety summary
a Subjects who received any rolapitant IV doses are combined.
b Other reasons include: behavioral issue (n=1), scabies infestation (n=2), and IV infusion pump malfunction (n=20); IV pump malfunction resulted in discontinuation due to the impact of incomplete dosing on pharmacokinetic analyses.

DDI Population

For the DDI study (PR-11-5021-C), a total of 102 subjects were randomized -- 36 subjects to Part A (digoxin), 30 subjects to Part B (sulfasalazine), and 36 subjects to Part C (Cooperstown cocktail). Of these subjects, >80.0% of subjects in each Part of the study completed the study. The most common reason for study discontinuation was IV pump malfunction. See Table 6, below.

Table 6. Subject Disposition, Study PR-11-5021-C (DDI Study)

Category	Part A N = 36 n (%)	Part B N = 30 n (%)	Part C N = 36 n (%)
Enrolled and treated	36 (100.0%)	30 (100.0%)	36 (100.0%)
Completed study	29 (80.6%)	27 (90.0%)	31 (86.1%)
Category	**Part A N = 36 n (%)**	**Part B N = 30 n (%)**	**Part C N = 36 n (%)**
Discontinued from study	7 (19.4%)	3 (10.0%)	5 (13.9%)
Safety Population	36 (100.0%)	30 (100.0%)	36 (100.0%)
Pharmacokinetic Population	36 (100.0%)	30 (100.0%)	36 (100.0%)
Reason for discontinuation			
Adverse event	1 (2.8%)	1 (3.3%)	3 (8.3%)
Physician decision[a]	2 (5.6%)	0	0
IV infusion pump stopped after 1 minute	0	1 (3.3%)	1 (2.8%)
IV infusion pump stopped after 10 minutes	0	0	1 (2.8%)
IV infusion pump stopped after 24 minutes	0	1 (3.3%)	0
IV infusion pumped stopped after 2 minutes[b]	1 (2.8%)	0	0
IV infusion stopped after 22 minutes[b]	1 (2.8%)	0	0
Subject failed to report for admission[b]	2 (5.6%)	0	0

Abbreviations: IV = intravenous
[a] Discontinuations due to baseline elevated CPK measurements prior to dosing
[b] Occurred during Period 2 of Part A
Part A = digoxin; Part B = sulfasalazine; Part C = Cooperstown cocktail plus dextromethorphan
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MAD Population

Similar to the rolapitant IV ISS population and the subjects who participated in the DDI Study, the majority of subjects who participated in the MAD portion of Study PR-11-5012-C completed the study. Specifically, two patients in the 40 mg group discontinued due to adverse events. The other 18 subjects completed the study. See Table 7 below.

Table 7. Subject Disposition, MAD portion of Study PR-11-5012-C

	20 mg n = 6	40 mg n = 8	60 mg n = 6
Enrolled	6 (100.0%)	8 (100.0%)	6 (100.0%)
Completed the study	6 (100.0%)	6 (75.0%)	6 (100.0%)
Discontinued from study	0	2 (25.0%)	0
Reason for discontinuation			
Adverse event	0	2 (25.0%)	0
Protocol deviation	0	0	0
Consent withdrawn	0	0	0
Lost to follow–up	0	0	0
Other	0	0	0

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Safety Population Demographics

IV ISS Population

The demographic characteristics were relatively well matched between the rolapitant IV dose groups (<185 mg, 185 mg, and >185 mg). Most of the patients in all rolapitant IV groups were male (77.6%) with an average age of 38.1 years. In contrast to most clinical trials in the US, the majority of patients in the All IV rolapitant group were African American (77.2%). This fact likely reflects the racial makeup of Baltimore, Maryland, the site of all the rolapitant IV healthy-subject studies submitted in support of the current Application. See Table 8, below.

Table 8. Demographics and Baseline Characteristics: IV ISS Pooled Analysis Group

Demographics:	Healthy Subjects [n (%)]				
	200 mg Oral Rolapitant (N = 67)	< 185 mg IV Rolapitant (N = 25)	185 mg IV Rolapitant (N = 78)	> 185 mg IV Rolapitant (N = 125)	All Rolapitant IV[a] (N = 228)
Age (yrs)					
Mean	38.2	35.0	39.7	37.7	38.1
SD	8.48	9.09	8.82	9.58	9.34
Median	39	33	43	38	38
Min, Max	22, 55	21, 53	19, 54	20, 55	19, 55
Age (y), n (%)					
< 45	53 (79.1)	20 (80.0)	51 (65.4)	94 (75.2)	165 (72.4)
≥ 45	14 (20.9)	5 (20.0)	27 (34.6)	31 (24.8)	63 (27.6)
Gender, n (%)					
Female	25 (37.3)	7 (28.0)	27 (34.6)	17 (13.6)	51 (22.4)
Male	42 (62.7)	18 (72.0)	51 (65.4)	108 (86.4)	177 (77.6)
Race, n (%)					
American Indian or Alaska Native	3 (4.5)	0	0	0	0
Asian	1 (1.5)	0	1 (1.3)	1 (0.8)	2 (0.9)
Black or African American	35 (52.2)	21 (84.0)	53 (67.9)	102 (81.6)	176 (77.2)
White	28 (41.8)	4 (16.0)	24 (30.8)	22 (17.6)	50 (21.9)
Ethnicity, n (%)					
Hispanic or Latino	20 (29.9)	4 (16.0)	13 (16.7)	11 (8.8)	28 (12.3)
Not Hispanic or Latino	47 (70.1)	21 (84.0)	65 (83.3)	114 (91.2)	200 (87.7)
Body Weight (kg)					
Mean	78.5	81.3	78.5	82.2	80.8
SD	11.57	14.15	12.93	11.79	12.52
Median	79	80	79	82	81
Min, Max	57, 103	59, 104	52, 111	54, 116	52, 116
Body Weight (kg), n (%)					
< 60 kg	3 (4.5)	1 (4.0)	6 (7.7)	5 (4.0)	12 (5.3)
≥ 60 to < 90 kg	53 (79.1)	15 (60.0)	56 (71.8)	93 (74.4)	164 (71.9)
≥ 90 kg	11 (16.4)	9 (36.0)	16 (20.5)	27 (21.6)	52 (22.8)

Demographics and Baseline Characteristics: IV ISS Pooled Analysis Group cont'd

Height (cm), n (%)					
Mean	172.6	175.2	173.2	176.5	175.2
SD	9.32	9.56	10.48	8.27	9.31
Median	174	176	174	176	175
Min, Max	154, 190	156, 193	151, 203	157, 198	151, 203

Abbreviations: IV, intravenous; max, maximum; min, minimum; SD, standard deviation; y, years

[a] Subjects who received any rolapitant IV doses are combined.

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DDI Population

For the DDI study (PR-11-5021), the majority of subjects were black/African American (75.0% in Part A, 46.7% in Part B, and 66.7% in Part C). Males accounted for the majority of the study population (80.6% in Part A, 76.7% in Part B, and 80.6% in Part C). The mean age was 37.1, 38.4, and 37.3 years for Parts A, B, and C, respectively. For additional details see, Table 9 below.

Table 9. Subject Demographics, Study PR-11-5021-C (DDI Study)

Characteristic	Part A Digoxin N = 36	Part B Sulfasalazine N = 30	Part C Cooperstown Cocktail N = 36
Gender - n (%)			
Male	29 (80.6%)	23 (76.7%)	29 (80.6%)
Female	7 (19.4%)	7 (23.3%)	7 (19.4%)
Age (y)			
Mean (SD)	37.1 (8.84)	38.4 (10.99)	37.3 (7.77)
Race - n (%)			
Black/African American	27 (75.0%)	14 (46.7%)	24 (66.7%)
White	7 (19.4%)	16 (53.3%)	11 (30.6%)
American Indian/Alaska Native	1 (2.8%)	0	0
Asian	1 (2.8%)	0	0
Other	0	0	1 (2.8%)
Ethnicity - n (%)			
Hispanic/Latino	8 (22.2%)	8 (26.7%)	4 (11.1%)
Non-Hispanic/Latino	28 (77.8%)	22 (73.3%)	32 (88.9%)
Weight (kg)			
Mean (SD)	83.0 (11.03)	77.4 (13.63)	78.8 (12.84)
Height (cm)			
Mean (SD)	176.6 (8.80)	172.0 (10.24)	175.3 (7.73)
BMI (kg/m²)			
Mean (SD)	26.64 (3.225)	26.03 (2.983)	25.59 (3.497)

Abbreviations: BMI = body mass index; SD = standard deviation; y = year
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MAD Population

For the MAD population (Study PR-22-5012), the majority (65%) of the 20 subjects were black/African American. Males accounted for the majority of subjects (50 % in the 20 mg group, 100 % of the 40 mg group, and 66.7% of the 60 mg group. The mean age was 37.7, 37.9, and 41.3 years for the 20 mg, 40 mg and 60 mg groups, respectively. . For additional details, see Table 10 below.

Table 10. Demographics of MAD portion of Study PR-22-5012

Parameter	20 mg n = 6	40 mg n = 8	60 mg n = 6
Continuous (Mean [SD])			
Age (years)	37.7 (11.9)	37.9 (7.7)	41.3 (9.4)
Height (cm)	168.3 (14.6)	179.9 (7.0)	172.8 (10.3)
Weight (kg)	73.22 (15.75)	79.34 (8.77)	85.02 (9.96)
BMI (kg/m^2)	25.60 (2.84)	24.59 (3.17)	28.45 (2.33)
Categorical (n, %)			
Ethnicity			
Hispanic or Latino	1 (16.7)	1 (12.5)	2 (33.3)
Not Hispanic or Latino	5 (83.3)	7 (87.5)	4 (66.7)
Race			
White	1 (16.7)	3 (37.5)	2 (33.3)
Asian	0	1 (12.5)	0
Native Hawaiian or other Pacific Islander	0	0	1 (16.7)
Black/African American	5 (83.3)	4 (50.0)	3 (50.0)
Gender			
Female	3 (50.0)	0	2 (33.3)
Male	3 (50.0)	8 (100.0)	4 (66.7)

SD = standard deviation; BMI = body mass index
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7.2.2 Explorations for Dose Response

IV ISS Population

In the rolapitant IV ISS population, no dose response in the number of reported TEAEs was noted between the <185 mg, 185 mg, and >185 mg treatment groups. The <185 mg IV rolapitant dose group contained only 25 subjects, therefore the increased incidence of TEAEs may not be reflective of what is expected in a larger group. The reported TEAE rate in the 185 mg IV group, the proposed dose, was similar to the reported TEAE rate in the 200 mg oral dose group, the currently approved dose—29.5% and 29.9%, respectively. Overall, the All rolapitant IV group had a TEAE rate of 39.5%. Of these TEAEs, none was reported as severe and no deaths were reported. See Table 11, below.

Table 11. Overall TEAEs, Rolapitant IV ISS Pooled Population

Number of Subjects with:	Healthy Subjects [n (%)]				
	200 mg Oral Rolapitant (N = 67)	< 185 mg IV Rolapitant (N = 25)	185 mg IV Rolapitant (N = 78)	> 185 mg IV Rolapitant (N = 125)	All Rolapitant IV[a] (N = 228)
≥ 1 TEAE	20 (29.9)	12 (48.0)	23 (29.5)	55 (44.0)	90 (39.5)
≥ 1 Treatment-related TEAE	4 (6.0)	7 (28.0)	9 (11.5)	45 (36.0)	61 (26.8)
TEAE leading to study drug or study discontinuation	2 (3.0)	1 (4.0)	0	2 (1.6)	3 (1.3)
≥ 1 severe TEAE	0	0	0	0	0
≥ 1 TESAE	0	0	0	0	0
TEAE with outcome of death	0	0	0	0	0

Abbreviations: IV, intravenous; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event
[a] Subjects who received any rolapitant IV doses are combined.
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DDI Population
Given the exposure of subjects to various drugs, no search for trends in rates of TEAEs reported was undertaken. There were no serious AEs and no deaths reported.

MAD Population
Among this group of subjects, TEAEs were reported in 100%, 75% and 66.7% of the 20 mg, 40 mg and 60 mg dose groups, respectively. There were no serious AEs and no deaths reported.

MO Comment:
When evaluating the safety results of Study PR-11-5012, the fact that only 20 patients were included in the study must be taken into account.

7.2.3 Special Animal and/or In Vitro Testing

N/A

7.2.4 Routine Clinical Testing

Routine clinical testing as described in Section 7.2 was included as part of the safety assessments in the three submitted studies. See Section 5.3.5 for detailed information on study visits and procedures.

7.2.5 Metabolic, Clearance, and Interaction Workup

For more information, see the Clinical Pharmacology Review in DARRTS by Elizabeth Shang, PhD.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Use of drugs in the NK-1 antagonist class is not known to be associated with any specific adverse events. None of the drugs in this class has a black box warning. The Warnings and Precautions section of labels for drugs in this class include the following:

Aprepitant Capsules/Emend (label revised 8/2014)

- *Coadministration of aprepitant with warfarin (a CYP2C9 substrate) may result in a clinically significant decrease in International Normalized Ratio (INR) of prothrombin time. (5.2)*
- *The efficacy of hormonal contraceptives during and for 28 days following the last dose of EMEND may be reduced. Alternative or back-up methods of contraception should be used. (5.3, 7.1)*
- *EMEND is a dose-dependent inhibitor of CYP3A4, and should be used with caution in patients receiving concomitant medications that are primarily metabolized through CYP3A4. (5.1)*
- *Caution should be exercised when administered in patients with severe hepatic impairment. (2.5, 5.4, 12.3)*

Netupitant and palonosetron/Akynzeo (label revised 10/2014)

There are no Warnings and precautions related to the netupitant part of the fixed dose combination product.

7.3 Major Safety Results

There were no serious adverse events or deaths reported in any of the studies submitted in support of the current Application.

7.3.1 Deaths

None reported.

7.3.2 Nonfatal Serious Adverse Events

No serious AEs were reported by subjects in the IV ISS group or patients in the DDI study (PR-11-5021) or in the MAD portion of Study PR-11-5012.

7.3.3 Dropouts and/or Discontinuations

IV ISS Population
Five subjects in the IV ISS Pooled Analysis Group had TEAEs that led to discontinuation -- 1 subject in the < 185 mg rolapitant IV group, 2 subjects in the > 185 mg rolapitant IV group, and 2 subjects in the 200 mg rolapitant oral group. None of the subjects who received rolapitant IV 185 mg discontinued treatment due to TEAEs.

Brief narratives of the rolapitant IV patients who discontinued study drug are provided below:

- **Subject** (b) (6) in Study PR-11-5012-C was a 21-year-old black or African American male who was assigned to 20 mg rolapitant IV on Day 1. Dosing was discontinued 3 minutes after the start of IV infusion due to moderate events of nausea, retching, cough, and hyperhidrosis, and mild events of abdominal pain, dry mouth, dyspnea, visual impairment, and feeling hot. All of these TEAEs were considered by the Investigator to be possibly related to the study drug. Study drug was withdrawn and all TEAEs resolved that day.

- **Subject** (b) (6) in Study PR-11-5012-C was a 54-year-old black or African American male who was assigned to 200 mg rolapitant IV on Day 1. Within minutes of the start of the infusion, the subject experienced mild events of abdominal discomfort, diarrhea, presyncope, feeling hot, headache, dizziness, and dry mouth. These TEAEs were considered by the Investigator to be related or probably related to the study drug. Study drug was withdrawn and all TEAEs resolved by Day 4.

- **Subject** (b) (6) in Study PR-11-5022-C was a 23-year-old black or African American male who was assigned to 300 mg rolapitant IV on Day 1. Dosing was discontinued 1 minute after the start of IV infusion due to a moderate infusion related reaction (not further described). Several hours following cessation of dosing, the subject experienced mild back pain and dizziness. These TEAEs were considered by the Investigator to be related or likely related to the study drug. Study drug was withdrawn and all TEAEs resolved by Day 2.

DDI Population
Among the102 subjects in the DDI Study (PR-11-5021), five subjects experienced TEAEs that led to study discontinuation. Brief narratives of these subjects are provided below:

Subject (b) (6) was a 35-year-old black/African American male enrolled in Part A of the Study. Dosing was discontinued 4 minutes after the start of IV infusion of rolapitant in Period 2 due to TEAEs of infusion related reactions characterized by severe infusion-related symptoms, moderate diaphoresis due to hypotension in infusion-related reaction, severe infusion-associated confusion due to hypotension, moderate infusion-related dizziness, moderate infusion-associated nausea, and moderate infusion-related skin coolness. Following cessation of dosing, mild headache, chills, muscular weakness

and nausea; and moderate headache were also reported. Most of the TEAEs were reported as resolved the same day (09 Jul 2015). The TEAEs of chills and muscular weakness were reported as resolved within 24 hours (10 Jul 2015). The TEAEs of infusion-related dizziness and moderate headache were reported as resolved on 11 Jul 2015. None of the TEAEs were considered to be serious, but all were considered by the Investigator to be related to study drug; the subject was subsequently discontinued from the study

Subject (b) (6) was a 42-year-old white female with a body weight of 59.1 kg and BMI of 23.1 kg/m2 at the Screening Visit. The subject had a prior medical history of cesarean section ((b) (6)) and right eye irritation (Nov 2012), no ongoing medical history, no history of smoking, and no history of alcohol or drug abuse. Subject (b) (6) was enrolled in Part B of the study. Dosing was discontinued 1 minute after the start of IV infusion of rolapitant on Day 3 (18 Jun 2015) due to a mild TEAE of infusion related reaction characterized by infusion-related symptoms of facial numbness, shortness of breath, chest heaviness, and generalized warmth. The TEAE was reported as resolved the same day, was not serious, and was considered by the Investigator to be related to study drug. The subject was subsequently discontinued from the study.

Subject (b) (6) was a 36-year-old white male with a body weight of 59.9 kg and BMI of 19.3 kg/m2 at the Screening Visit. The subject had a prior medical history of appendicitis and appendectomy (2000), no ongoing medical history, no history of smoking, and no history of alcohol or drug abuse. Subject (b) (6) was enrolled in Part C of the study. Dosing was discontinued 2 minutes after the start of IV infusion of rolapitant on Day 7 (08 Jun 2015) due to a mild TEAE of infusion related reaction characterized by infusion-related symptoms of dizziness, shortness of breath, flushing, and diaphoresis. The TEAE was reported as resolved the same day, was not serious, and was considered by the Investigator to be related to study drug. The subject was subsequently discontinued from the study.

Subject (b) (6) was a 29-year-old black/African American female with a body weight of 58.4 kg and BMI of 20.9 kg/m2 at the Screening Visit. The subject had no prior medical history, no ongoing medical history no history of smoking, and no history of alcohol or drug abuse. Subject (b) (6) was enrolled in Part C of the study. Dosing was discontinued 3 minutes after the start of IV infusion of rolapitant on Day 7 (08 Jun 2015 due to a mild TEAE of infusion related reaction characterized by infusion-related symptoms of chest heaviness, dizziness, flushed, heart racing, and paresthesia. Following cessation of dosing, mild palpitations were also reported. The TEAE of infusion related reaction was reported as resolved the same day (08 Jun 2015) and the TEAE of palpitations was reported as resolved within 24 hours (09 Jun 2015). Neither of these TEAEs was considered to be serious and both were considered by the Investigator to be related to study drug. The subject was subsequently discontinued from the study.

Subject (b) (6) was a 27-year-old black/African American female with a body weight of 70.8 kg and BMI of 28.7 kg/m2 at the Screening Visit. The subject had no prior medical history, no ongoing medical history, no history of smoking, and no history of alcohol or

drug abuse. Subject (b) (6) experienced 3 TEAEs that were considered serious and of severe or disabling intensity. These events were presyncope and autonomic dysfunction on Day 31, and iron deficiency anemia on Day 32 (3 and 4 days post dextromethorphan dosing, respectively). The TEAE of presyncope was reported as resolved within 24 hours (17 Jul 2015) and the TEAE of iron deficiency was reported as resolved on 23 Jul 2015 after receiving a blood transfusion. The outcome of autonomic nervous system imbalance TEAE was not reported. All these TEAEs were serious, considered by the Investigator to be unrelated to study drug, and subsequently led to discontinuation of study drug.

MAD Population
Two subjects in the 40 mg group were discontinued due to abnormal liver function test which began prior to infusion non Day 1 and were reported as resolved by the end of the study. These abnormal liver tests were not associated with any other safety findings.

7.3.4 Significant Adverse Events

There were no significant adverse events reported in the rolapitant IV development program.

7.3.5 Submission Specific Primary Safety Concerns

There were no specific safety concerns related specifically to rolapitant hydrochloride IV that were not addressed by the oral program.

TEAEs were summarized in the IV ISS Pooled Analysis Group as subject incidence tables for nervous system events, infusion-related reaction, leukopenia, anemia, acute renal failure, hepatic dysfunction, cardiac arrhythmia, embolic and thrombotic events, and rhabdomyolysis/myopathy events.

Nervous System
All nervous system disorders were mild to moderate in severity. Two subjects discontinued due to nervous system disorders. Subject (b) (6) (Study PR-11-5012, SAD portion) was assigned to rolapitant IV 200 mg group and discontinued due to pre-syncope, headache and dizziness. No subjects in the IV ISS group had TEAEs in the SMAQ for convulsion. Subject (b) (6) (PR-11-5022-C) was assigned to rolapitant IV 300 mg and discontinued due to moderate infusion-related reaction of mild lower back pain and dizziness also discontinued from the study. See a more detailed narrative for each of these patients in Section 7.3.3 above.

Infusion-related Reactions
Across all rolapitant IV dose groups, the incidence of infusion related reactions increased with dose (although no reactions were seen in the <185 mg IV group). See Section 7.3.3 above for narratives of patients who discontinued due to infusion-related TEAEs.

Cardiac Arrhythmias
Two TEAEs in the MedDRA SMQ of cardiac arrhythmia events were reported in the IV ISS All Rolapitant Pooled Analysis Group. One subject in the < 185 mg rolapitant group experienced syncope (see detailed narrative in Section 7.3.3 above) and 1 subject in the 200 mg rolapitant oral group experienced palpitations.

No subjects in the IV ISS Pooled Analysis Group had TEAEs in the SMQ of hematopoietic leukopenia, anemia, hepatic dysfunction, rhyabdomyolysis/myopathy events, or embolic and thrombotic events.

7.4 Supportive Safety Results

Supportive safety results are provided by the safety profile of rolapitant oral (NDA 206,500).

7.4.1 Common Adverse Events

The most common preferred terms (PTs) reported as TEAEs in the All Rolapitant IV analysis group were headache (11.4%), dizziness (7.5%) and infusion related reaction (6.1%). All other TEAEs had an incidence rate (among the All Rolapitant IV group) of less than 5%.

The SOC with the highest incidence was Nervous system disorders (20.6% of the All Rolapitant IV group).

Table 12. Most Common TEAEs (>1%) by MedDRA Preferred Term in the Order of Decreasing Frequency in the All Rolapitant IV Group, IV ISS Pooled Analysis Group

Preferred Term	Healthy Subjects [n (%)]				
	200 mg Rolapitant Oral (N = 67)	< 185 mg Rolapitant IV (N = 25)	185 mg Rolapitant IV (N = 78)	> 185 mg Rolapitant IV (N = 125)	All Rolapitant IV[a] (N = 228)
Subjects with ≥ 1 TEAE	*20 (29.9)*	*12 (48.0)*	*23 (29.5)*	*55 (44.0)*	*90 (39.5)*
Headache	2 (3.0)	6 (24.0)	6 (7.7)	14 (11.2)	26 (11.4)
Dizziness	0	1 (4.0)	1 (1.3)	15 (12.0)	17 (7.5)
Infusion related reaction	0	0	2 (2.6)	12 (9.6)	14 (6.1)
Somnolence	1 (1.5)	1 (4.0)	0	9 (7.2)	10 (4.4)
Fatigue	2 (3.0)	2 (8.0)	1 (1.3)	3 (2.4)	6 (2.6)
Paraesthesia	0	0	0	6 (4.8)	6 (2.6)
Abdominal pain	0	1 (4.0)	3 (3.8)	1 (0.8)	5 (2.2)
Dry mouth	0	1 (4.0)	0	3 (2.4)	4 (1.8)
Feeling hot	0	1 (4.0)	0	3 (2.4)	4 (1.8)
Presyncope	1 (1.5)	0	0	4 (3.2)	4 (1.8)
Acne	0	1 (4.0)	0	2 (1.6)	3 (1.3)
Back pain	0	0	1 (1.3)	2 (1.6)	3 (1.3)
Catheter site reaction	0	2 (8.0)	0	1 (0.8)	3 (1.3)
Constipation	2 (3.0)	0	3 (3.8)	0	3 (1.3)
Dysmenorrhoea	2 (3.0)	0	3 (3.8)	0	3 (1.3)

Abbreviations: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event

[a] Subjects who received any rolapitant IV doses are combined.

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Table 13. Most Common TEAEs (> 1% in the All Rolapitant IV Group) by MedDRA System Organ Class and Preferred Term in Order of Decreasing Frequency in the All Rolapitant IV Group – Subject Incidence, IV ISS Pooled Analysis Group

System Organ Class Preferred Term	Healthy Subjects [n (%)]				
	200 mg Rolapitant Oral (N = 67)	< 185 mg Rolapitant IV (N = 25)	185 mg Rolapitant IV (N = 78)	> 185 mg Rolapitant IV (N = 125)	All Rolapitant IV[a] (N = 228)
Subjects with ≥ 1 TEAE	*20 (29.9)*	*12 (48.0)*	*23 (29.5)*	*55 (44.0)*	*90 (39.5)*
Nervous system disorders	**4 (6.0)**	**6 (24.0)**	**7 (9.0)**	**34 (27.2)**	**47 (20.6)**
Headache	2 (3.0)	6 (24.0)	6 (7.7)	14 (11.2)	26 (11.4)
Dizziness	0	1 (4.0)	1 (1.3)	15 (12.0)	17 (7.5)
Somnolence	1 (1.5)	1 (4.0)	0	9 (7.2)	10 (4.4)
Paraesthesia	0	0	0	6 (4.8)	6 (2.6)
Presyncope	1 (1.5)	0	0	4 (3.2)	4 (1.8)
General disorders and administration site conditions	**4 (6.0)**	**4 (16.0)**	**1 (1.3)**	**13 (10.4)**	**18 (7.9)**
Fatigue	2 (3.0)	2 (8.0)	1 (1.3)	3 (2.4)	6 (2.6)
Feeling hot	0	1 (4.0)	0	3 (2.4)	4 (1.8)
Catheter site pain	0	2 (8.0)	0	1 (0.8)	3 (1.3)
Gastrointestinal disorders	**5 (7.5)**	**2 (8.0)**	**8 (10.3)**	**6 (4.8)**	**16 (7.0)**
Abdominal pain	0	1 (4.0)	3 (3.8)	1 (0.8)	5 (2.2)
Dry mouth	0	1 (4.0)	0	3 (2.4)	4 (1.8)
Constipation	2 (3.0)	0	3 (3.8)	0	3 (1.3)
Injury, poisoning and procedural complications	**0**	**0**	**2 (2.6)**	**13 (10.4)**	**15 (6.6)**
Infusion related reaction	0	0	2 (2.6)	12 (9.6)	14 (6.1)
Skin and subcutaneous tissue disorders	**4 (6.0)**	**2 (8.0)**	**2 (2.6)**	**6 (4.8)**	**10 (4.4)**
Acne	0	1 (4.0)	0	2 (1.6)	3 (1.3)
Musculoskeletal and connective tissue disorders	**4 (6.0)**	**1 (4.0)**	**2 (2.6)**	**4 (3.2)**	**7 (3.1)**
Back pain	0	0	1 (1.3)	2 (1.6)	3 (1.3)
Reproductive system and breast disorders	**2 (3.0)**	**1 (4.0)**	**3 (3.8)**	**3 (2.4)**	**7 (3.1)**
Dysmenorrhoea	2 (3.0)	0	3 (3.8)	0	3 (1.3)
Eye disorders	**1 (1.5)**	**3 (12.0)**	**2 (2.6)**	**0**	**5 (2.2)**
Respiratory, thoracic and mediastinal disorders	**0**	**3 (12.0)**	**1 (1.3)**	**1 (0.8)**	**5 (2.2)**
Infections and infestations	**4 (6.0)**	**1 (4.0)**	**2 (2.6)**	**1 (0.8)**	**4 (1.8)**

Abbreviations: IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event
[a] Subjects who received any rolapitant IV doses are combined.
Note: This table includes all SOCs and PTs that were reported in > 1% of subjects in the All Rolapitant IV group; for SOCs that did not have PTs that met this threshold, only the SOC is listed.

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Table 14. TEAEs by SOC, MAD Population (Study PR-11-5021)

System Organ Class Preferred Term	20 mg (N = 6) n (%)	40 mg (N = 8) n (%)	60 mg (N = 6) n (%)
General disorders and administration site conditions	**6 (100)**	**6 (75.0)**	**4 (66.7)**
Infusion site pain	4 (66.7)	3 (37.5)	2 (33.3)
Infusion site erythema	1 (16.7)	1 (12.5)	2 (33.3)
Infusion site swelling	0	1 (12.5)	3 (50.0)
Catheter site bruise	0	3 (37.5)	0
Infusion site bruising	1 (16.7)	0	1 (16.7)
Infusion site induration	2 (33.3)	0	0
Catheter site erythema	0	0	1 (16.7)
Catheter site haematoma	1 (16.7)	0	0
Catheter site pain	0	1 (12.5)	0
Chills	0	1 (12.5)	0
Fatigue	0	1 (12.5)	0
Infusion site discomfort	0	1 (12.5)	0
Nervous system disorders	**1 (16.7)**	**1 (12.5)**	**0**
Headache	1 (16.7)	1 (12.5)	0
Skin and subcutaneous tissue disorders	**0**	**2 (25.0)**	**0**
Dermatitis contact	0	2 (25.0)	0
Gastrointestinal disorders	**0**	**0**	**1 (16.7)**
Constipation	0	0	1 (16.7)
Injury, poisoning and procedural complications	**0**	**0**	**1 (16.7)**
Contusion	0	0	1 (16.7)
Thermal burn	0	0	1 (16.7)
Musculoskeletal and Connective Tissue Disorders	**0**	**0**	**1 (16.7)**
Back pain	0	0	1 (16.7)
Vascular Disorders	**0**	**0**	**1 (16.7)**
Hot flush	0	0	1 (16.7)

Abbreviations: IV, intravenous; min, minute; SOC, system organ class; PT, preferred term.
Note: SOCs and PTs are presented in decreasing order of frequency based on the total incidence across all 20 subjects in Part 2.
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7.4.2 Laboratory Findings

In general, the mean baseline values and mean changes from baseline over time observed in the hematology and chemistry parameters were similar between the rolapitant IV groups and the rolapitant oral groups. And none of the changes was considered to be clinically significant by the Investigator.

In the rolapitant IV healthy subject studies, no cases met Hy's Law criteria.

7.4.3 Vital Signs

There was a trend seen for a transient dose-dependent decrease in blood pressure associated with the use of rolapitant IV. The changes seen in the 185 mg IV rolapitant group were similar to those seen in the 200 mg oral rolapitant group.

7.4.4 Electrocardiograms (ECGs)

In a human ECG study, rolapitant oral demonstrated no effects on QTc interval prolongation at both therapeutic dose (200 mg) and supra-therapeutic dose (800 mg).

During the rolapitant IV clinical studies, no clinically significant changes were observed in ECG parameters and no patient had a QTcF >450 msec.

7.4.5 Special Safety Studies/Clinical Trials

No special clinical safety studies were submitted.

7.4.6 Immunogenicity

N/A

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

There was no clear trend of increasing AEs for increasing rolapitant dose. However, only one dose of rolapitant was studied in phase 3.

7.5.2 Time Dependency for Adverse Events

No particular explorations for time dependency of adverse events were conducted for patients who received a single dose of study medication.

For patients in the MAD portion of Study PR-11-5012, an assessment of infusion site events during the 10 infusion days was done given that AEs in the General disorders and administration site conditions SOC were the most commonly reported events (80%, (16/20 subjects). Within this SOC, administration site AEs were the most frequently reported. During the MAD portion of the study, patients had IV access placed which was to be used for the entire 10 day treatment period.

Table 15. Study PR-11-5012 (MAD population), Infusion Site Events by Day of

Infusion Day	1	2	3	4	5	6	7	8	9	10
Subjects experiencing onset of new event on this day (n)	2	3	2	0	3	4	1	1	2	1
Number of events[a]	2	3	2	0	5	8	1	1	2	1

[a] Infusion site pain, erythema, swelling, discomfort, bruising, induration. One subject only received rolapitant IV infusion on Day 1 but reported infusion site pain on Day 2; the Day 2 event of infusion site pain is included in this table.

Electronically copied and reproduced from the Summary of Clinical Safety, p 43

MO Comment:
It is not clear why the number of administration site TEAEs was highest on days 5 and 6 of the study. Line failure and administration site conditions can occur at any time. It should be noted that rolapitant IV labeling will recommend a dosing interval of at least 14 days and patients receiving chemotherapy are likely to have indwelling catheters instead of peripheral access lines which would likely result in fewer administration site condition TEAEs related specifically to rolapitant IV administration.

7.5.3 Drug-Demographic Interactions

No particular explorations for drug-demographic interactions related to adverse events were conducted.

7.5.4 Drug-Disease Interactions

No particular explorations for drug-disease interactions were conducted.

7.5.5 Drug-Drug Interactions

The results from the IV DDI study suggest that no dosage adjustment is required when rolapitant IV is coadministered with P-gp, BCRP, CYP3A4, CYP2C9, CYP2C19, and CYP1A2 substrates. The CYP2C9 substrate warfarin did not show an increased concentration; however, INR levels were not measured. Dr. Elizabeth Shang recommends adding wording to the label to instruct prescribers to monitor INR levels when warfarin and rolapitant IV are used concomitantly.

MO Comment:
I agree with the recommendation to include instructions to monitor INR levels in patients receiving rolapitant IV and warfarin concomitantly.

Caution is warranted when rolapitant IV is coadministered with CYP2D6 substrates. Rolapitant is known to be a moderate CYP2D6 inhibitor. Current oral rolapitant labeling contraindicates the use of VARUBI in patients receiving thioridazine, a CYP2D6 substrate with a narrow therapeutic index due to the risk of significant increase in

plasma concentrations of thioridazine which may result in QT prolongation and Torsades de Pointes.

In the rolapitant IV DDI Study submitted in support of the current Application, concomitant use of a single dose of rolapitant IV with other CYP2D6 substrates revealed prolonged inhibition of CYP2D6 (for at least 4 weeks). The currently labeled minimum dosing interval for rolapitant is 14 days. There is a concern that dosing rolapitant at this interval and concomitant use of any CYP2D6 substrate could result in an adverse drug-drug interaction.

Mo Comment:
Rolapitant labeling (both oral and IV) should include a contraindication to the concomitant use of all CYP2D6 substrates given the recommended dosing interval of rolapitant to avoid the potential additive inhibitory effect. For further discussion of CYP2D6 inhibition and rolapitant, see the clinical pharmacology review by Dr. Elizabeth Shang.

7.6.1 Human Carcinogenicity

The carcinogenicity potential of rolapitant was assessed in two-year carcinogenicity studies in mice and rats as recommended by the FDA Carcinogenicity Assessment Committee (CAC). There were no statistically significant drug-related neoplastic findings in the mice or rat studies.

For further details see the pharmacology/toxicology review for NDA 206,500 by Dr. Tracy Behrsing, PhD.

7.6.2 Human Reproduction and Pregnancy Data

Adequate and well-controlled studies with rolapitant IV have not been conducted in pregnant women. There were no pregnant subjects included in the clinical rolapitant IV studies.

7.6.3 Pediatrics and Assessment of Effects on Growth

The rolapitant IV program for this NDA included only adult patients.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

N/A

9 Appendices

9.1 Literature Review/References

N/A

9.2 Labeling Recommendations

See the final approved label for final labeling recommendations.

9.3 Advisory Committee Meeting

N/A

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/s/

AISHA P JOHNSON
12/01/2016

ANIL K RAJPAL
12/01/2016