

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

VARUBI™ (rolapitant) tablets, for oral use

Initial U.S. Approval: 2015

INDICATIONS AND USAGE

VARUBI 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. (1)

DOSAGE AND ADMINISTRATION

- The recommended dosage is 180 mg rolapitant administered approximately 1 to 2 hours prior to the start of chemotherapy (2)
- Administer in combination with dexamethasone and a 5-HT₃ receptor antagonist, see full prescribing information for dosing information (2)
- No dosage adjustment for dexamethasone is required. (2)

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg of rolapitant (3)

CONTRAINDICATIONS

Concurrent use with thioridazine, a CYP2D6 substrate (4)

WARNINGS AND PRECAUTIONS

Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index: The inhibitory effect of a single dose of VARUBI on CYP2D6 lasts at least 7 days and may last longer. Avoid use of pimozone; monitor for adverse reactions if concomitant use with other CYP2D6 substrates with a narrow therapeutic index cannot be avoided (4, 5.1, 7.1)

ADVERSE REACTIONS

Most common adverse reactions (≥ 5%) are:

- Cisplatin Based Highly Emetogenic Chemotherapy: neutropenia and hiccups (6.1)
- Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide: decreased appetite, neutropenia and dizziness (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tesaro at 1-844-4-tesaro or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- BCRP and P-gp Substrates with a Narrow Therapeutic Index: inhibition of BCRP and P-gp by VARUBI can increase plasma concentrations of the concomitant drug and potential for adverse reactions. See full prescribing information for specific examples. (7.1)
- 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)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 09/2015

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

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.

2 DOSAGE AND ADMINISTRATION

Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

The recommended dosage of VARUBI in adults in combination with a 5-HT₃ receptor antagonist and dexamethasone is shown in Table 1. There is no drug interaction between rolapitant and dexamethasone, so no dosage adjustment for dexamethasone is required.

Administer a dexamethasone dose of 20 mg on Day 1 [see *Clinical Pharmacology (12.3)*].

Administer VARUBI prior to the initiation of each chemotherapy cycle, but at no less than 2 week intervals.

Administer VARUBI without regards to meals.

Table 1: Recommended Dosing Regimen

	Day 1	Day 2	Day 3	Day 4
Prevention of Nausea and Vomiting Associated with Cisplatin-Based Highly Emetogenic Cancer Chemotherapy				
VARUBI	180 mg; Approximately 1 to 2 hours prior to chemotherapy	None		
Dexamethasone	20 mg; 30 min prior to chemotherapy	8 mg twice daily	8 mg twice daily	8 mg twice daily
5-HT ₃ receptor antagonist	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.	None		
Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy and Combinations of Anthracycline and Cyclophosphamide				
VARUBI	180 mg; Approximately 1 to 2 hours prior to chemotherapy	None		
Dexamethasone	20 mg; 30 min prior to chemotherapy	None		
5-HT ₃ receptor antagonist	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.		

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

VARUBI is contraindicated in patients receiving thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Pointes.

5 WARNINGS AND PRECAUTIONS

5.1 Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index

The inhibitory effect of VARUBI on CYP2D6 lasts at least 7 days and may last longer after a single dose administration of VARUBI [*see Contraindications (4), Drug Interactions (7), Clinical Pharmacology (12.3)*]. Avoid use of VARUBI in patients who are receiving pimozide, a CYP2D6 substrate. An increase in plasma concentrations of pimozide may result in QT prolongation. Monitor for adverse reactions if concomitant use of VARUBI and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The safety of VARUBI was evaluated in approximately 2800 patients in 4 controlled clinical trials in patients receiving emetogenic cancer chemotherapy. VARUBI was given in combination with a 5-HT₃ receptor antagonist and dexamethasone. On Day 1 of Cycle 1 of chemotherapy, 1567 patients were treated with VARUBI and 1198 of these patients continued into the optional multiple cycle extension for up to 6 cycles of chemotherapy. The median number of cycles administered 180 mg of VARUBI was four. VARUBI 180 mg was administered to 1294 patients.

In Cycle 1 adverse reactions were reported in approximately 7% of patients treated with VARUBI compared with approximately 6% of patients treated with control therapy. The most common adverse reactions reported with an incidence of $\geq 3\%$ and greater than control are listed in [Table 2](#) and [Table 3](#).

Table 2: Most Common Adverse Reactions in Patients Receiving Cisplatin-Based Highly Emetogenic Chemotherapy (Cycle 1)*

	VARUBI Regimen (VARUBI, Dexamethasone, and 5-HT₃ Receptor Antagonist) N = 624	Control (Placebo, Dexamethasone, and 5-HT₃ Receptor Antagonist) N = 627
Neutropenia	9%	8%
Hiccups	5%	4%
Abdominal Pain	3%	2%

*all reactions occurring at $\geq 3\%$ in the VARUBI group and for which the rate for VARUBI exceeds the rate for control

Table 3: Most Common Adverse Reactions in Patients Receiving Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide (Cycle 1)*

	VARUBI Regimen (VARUBI, Dexamethasone, and 5-HT₃ Receptor Antagonist) N = 670	Control (Placebo, Dexamethasone, and 5-HT₃ Receptor Antagonist) N = 674
Decreased appetite	9%	7%
Neutropenia	7%	6%
Dizziness	6%	4%
Dyspepsia	4%	2%
Urinary tract infection	4%	3%
Stomatitis	4%	2%
Anemia	3%	2%

*all reactions occurring at $\geq 3\%$ in the VARUBI group and for which the rate for VARUBI exceeds the rate for control.

Adverse reactions in the multiple-cycle extensions of highly and moderately emetogenic chemotherapy studies for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.

7 DRUG INTERACTIONS

7.1 Effect of VARUBI on Other Drugs

Rolapitant is not an inhibitor or inducer of CYP3A4. Therefore, no dosage adjustment for dexamethasone (CYP3A4 substrate) is needed when co-administered with VARUBI [*see Dosage and Administration (2)*].

Rolapitant is a moderate CYP2D6 inhibitor, an inhibitor of Breast-Cancer-Resistance Protein (BCRP) and an inhibitor of P-glycoprotein (P-gp) [*see Clinical Pharmacology (12.3)*].

CYP2D6 Substrates with a Narrow Therapeutic Index: Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A 3-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single dose of VARUBI. The duration of CYP2D6 inhibition was not studied beyond 7 days and may last longer [see *Clinical Pharmacology (12.3)*]. Concomitant use with Thioridazine is contraindicated [see *Contraindications (4)*]. Avoid use of VARUBI with pimozide [see *Warnings and Precautions (5.1)*]. Monitor for QT prolongation if concomitant use with pimozide cannot be avoided. Monitor for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

BCRP Substrates with a Narrow Therapeutic Index (e.g., Methotrexate, topotecan, or irinotecan): Increased plasma concentrations of BCRP substrates may result in potential adverse reactions. Monitor for adverse reactions related to the concomitant drug if use of VARUBI cannot be avoided. Use the lowest effective dose of rosuvastatin (see prescribing information for additional information on recommended dosing).

P-gp Substrates with a Narrow Therapeutic Index: Increased plasma concentrations of digoxin, or other P-gp substrates, may result in potential adverse reactions [see *Clinical Pharmacology (12.3)*]. Monitor for increased digoxin concentrations. Monitor for adverse reactions if concomitant use of VARUBI with other P-gp substrates with a narrow therapeutic index cannot be avoided.

7.2 Effect of Other Drugs on VARUBI

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg per day rolapitant free base throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg per day rolapitant free

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

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

8.2 Lactation

Risk Summary

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

Data

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

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 1294 subjects treated with VARUBI, 25% were 65 years and over, while 5% were 75 and over. No overall differences in safety or efficacy were reported between the elderly subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh Class C). Avoid use of VARUBI in patients with severe hepatic impairment. If use cannot be avoided, monitor patients for adverse reactions related to rolapitant [see *Adverse Reactions* (6.1)].

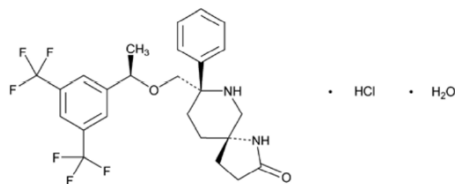
10 OVERDOSAGE

There are no data on overdose with VARUBI.

There is no antidote for VARUBI overdose. Discontinue VARUBI in the event of overdose, and institute general supportive measures and close observation.

11 DESCRIPTION

VARUBI tablets contain 90 mg rolapitant (equivalent to 100 mg rolapitant hydrochloride), a substance P/neurokinin 1 (NK1) receptor antagonist. Rolapitant hydrochloride is chemically described as (5S,8S)-8- { [(1R)-1-[3,5-bis(trifluoromethyl)phenyl]ethoxy]methyl} -8-phenyl-1,7-diazaspiro[4.5]decan-2-one monohydrochloride monohydrate. Its empirical formula is $C_{25}H_{26}F_6N_2O_2 \cdot HCl \cdot H_2O$ and its structural formula is:



rolapitant hydrochloride

Rolapitant hydrochloride is a white to off-white powder, with a molecular weight of 554.95. Solubility of rolapitant hydrochloride in aqueous solution is pH-dependent and is more soluble at lower pH. Rolapitant hydrochloride has good solubility in common pharmaceutical solvents such as ethanol, propylene glycol, and 40% hydroxypropyl beta cyclodextrin.

Each tablet for oral administration contains 90 mg rolapitant and the following inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. The tablets are coated in non-functional blue and clear coats. The tablet coating comprises the following inactive

ingredients: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue No. 2-Indigo Carmine Lake and polysorbate 80.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Rolapitant is a selective and competitive antagonist of human substance P/NK1 receptors. Rolapitant does not have significant affinity for the NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes and ion channels. Rolapitant is also active in animal models of chemotherapy-induced emesis.

12.2 Pharmacodynamics

NK1 Receptor Occupancy

A human Positron Emission Tomography (PET) study with rolapitant demonstrated that rolapitant crosses the blood brain barrier and occupies brain NK1 receptors. A dose-dependent increase in mean NK1 receptor occupancy was observed in the dose range from 4.5 mg to 180 mg of rolapitant. At the 180 mg dose of rolapitant, the mean NK1 receptor occupancy was 73% in the striatum at 120 hours after a single dose administration in healthy subjects. The relationship between NK1 receptor occupancy and the clinical efficacy of rolapitant has not been established.

Cardiac Electrophysiology

In a thorough QT study, rolapitant at doses up to 4 times higher than the recommended dose had no significant effects on the QT intervals.

12.3 Pharmacokinetics

Absorption

Following a single dose administration of 180 mg VARUBI under fasting conditions to healthy subjects, rolapitant was measurable in plasma between 30 minutes and the peak plasma concentration (C_{max}) for rolapitant was reached in about 4 hours and mean C_{max} was 968 ng/mL (%CV:28%).

Following multiple oral doses 9 to 45 mg once daily of rolapitant, accumulation of rolapitant was approximately 5-fold.

The systemic exposures (C_{max} and AUC) to rolapitant increased in a dose-proportional manner when the dose of rolapitant increased from 4.5 mg to 180 mg. With an increase in dose by 4 times from the recommended clinical dose of 180 mg, the C_{max} and AUC of rolapitant increased by 3.1 fold and 3.7 fold, respectively.

Concomitant administration of a high fat meal did not significantly affect the pharmacokinetics of rolapitant after administration of 180 mg VARUBI [*see Dosage and Administration (2)*].

Distribution

Rolapitant was highly protein bound to human plasma (99.8%). The apparent volume of distribution (Vd/F) was 460 L in healthy subjects, indicating an extensive tissue distribution of rolapitant. In a population pharmacokinetic analysis of rolapitant, the Vd/F was 387 L in cancer patients.

Elimination

Following single oral doses (4.5 to 180 mg) of rolapitant, the mean terminal half-life (t_{1/2}) of rolapitant ranged from 169 to 183 hours (approximately 7 days) and was independent of dose. In a population pharmacokinetic analysis the apparent total clearance (CL/F) of rolapitant was 0.96 L/hour in cancer patients.

Metabolism

Rolapitant is metabolized primarily by CYP3A4 to form a major active metabolite, M19 (C4-pyrrolidine-hydroxylated rolapitant). In a mass balance study, the metabolite M19 was the major circulating metabolite. The formation of M19 was significantly delayed with the median T_{max} of 120 hours (range: 24-168 hours) and the mean half-life of M19 was 158 hours.

The exposure ratio of M19 to rolapitant was approximately 50% in plasma.

Excretion

Rolapitant is eliminated primarily through the hepatic/biliary route. Following administration of a single oral 180-mg dose of [¹⁴C]-rolapitant, on average 14.2% (range 9% to 20%) and 73% (range 52% to 89%) of the dose was recovered in the urine and feces, respectively over 6 weeks. In pooled samples collected over 2 weeks, 8.3% of the dose was recovered in the urine primarily as metabolites and 37.8% of the dose was recovered in the feces primarily as unchanged rolapitant. Unchanged rolapitant or M19 were not found in pooled urine sample.

Specific Populations

Age, Sex and Race/Ethnicity

Population pharmacokinetic analyses indicated that age, sex and race had no significant impact on the pharmacokinetics of rolapitant.

Hepatic Impairment

Following administration of a single dose of 180 mg rolapitant to patients with mild hepatic impairment (Child-Pugh Class A), the pharmacokinetics of rolapitant were comparable with those of healthy subjects. In patients with moderate hepatic impairment (Child-Pugh Class B), the mean C_{max} was 25% lower while mean AUC of rolapitant was similar compared to those of healthy subjects. The median T_{max} for M19 was delayed to 204 hours in patients with mild or moderate hepatic impairment compared to 168 hours in healthy subjects. The pharmacokinetics of rolapitant was not studied in patients with severe hepatic impairment (Child-Pugh Class C) [*see Use in Specific Populations (8.6)*].

Renal Impairment

In population pharmacokinetic analyses, creatinine clearance (CL_{cr}) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CL_{cr}: 60 to 90 mL/min) or moderate (CL_{cr}: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal

impairment. The pharmacokinetics of rolapitant was not studied in patients with end-stage renal disease requiring hemodialysis.

Drug Interaction Studies

Effect of Other Drugs on VARUBI

Rolapitant is a substrate for CYP3A4.

CYP3A4 inducers

Concomitant administration of a CYP3A4 inducer significantly decreased the systemic exposure to rolapitant. When 600 mg rifampin was administered once daily for 7 days before and 7 days after administration of a single dose of 180 mg rolapitant, the mean C_{max} of rolapitant was reduced by 30% and the mean AUC was reduced by 85% compared to administration of rolapitant alone. The mean half-life of rolapitant decreased from 176 hours without rifampin to 41 hours with concurrent rifampin [*see Drug Interactions (7)*].

CYP3A4 inhibitors

No clinically significant effect was seen on the pharmacokinetics of rolapitant when ketoconazole, a strong CYP3A4 inhibitor was administered with rolapitant. Concurrent administration of 400 mg ketoconazole once daily for 21 days following a single 90 mg dose of rolapitant, did not significantly affect the C_{max} of rolapitant while the AUC increased by 21%.

Effect of VARUBI on Other Drugs

The effect of VARUBI on CYP450 enzymes and transporters is summarized below. See [Table 4](#) for a summary of the effects of the clinical dose of VARUBI on the pharmacokinetics of co-administered drugs.

CYP3A4 substrates

Rolapitant is neither an inhibitor nor an inducer of CYP3A4.

Midazolam: A single dose of 180 mg rolapitant had no significant effects on the pharmacokinetics of midazolam when oral midazolam 3 mg was co-administered on Day 1 and administered alone on Days 6, and 9.

Ondansetron: Rolapitant had no significant effects on the pharmacokinetics of intravenous ondansetron when concomitantly administered with a single 180 mg dose of rolapitant on the same day.

Dexamethasone: Rolapitant had no significant effects on the pharmacokinetics of dexamethasone when oral dexamethasone was administered on Days 1 to 3 after a single 180 mg dose of rolapitant was co-administered on Day 1 [*see Dosage and Administration (2)*].

CYP2D6 substrates

Rolapitant is a moderate inhibitor of CYP2D6 [*see Contraindications (4), Warning and Precautions (5.1), Drug Interactions (7)*].

BCRP transporter

Rolapitant is an inhibitor of BCRP transporter [*see Drug Interactions (7)*].

P-glycoprotein substrates

Rolapitant is an inhibitor of P-gp transporter [see Drug Interactions (7)].

Substrates for other CYP enzymes

In vitro studies suggest that rolapitant is not an inhibitor of CYP1A2 and CYP2E1. A clinically meaningful drug interaction via an inhibition of CYP2A6 appears unlikely based on in vitro study.

No clinically significant interaction was seen on the pharmacokinetics of the following drugs when administered with a single dose of 180 mg rolapitant on Day 1 and without rolapitant on Day 8: repaglinide (CYP2C8 substrate; no effect on repaglinide 0.25 mg on Day 1; on Day 8 : 29% and 24% increase in C_{max} and AUC, respectively), efavirenz (CYP2B6 substrate; 18% decrease in C_{max} and no effect on AUC of efavirenz 600 mg on Day 1; on Day 8: no effect on C_{max} and 28% increase in AUC), tolbutamide (CYP2C9 substrate; no effect on tolbutamide 500 mg on Day 1 and on Day 8), or omeprazole (CYP2C19 substrate; 44% increase in C_{max} and 23% increase in AUC of omeprazole 40 mg on Day 1; on Day 8: 37% and 15% increase in C_{max} and AUC, respectively).

Table 4: Effect of VARUBI on the Pharmacokinetics of Co-administered Drugs*

Enzyme/ transporter	Co-administered drug	% Change for Co-administered Drug			
		Day 1 with rolapitant		Day 8 without rolapitant	
		Change in C _{max}	Change in AUC	Change in C _{max}	Change in AUC
CYP2D6	Dextromethorphan 30mg	120% ↑	160% ↑	180% ↑	230% ↑
BCRP	Sulfasalazine 500 mg	140% ↑	130% ↑	17% ↑	32% ↑
P-gp	Digoxin 0.5 mg	70% ↑	30% ↑	n/a	n/a

*A single dose of 180 mg rolapitant was administered on day 1; the interacting drug was administered on day 1 with rolapitant and alone on day 8

↑ Denotes an average increase in exposure by the percentage indicated.

n/a: Not studied

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenic potential of rolapitant hydrochloride was assessed in 2-year carcinogenicity studies in CD-1 mice and Sprague-Dawley rats. In mice, there were no drug-related neoplastic findings at doses equivalent to up to 135 mg/kg per day rolapitant free base (approximately 3.6 times the recommended human dose on a body surface area basis). In rats, there were no drug-related neoplastic findings at doses equivalent to up to 90 mg/kg per day rolapitant free base (approximately 4.9 times the recommended human dose on a body surface area basis).

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

In a fertility and early embryonic development study in female rats, rolapitant hydrochloride at an oral dose equivalent to 9 mg/kg per day free base (approximately 0.5 times the recommended

human dose on a body surface area basis) caused a transient decrease in maternal body weight gain and increases in the incidence of pre- and post-implantation loss. At a dose equivalent to 4.5 mg/kg per day free base (approximately 0.2 times the recommended human dose on a body surface area basis), there were slight decreases in the number of corpora lutea and implantation sites. Rolapitant hydrochloride did not affect the fertility or general reproductive performance of male rats at doses equivalent to up to 90 mg/kg per day rolapitant free base (approximately 4.9 times the recommended human dose on a body surface area basis).

14 CLINICAL STUDIES

Cisplatin-Based Highly Emetogenic Chemotherapy (HEC)

In two multicenter, randomized, double-blind, parallel group, controlled clinical studies (Study 1 and Study 2), the VARUBI regimen (VARUBI, granisetron and dexamethasone) was compared with control therapy (placebo, granisetron and dexamethasone) in patients receiving a chemotherapy regimen that included cisplatin >60 mg/m². See Table 5 for the treatment regimens.

Table 5: Treatment Regimens in Studies 1 and 2

	Day 1	Day 2 to 4
VARUBI Regimen		
Oral VARUBI [†]	180 mg	none
Oral Dexamethasone	20 mg [‡]	8 mg twice daily
Intravenous Granisetron	10 mcg/kg [§]	none
Control Regimen*		
Oral Dexamethasone	20 mg [‡]	8 mg twice daily
Intravenous Granisetron	10 mcg/kg [§]	none

* VARUBI placebo was used to maintain blinding

[†] VARUBI was administered 1 to 2 hours prior to chemotherapy treatment on Day 1

[‡] Dexamethasone was administered 30 minutes prior to chemotherapy on Day 1. There is no drug interaction between VARUBI and dexamethasone, so no dosage adjustment for dexamethasone is required [see *Clinical Pharmacology (12.3)*].

[§] The dose of granisetron was administered 30 minutes prior to chemotherapy on Day 1.

Study 1

A total of 532 patients were randomized to either the VARUBI regimen (N =266) or control therapy (N =266). A total of 526 patients were included in the evaluation of efficacy. Of those randomized 42% were women, 58 % men, 67% White, 23% Asian, 1% Black, and 9% multi-racial/other/unknown. The proportion of patients from North America was 16%. Patients in this clinical study ranged from 20 to 90 years of age, with a mean age of 57 years. In Study 1, 26% of patients were 65 years or older, with 3% of patients being 75 years or older. The mean cisplatin dose was 77 mg/m².

During this study, 82% of the patients received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common concomitant chemotherapeutic agents administered during Cycle 1 were: gemcitabine (17%), paclitaxel (12%), fluorouracil (11%), etoposide (10%), vinorelbine (9%), docetaxel (9%), pemetrexed (7%), doxorubicin (6%) and cyclophosphamide (5%).

Study 2

A total of 555 patients were randomized to either the VARUBI regimen (N =278) or control therapy (N =277). A total of 544 patients were included in the evaluation of efficacy. Of those randomized, 32% were women, 68 % men, 81% White, 14% Asian, 1% Black, and 5% multi-racial/other/unknown. The proportion of patients from North America was 7%. Patients in this clinical study ranged from 18 to 83 years of age, with a mean age of 58 years. In this study, 27% of patients were 65 years or older, with 3% of patients being 75 years or older. The mean cisplatin dose was 76 mg/m².

During this study, 85% of the patients received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin. The most common concomitant chemotherapeutic agents administered during Cycle 1 were: vinorelbine (16%), gemcitabine (15%), fluorouracil (12%), etoposide (11%), pemetrexed (9%), docetaxel (7%), paclitaxel (7%), epirubicin (5%) and capecitabine (4%).

The primary endpoint in both studies was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting.

Moderately Emetogenic Chemotherapy (MEC) and Combinations of Anthracycline and Cyclophosphamide Chemotherapy

Study 3

In Study 3, a multicenter, randomized, double-blind, parallel group, controlled clinical study in moderately emetogenic chemotherapy, the VARUBI regimen (VARUBI, granisetron and dexamethasone) was compared with control therapy (placebo, granisetron and dexamethasone) in patients receiving a moderately emetogenic chemotherapy regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide. The percentage of patients who received carboplatin in Cycle 1 was 30%. Treatment regimens for the VARUBI and control arms are summarized in Table 6.

Table 6: Treatment Regimens in Study 3

	Day 1	Day 2 to 3
VARUBI Regimen		
Oral VARUBI [†]	180 mg	none

Oral Dexamethasone	20 mg [‡]	none
Oral Granisetron	2 mg [§]	2 mg once daily
Control Regimen*		
Oral Dexamethasone	20 mg [‡]	none
Oral Granisetron	2 mg [§]	2 mg once daily

* VARUBI placebo was used to maintain blinding

† VARUBI was administered 1 to 2 hours prior to chemotherapy treatment on Day 1

‡ Dexamethasone was administered 30 minutes prior to chemotherapy on Day 1. There is no drug interaction between VARUBI and dexamethasone, so no dosage adjustment for dexamethasone is required [see *Clinical Pharmacology (12.3)*].

§ The dose of granisetron was administered 30 minutes prior to chemotherapy on Day 1.

A total of 1369 patients were randomized to either the VARUBI regimen (N = 684) or control therapy (N = 685). A total of 1332 patients were included in the evaluation of efficacy. Of those randomized 80% were women, 20% men, 77% White, 13% Asian, 4% Black, and 6% multi-racial/other/unknown. The proportion of patients from North America was 33%. Patients in this clinical study ranged from 22 to 88 years of age, with a mean age of 57 years. In this study, 28% of patients were 65 years or older, with 7% of patients being 75 years or older.

The primary endpoint was complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting.

A summary of the study results from HEC Studies 1 and 2, and for the MEC Study 3 is shown in [Table 7](#).

Table 7: Percent of Patients Receiving Emetogenic Chemotherapy Responding by Treatment Group for the HEC Studies 1 and 2 and for the MEC Study 3

Endpoint	HEC Study 1			HEC Study 2			MEC Study 3		
	VARUBI† (N=264) Rate (%)	Control† (N=262) Rate (%)	P-Value Treatment Difference (95% C.I.)	VAR UBI† (N=27 1) Rate (%)	Control † (N=273) Rate (%)	P-Value Treatment Difference (95% C.I.)	VARUB I† (N=666) Rate (%)	Control† (N=666) Rate (%)	P-Value Treatment Difference (95% C.I.)
Primary Endpoint : Complete Response in the Delayed Phase	72.7	58.4	<0.001* 14.3 (6.3,22.4)	70. 1	61.9	0.043* 8.2 (0.3, 16.1)	71.3	61.6	<0.001* 9.8 (4.7, 14.8)

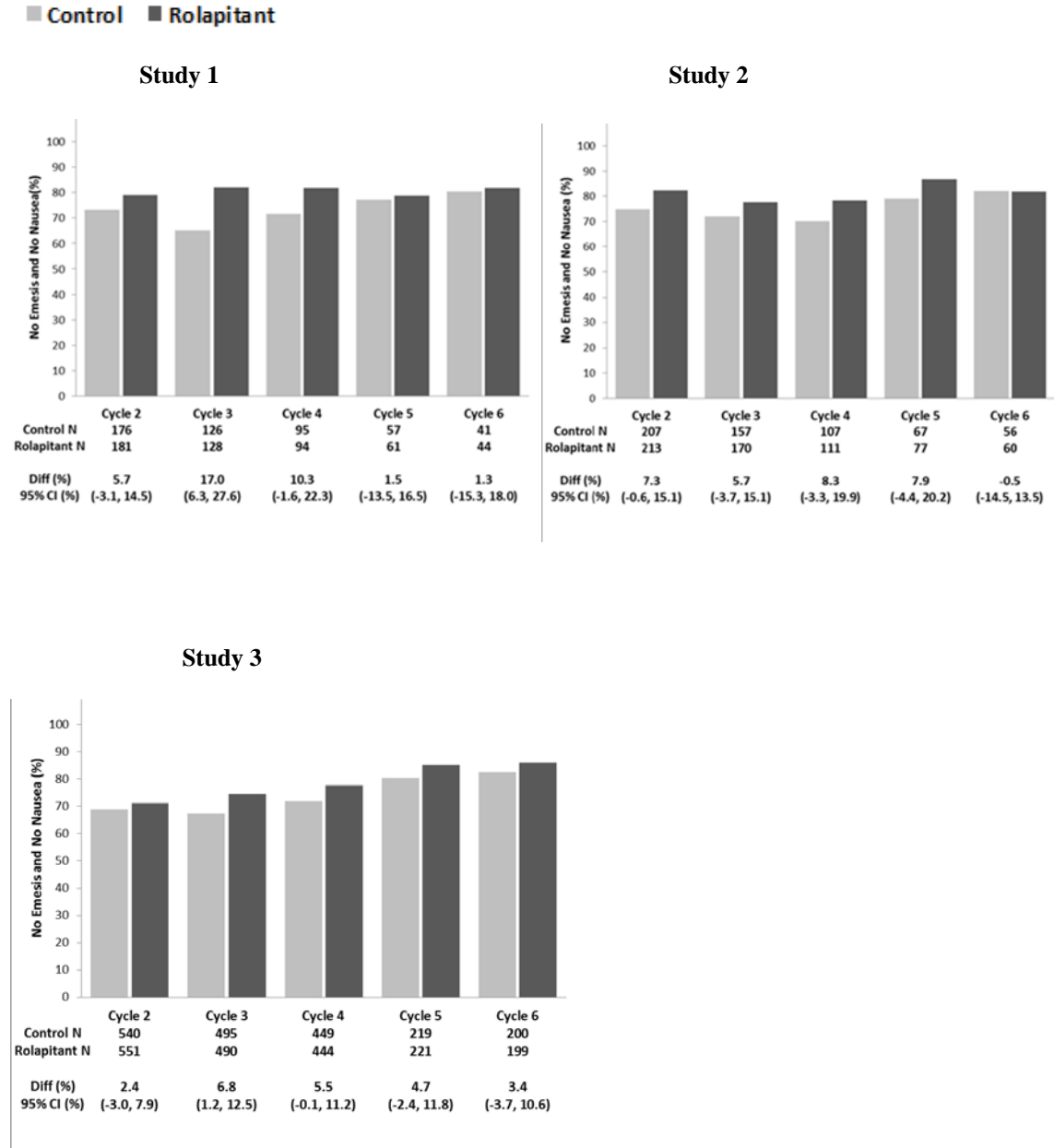
† Granisetron and dexamethasone were used as concomitant drugs.

* Results were obtained based on the Cochran-Mantel-Haenszel test stratified by gender.

Multiple-Cycle Extension: In Studies 1, 2, and 3, patients had the option of continuing into a multiple-cycle extension for up to 5 additional cycles of chemotherapy receiving the same treatment as assigned in cycle 1. At day 6 to 8 following initiation of chemotherapy, patients

were asked to recall whether they had any episode of vomiting or retching or nausea that interfered with normal daily life. The results are summarized by study and treatment group in the figure below.

Figure 1: No Emesis and No Nausea Interfering with Daily Life over Cycles 2-6



16 HOW SUPPLIED/STORAGE AND HANDLING

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

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

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

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. The inhibitory effect of VARUBI on CYP2D6 lasts at least 7 days and may last longer than 7 days after a single dose [*see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7)*].

Manufactured for: TESARO, Inc. 1000 Winter St., #3300, Waltham, MA 02451

Patient Information
VARUBI™ (vuh ROO bee)
(rolapitant)
tablets

What is VARUBI?

VARUBI is a prescription medicine called an “antiemetic.” VARUBI is used with other medicines in adults to help prevent nausea and vomiting that happens later with certain anti-cancer medicines (chemotherapy). It is not known if VARUBI is safe and effective in children.

Who should not take VARUBI?

Do not take VARUBI if you take thioridazine. Taking VARUBI with thioridazine can cause serious or life-threatening heart rhythm changes.

What should I tell my doctor before taking VARUBI?

Before taking VARUBI, tell your doctor about all of your medical conditions, including if you:

- have liver problems
- are pregnant or plan to become pregnant. It is not known if VARUBI will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if VARUBI passes into your breast milk or could harm your baby.

Tell your doctor about all the medicines you take or stop taking, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Keep a list of your medicines to show your doctor and pharmacist when you get a new medicine.

VARUBI and other medicines may affect each other and could cause serious side effects.

How should I take VARUBI?

- Take VARUBI exactly as your doctor tells you to take it.
- On Day 1 of chemotherapy, take 2 VARUBI tablets by mouth about 1 to 2 hours before you receive your anti-cancer medicine (chemotherapy).
- Do not take VARUBI more than 1 time every 14 days.
- VARUBI can be taken with or without food.
- If you take too much VARUBI, call your doctor or go to the nearest hospital emergency room right away.

What are the possible side effects of VARUBI?

VARUBI may cause serious side effects, including:

Change in the level of some medicines in your blood. Serious or life-threatening reactions, including heart rhythm changes, may occur if VARUBI is used with certain other medicines. You should not take VARUBI if you take pimozide.

The most common side effects of VARUBI in people who take VARUBI and receive Cisplatin chemotherapy medicine include: low white blood cell count, hiccups, and stomach (abdominal) pain.

The most common side effects of VARUBI in people who take VARUBI and receive Anthracycline and Cyclophosphamide chemotherapy medicines include: decreased appetite, low white blood cell count, dizziness, indigestion, urinary tract infection, mouth sores, and low red blood cell count.

These are not all the possible side effects of VARUBI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store VARUBI?

Store VARUBI at room temperature between 68°F to 77°F (20°C to 25°C).

Keep VARUBI and all medicines out of the reach of children.

General Information about the safe and effective use of VARUBI

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use VARUBI for a condition for which it was not prescribed. Do not give VARUBI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your doctor or pharmacist for information about VARUBI that is written for health professionals.

What are the ingredients in VARUBI?

Active ingredient: rolapitant hydrochloride

Inactive ingredients: lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide and magnesium stearate. Tablet coating: polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue No. 2-Indigo Carmine Lake and polysorbate 80.

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