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APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 23, 2017
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	April 25, 2017
PDUFA Goal Date	October 26, 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:	**Approval**

Material Reviewed/Consulted	Names of discipline reviewers
Clinical Safety	Aisha Johnson, MD, MPA, MBA
Pharmacology Toxicology Review	Tamal Chakraborti, Ph. D.
CMC Review	Drug Product: Hitesh Shroff, Ph. D.; Drug Substance: Debasis Ghosh, Ph. D.; Biopharm: Hansong Chen, Ph. D.; Process: Yuesheng Ye, Ph. D.; Facilities: Vidya Pai, Ph. D. ; Microbiology: Eric Adeeku, Ph.D.; ATL: Hitesh Shroff, Ph. D.
Clinical Pharmacology Review	Elizabeth Shang, Ph. D., R. Ph.
DDMAC/OPDP	Meeta Patel, Pharm. D.
OSE/DMEPA	Matthew Barlow, RN, BSN
OSE/DPV Pharmacovigilance Review	Kimberly Swank, Pharm. D.
OMP/DMPP Patient Labeling Review	Nyedra W. Booker, Pharm. D., MPH
Division of Pediatric and Maternal Health	Pediatrics: Erica Radden, M. D. Maternal: 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
OPDP=Office of Prescription Drug Promotion
OMP=Office of Medical Policy Initiatives
DMPP=Division of Medical Policy Program

1. Introduction

Chemotherapy induced nausea and vomiting (CINV) is the most common side effect of cancer treatments. There are a number of oral, intravenous, subcutaneous and transdermal treatments available to control CINV. Often CINV treatments include a combination of corticosteroids with 5-hydroxytyramine (5-HT3) antagonists such as ondansetron, palonosetron etc. or neurokinin-1 (NK1) receptor antagonists such as aprepitant, fosaprepitant etc.

Tesaro has filed this NDA for Varubi (rolapitant) injectable emulsion, 166.5 mg/92.5 mL (1.8 mg/mL). The active pharmaceutical ingredient, rolapitant, is a substance P/neurokinin 1 (NK1) receptor antagonist 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.

Varubi injectable emulsion is supplied as a sterile, translucent, white homogenous liquid in a (b) (4) stoppered single-dose clear glass vials. 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, water for injection, hydrochloric acid and/or sodium hydroxide to adjust pH to 7.0 to 8.0. The drug product will be manufactured at (b) (4).

For this 505 (b)(2) application Tesaro relied on the efficacy and safety findings of Varubi tablets for Chemotherapy Induced Nausea and Vomiting (CINV). Tesaro conducted a pivotal bioavailability (BA) study (PT-11-5016-C) to establish a bridge between the emulsion formulation manufactured at (b) (4) and the approved Varubi tablet.

Based on the *in vitro* drug release method (IVDR) and acceptance criteria proposed in resubmission, a biowaiver request from Tesaro is accepted. Thus, an *in vivo* bioequivalence (BE) bridging study to demonstrate that the to-be marketed drug product manufactured at (b) (4) and tablet is not needed.

The recommended dosage in adults is 166.5 mg rolapitant administered as an intravenous infusion over 30 minutes within 2 hours prior to the initiation of chemotherapy on Day 1.

2. Background

NDA 208399 was originally submitted on March 11, 2016. The drug product packaged in plastic was manufactured at (b) (4). The drug product packaged in glass vials was manufactured at (b) (4). A Complete Response letter was issued on January 11, 2017 because of the following deficiencies related to biopharmaceutics, drug product manufacturing process, manufacturing facility and clinical pharmacology issues.

- The drug product manufacturing facility (b) (4) was not acceptable due to deficiencies related to (b) (4) processing at that site. Therefore, the

Office or Process and Facilities (OPF) made a final "Unacceptable" recommendation of the facilities involved in this application.

- Biopharmaceutics issues regarding lack of an in-vitro release method for assessing the drug product quality when changes in manufacturing process, globule size and reagents are slightly modified or changed were not adequately resolved.
- Lack of bridge between the "to be marketed" product manufactured at (b) (4) and the original drug product manufacturing facility, (b) (4) or rolapitant tablets
- The label/labeling issues were not completely resolved.

On April 25, 2017 Tesaro Inc. submitted a complete response to the deficiencies outlined in the Division's CR letter containing the following information:

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

The resubmission adequately addresses all deficiencies outlined in the complete response letter.

3. Office of Process and Quality (OPQ)

Drug Substance: The active pharmaceutical ingredient (API) in Varubi injectable emulsion is, rolapitant, hydrochloride. It is a white to off-white powder. The proposed structure was confirmed by the spectroscopic methods such as NMR, IR, MS and UV. The quality of the API is controlled by its specification which includes appearance, identification, assay, impurities, heavy metals, particle size and microbial limits. The API specification was deemed adequate per the drug substance reviewer. The API manufacturing facility is acceptable from the Office of Process and Facilities perspective. Tesaro did not submit any new drug substance related information in this submission.

Drug Product: In this submission Tesaro provided the drug product manufacturing and sterilization processes utilized at (b) (4) They were reviewed and found to be adequate. The drug product quality is controlled by its specification. Tesaro has adequately addressed all drug product manufacturing related issues cited in the CR letter. The drug product manufacturing facility is acceptable from the Office of Process and Facilities. Based on the stability studies provided 12-month of expiration dating period is granted.

Biopharmaceutics: The in vitro drug release method (IVDR) and acceptance criteria proposed in this submission were reviewed and deemed acceptable. The biowaiver request from Tesaro was accepted therefore an additional *in vivo* bioequivalence (BE) bridging study is not needed.

Overall OPQ Recommendation: In this submission Tesaro has adequately addressed all deficiencies outlined in the CR letter. The overall recommendation of "Acceptable" has been issued for all facilities involved in the manufacture of Varubi injectable emulsion. All process and Biopharmaceutics related issues are resolved satisfactorily. The label/labeling issues are also satisfactorily addressed. Therefore, from the OPQ perspective this NDA is recommended for approval.

4. Nonclinical Pharmacology/Toxicology

The applicant did not provide any new nonclinical study report in this submission. The nonclinical studies have been conducted with rolapitant in support of Varubi tablets and Varubi injectable emulsion under NDA 206500 as well as in the original submission of this NDA dated March 11, 2016. No nonclinical safety issues were identified in the initial submission. No nonclinical safety issues and no nonclinical approvability issues were identified in this resubmission from the nonclinical standpoint.

Tesaro conducted a juvenile rat toxicity study to fulfill PMR 2879-1 for the approved Varubi tablets. Based on the adverse effects observed with sexual development and fertility in the juvenile toxicity studies with oral and IV rolapitant a recommendation was made to make a few labeling changes in non-clinical related sections and add the findings of the oral juvenile rat toxicity study in Section 8.4 of the label.

The following labeling addition was recommended in Section 8.4 Pediatric Use of the label:

> Juvenile Animal Toxicity Data
> In an oral juvenile toxicity study in rats the animals received rolapitant at dose levels of 11.3, 22.5 and 45 mg/kg/day from postnatal Day 7 through PND 70 (equivalent human age of newborn to 16 years), rolapitant caused a delay in the attainment of balanopreputial separation in males and acceleration of the attainment of vaginal patency in females at 22.5 and 45 mg/kg/day (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis). Treated males and females were mated following a 2-week wash-out period after the last dose. Early embryonic toxicity was observed at 22.5 and 45 mg/kg/day (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis). There were lower mean numbers of implantation sites, corpora lutea, and mean number of viable embryos at these doses when compared to control.

5. Clinical Pharmacology/Biopharmaceutics

There are no new clinical pharmacology data in the resubmission dated April 25, 2017.

The clinical pharmacology data supporting the changes in Varubi labeling and the results of two PMC studies issued under NDA 206500 for Varubi tablets were submitted in the original submission for Varubi injectable emulsion. The clinical pharmacology reviewer, Dr. Elizabeth Shang, reviewed it and found the application acceptable from the clinical pharmacology standpoint.

The Office of Clinical Pharmacology recommended the following changes to the label regarding drug interaction with CYP2D6 substrates.

1) The repeated doses of Varubi may result in additive inhibitory effect on CYP2D6 with long lasting period of inhibition. Thus, the CYP2D6 substrates with a narrow therapeutic index should be contradicted during the entire course including multiple cycles of chemotherapy and at least 28 days from the last dose of rolapitant. If patients require CYP2D6 medications then use an alternative antiemetic to rolapitant or they should be prescribed other medications that are not metabolized by CYP2D6.

2) The label should include new data obtained from Varubi injectable emulsion including ADME and DDI studies other than CYP2D6 inhibition using IV formulation. The sponsor conducted a study to evaluate the effect of IV rolapitant on warfarin and found that no clinical significant changes in systemic exposures to S-warfarin. However, the change of INR was not measured. Since warfarin is a narrow therapeutic index drug, the prescribers should monitor INR changes when using rolapitant concomitantly with warfarin.

3) Based on the results of two PMC studies the potential drug interaction between IV and oral rolapitant and renal and hepatic transporters should be added in the label.

The Approval letter will contain the following post-marketing requirements and commitments:

1) *Post- Marketing Requirements*
   Recommended study: 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 intravenous administration of rolapitant. The duration of the study should be long enough to demonstrate when the CYP2D6 inhibition is resolved.
2) *Post-Marketing Commitments*
   Recommended study: In vitro studies to evaluate the inhibitory potential of Varubi on MATE1 and OATP1B1 transporters and the IC50 values for each transporter

The data from in vitro drug release tests provided in this submission were deemed acceptable and can be used for a biowaiver to support (b) (4) manufacturing site. A biowaiver request for an in vivo BA/BE was granted by the biopharmaceutics reviewer.

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 3 (OCP/DCP3) reviewed this NDA and found the application acceptable from the OCP standpoint.

6. Clinical Microbiology

Not Applicable

7. Clinical/Statistical- Efficacy

No efficacy evaluation was conducted to support the current application. This application relied on the prior evidence of effectiveness for rolapitant tablets. The proposed indication for Varubi injectable emulsion is identical to the indication for the currently marketed Varubi tablets.

8. Safety

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

In the original submission Tesaro provided results of the following clinical studies. 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 ≤166.5 mg and 125 subjects received >166.5 mg of rolapitant. There were no serious adverse events or deaths reported in these heathy subjects.

Dr. Aisha Johnson, the clinical reviewer, recommended the approval of this NDA for the proposed indication.

9. Advisory Committee Meeting

No Applicable

10. Pediatrics

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

NDA 206500 for Varubi (rolapitant) tablets was approved on September 1, 2015 for the same indication. At that time the following pediatric study post-marketing requirements were issued for patients 0 to 17 years of age:

2879-1 A Good Laboratory Practice (GLP) toxicology study in juvenile rats

2879-2 A dose-ranging study assessing the pharmacokinetics, safety, tolerability, and effectiveness of Varubi (rolapitant) in pediatric patients ages 0-17 years old

2879-3 A study to evaluate the efficacy and safety of a single oral dose of Varubi (rolapitant) in pediatric patients ages 0-17 years old

Tesaro conducted a juvenile rat toxicity study to fulfill PMR 2879-1 for the approved Varubi tablets. This study revealed that rolapitant caused a delay in attainment of balanopreputial

separation in males and acceleration of the attainment of vaginal patency in females. In addition, early embryonic toxicity, lower mean numbers of implantation sites, corpora lutea and mean number of viable embryos at 22.5 and 45 mg/kg/day when compared to control were also observed. DPMH commented that the observed adverse effects on sexual development and fertility appear to be product-specific finding unique to juvenile animals.

Based on the adverse effects observed with sexual development and fertility in the juvenile toxicity studies with oral and IV rolapitant DPMH recommended that pediatric clinical trials should not be initiated until additional confirmatory segmented dose toxicity study has been conducted and reviewed to inform the risks of product use in pediatric patients.

DPMH recommended the following post-marketing requirements (PMRs) be issued under the Pediatric Research Equity Act for Varubi injectable emulsion.

Post-marketing requirements (PMRs):

Non-Clinical Studies:

- Confirmatory GLP toxicology study in juvenile animals
  Report Submission: 12/2017

- GLP segmented dosing toxicology study in juvenile rats
  Protocol submission: 03/2018
  Study completion: 11/2018
  Report Submission: 03/2019

Clinical Studies:

- Clinical effectiveness, safety and PK study
  Protocol Submission: 12/2019
  Study Completion: 06/2024
  Study Submission: 10/2024

The DPMH-Pediatrics team reviewed Section 8.4 Pediatric Use of the label and concluded that rolapitant injectable emulsion has not been studied in pediatric patients and will not be approved for use in pediatric population. The juvenile toxicity findings should be described in Sec. 8.4 of the label and updated when further information is available from the ongoing and planned studies.

11. Other Relevant Regulatory Issues

Tesaro filed the original NDA for Varubi (rolapitant) injectable emulsion on March 11, 2016. A complete response letter was issued on January 11, 2017. The end of review meeting was held on March 22, 2017 to discuss the applicant's plan to address the deficiencies noted in the CR letter. On April 25, 2017 Tesaro submitted a complete response to the deficiencies outlined in the CR letter.

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

FDA granted five years of new chemical exclusivity to Tesaro's Varubi (rolapitant) tablets NDA 206500 under 21 CFR 314.108(b)(2) because the active moiety, rolapitant, was not previously approved. This exclusivity will expire on September 1, 2020.

Tesaro has requested the Agency to apply the remaining portion of the NCE exclusivity period to the current application on the basis that Varubi injectable emulsion also contains the same active ingredient, rolapitant, as Varubi tablets.

There are no financial disclosure issues and no relevant regulatory issues with this application.

12. Labeling

The oral dosage form of rolapitant (Varubi tablets, NDA 206500) approved on September 1, 2015 and the IV form of rolapitant in the current application (Varubi injectable emulsion, NDA 208399) are indicated for CINV. Due to their similarities, the PI for Varubi injectable emulsion is combined with Varubi tablets PI.

In addition to primary review disciplines, the labeling was also reviewed by Division of Pediatric and Maternal Health (DPMH), Division of Medication Error Prevention and Analysis (DMEPA), Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP).

In the Highlights of Prescribing Information section Warnings and Precautions and Drug Interactions were revised to include labeling changes related to CYP2D6 inhibition and drug interaction with narrow therapeutic index such as Warfarin as recommended by the clinical pharmacology reviewer.

----------WARNINGS AND PRECAUTIONS----------

CYP2D6 Substrates: Rolapitant is a moderate inhibitor of CYP2D6 and significantly increases the plasma concentrations of CYP2D6 substrates for at least 28 days following single dose administration of VARUBI. Before starting VARUBI, consider if patients require:

- thioridazine or pimozide; if so, use an alternative antiemetic to VARUBI or an alternative to thioridazine or pimozide that is not metabolized by CYP2D6.
- other CYP2D6 substrates; if so, consult the prescribing information for the CYP2D6 substrate for additional information about interactions with CYP2D6 inhibitors. (4, 5.1, 7.1)

----------DRUG INTERACTIONS----------

- Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of VARUBI; avoid use of VARUBI in patients who require chronic administration of such drugs. (7.2)
- BCRP and P-gp Substrates with a Narrow Therapeutic Index: Oral VARUBI is an inhibitor of BCRP and P-gp and can increase plasma concentrations of the concomitant drug and potential for adverse reactions. See full prescribing information for specific examples. (7.3, 7.4)
- Warfarin: Monitor for increased INR or prothrombin time; adjust the dose of warfarin as needed. (7.5)

In Full Prescribing information: Contents Section 4 Contraindication and Section 5.1 Interaction with CYP2D6 Substrates were revised to include labeling changes related to CYP2D6.

4 CONTRAINDICATIONS

VARUBI is contraindicated in patients taking CYP2D6 substrates with a narrow therapeutic index, such as thioridazine and pimozide. VARUBI can significantly increase the plasma concentrations of thioridazine and pimozide, which may result in QT prolongation and Torsades de Pointes *[see Warnings and Precautions (5.1)]*.

5.1 Interaction with CYP2D6 Substrates

Rolapitant is a moderate inhibitor of CYP2D6. Exposure to dextromethorphan, a CYP2D6 substrate, following a single dose of rolapitant increased about 3-fold on Days 8 and Day 22. The inhibition of CYP2D6 persisted on Day 28 with a 2.3-fold increase in dextromethorphan concentrations, the last time point measured. The inhibitory effect of rolapitant on CYP2D6 is expected to persist beyond 28 days for an unknown duration following administration of VARUBI *[see Drug Interactions (7.1), Clinical Pharmacology (12.3)]*.

Narrow Therapeutic Index Drugs (Thioridazine and Pimozide)
VARUBI is contraindicated in patients taking CYP2D6 substrates with a narrow therapeutic index such as thioridazine and pimozide. Increased plasma concentrations of thioridazine and pimozide are associated with serious and/or life-threatening events of QT prolongation and Torsades de Pointes *[see Contraindications (4)]*.

Before starting treatment with VARUBI, consider whether patients require treatment with thioridazine or pimozide. If patients require these drugs, use an alternative antiemetic to VARUBI or an alternative to thioridazine or pimozide that is not metabolized by CYP2D6.

Other Drugs
VARUBI can also increase plasma concentrations of other CYP2D6 substrates for at least 28 days following administration of VARUBI and may result in adverse reactions.

Before starting treatment with VARUBI, consult the prescribing information for CYP2D6 substrates to obtain additional information about interactions with CYP2D6 inhibitors.

In Section 7 Drug Interaction subsection 7.5 was added about monitoring INR changed while using warfarin.

7.5 Warfarin

Although co-administration of intravenous VARUBI with warfarin did not substantially increase the systemic exposure to S-warfarin, the active enantiomer, the effects on INR and prothrombin time were not studied. Monitor INR and prothrombin time and adjust the dosage of warfarin, as needed, to maintain the target INR range.

The Section 8.3 was added based on the results of animal fertility studies.

8.3 Females and Males of Reproductive Potential

Infertility

Females
In animal fertility studies, rolapitant impaired the fertility in females in a reversible fashion *[see Nonclinical Toxicology (13.1)]*.

In Sec. 8.4 Pediatric Use Juvenile Animal Toxicity Data information was added based on the results of the juvenile animal study conducted as PMR for Varubi tablet application.

8.4 Pediatric Use

Safety and efficacy of VARUBI have not been established in pediatric patients.

In non-clinical studies, sexual development and fertility of juvenile rats (human age equivalent of birth to 16 years) were affected following oral administration of VARUBI, as described below in Juvenile Animal Toxicity Data.

Juvenile Animal Toxicity Data

In an oral juvenile toxicity study in rats, at rolapitant doses of 11.3, 22.5 and 45 mg/kg/day from postnatal (PND) Day 7 through PND 70 (equivalent human age of newborn to 16 years), there was a delay in the attainment of balanopreputial separation in males and an acceleration of the attainment of vaginal patency in females with rolapitant doses of 22.5 and 45 mg/kg/day (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis). Treated males and females were mated following a 2-week wash-out period after the last dose. There were lower mean numbers of implantation sites, corpora lutea, and mean number of viable embryos at 22.5 and 45 mg/kg/day (approximately 1.3 and 2.6 times, respectively, the recommended intravenous human dose on a body surface area basis) when compared to control.

Based on the results of two PMC studies Section 12.3 Pharmacokinetics was revised to add drug interaction potential between Varubi injectable emulsion or Varubi tablets and renal and hepatic transporters.

Section 17 Patient Counseling Information was modified to provide information regarding potential drug interaction and infertility issues.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions
Advise patients to tell their healthcare provider when they start or stop taking any concomitant medications. VARUBI is a moderate CYP2D6 inhibitor and can increase plasma concentrations of CYP2D6 substrates if they are co-administered *[see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7.1)]*.

Infertility

Advise females of reproductive potential that VARUBI may impair fertility *[see Use in Specific Populations (8.3), Nonclinical Toxicology (13.1)]*.

13. Recommendations/Risk Benefit Assessment

On April 25, 2017 Tesaro Inc. submitted a complete response to the CR letter issued on January 11, 2017.

The clinical reviewer, Dr. Aisha Johnson concluded that given the totality of the information submitted in support of this application, the benefits associated with the use of Varubi injectable injection currently outweigh the possible risks associated with the use of the therapy in patients receiving emetogenic chemotherapy. The safety update submitted in the current submission did not reveal any new safety signals or other areas of concern. The risks associated with the DDI can be managed with labeling. This application is recommended for approval from clinical safety perspective.

The clinical safety, clinical pharmacology, pharmacology/toxicology, DPMP and DMPP recommended this NDA for approval.

Tesaro proposed a satisfactory in vitro drug release method (IVDR) and acceptance criteria in this submission. The biowaiver request from Tesaro was accepted and an additional in vivo bioequivalence (BE) bridging study is not needed from Biopharmaceutics perspective. Therefore, this application is recommended for approval from Biopharmaceutics perspective.

In this submission Tesaro has adequately addressed all drug product manufacturing process related issues.

The Office of Process and Facilities has made the final overall "Approval" recommendation for the facilities involved in this NDA.

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

Risk Evaluation and Management Strategy (REMS) is not required for this application.

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 patients 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 will be included in the Approval letter.

- 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 submitted to the FDA and reviewed.

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/s/

HITESH N SHROFF
10/23/2017