PDL DRUG REVIEW

Proprietary Name: Varubi®
Common Name: rolapitant
PDL Category: Antiemetic Agents

Comparable Products	Preferred Drug List Status
Emend	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Rolapitant, the active ingredient of Varubi®, is a selective and competitive antagonist of human substance P/neurokinin 1 (NK1) receptors. Rolapitant is metabolized to form a major active metabolite, which has a mean half-life of 158 hours.

Indication: 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.

There is no pregnancy category associated with this product; however, the pregnancy risk summary indicates there is no available data on Varubi® use in pregnant women to inform any drug associated risks. There were no teratogenic or embryo-fetal effects seen with oral administration of rolapitant in animal reproduction studies at doses up to 1.2-2.9 times the maximum recommended human dose. The safety and efficacy of use in children under the age of 18 years have not been established.

Dosage Forms: Film-coated capsule-shaped Tablets: 90mg (equivalent to 100mg rolapitant HCl)

Recommended Dosage: Use Varubi® in combination with a 5HT3 receptor antagonist (RA) and dexamethasone, as per the table below (which was adapted from the prescribing information). Administer Varubi® prior to the start of each chemotherapy cycle, but at no less than 2 week intervals.

	Day 1	Day 2	Day 3	Day 4
Prevention of nausea/vomiting associated with Cisplatin-based Highly Emetogenic Cancer Chemotherapy				
Varubi®	180mg about 1-2hrs prior to chemo	None		
Dexamethasone	20mg, 30mins prior to chemo	8mg BID	8mg BID	8mg BID
5HT3 Receptor Antagonist	See PI for co-administered 5HT3 RA for appropriate dosing	None		
Prevention of nausea/vomiting associated with Moderately Emetogenic Cancer Chemotherapy & Combinations of Anthracycline and Cyclophosphamide				

	Day 1	Day 2	Day 3	Day 4
Varubi®	180mg about 1-2hrs prior to chemo	None		
Dexamethasone	20mg, 30mins prior to chemo	None		
5HT3 Receptor Antagonist	See PI for co-administered 5HT3 RA for appropriate dosing			

Varubi® dose adjustments are not required in those with mild or moderate hepatic impairment; however, as there is no data on use in those with severe hepatic impairment. Therefore, it is recommended to avoid use in this population. If use cannot be avoided in those with severe hepatic impairment, it is recommended to monitor for adverse reactions related to Varubi®. Dose adjustments are not required for use in mild or moderate renal impairment; however, data is not sufficient for the effect of use in those with severe renal impairment.

Drug Interactions: Rolapitant is a moderate CYP2D6 inhibitor, an inhibitor of Breast-Cancer-Resistance Protein (BCRP) and an inhibitor of P-glycoprotein (P-gp). Concomitant use with thioridazine is contraindicated. It is recommended to avoid use with pimozide; however, if concomitant use cannot be avoided, it is recommended to monitor for QT prolongation. In general, it is recommended to monitor for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided. Concomitant use of Varubi® with BCRP substrates with a narrow therapeutic index (e.g. methotrexate, topotecan, or irinotecan) may cause an increase in plasma levels of these BCRP substrates. It is recommended to monitor for adverse reactions if concomitant use with Varubi® cannot be avoided. In addition, use the lowest effective dose of rosuvastatin. It is recommended to monitor for increased digoxin levels and for adverse reactions with other P-gp substrates with a narrow therapeutic index if concomitant use of Varubi® cannot be avoided.

Strong CYP3A4 inducers (e.g. rifampin) can significantly reduce the plasma levels of rolipitant. Therefore, it is recommended to avoid use of Varubi® in those who require chronic administration of such drugs.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (regimen of Varubi®, dexamethasone, and 5HT3 RA) minus reported % incidence for control/dexamethasone/5HT3 RA in patients receiving moderately emetogenic chemotherapy and combinations of anthracycline and cyclophosphamide. Please note that an incidence of 0% means the incidence was the same or that the active drug was less than the control regimen.* The most frequently reported adverse events included decreased appetite (2%), neutropenia (1%), dizziness (2%), dyspepsia (2%), urinary tract infection (1%), stomatitis (2%), and anemia (1%).

Contraindications: In patients receiving thioridazine (as a significant increase in plasma levels of thioridazine may occur and result in QT prolongation and Torsade de Pointes)

Manufacturer: Tesaro

Analysis: The safety and efficacy of Varubi® for use with cisplatin-based highly emetogenic chemotherapy (HEC) were established in 2 double-blind, parallel-group studies where adults receiving a chemotherapy regimen that included cisplatin were randomized to the Varubi® regimen (Varubi®, IV granisetron, and PO dexamethasone) or the control therapy (placebo, IV granisetron, and PO dexamethasone). Study 1 (N=532) and study 2 (N=555) had the same primary endpoint of complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25-120 hours) of chemotherapy induced nausea and vomiting. Results, obtained from the prescribing information, are included in the table below.

Primary Endpoint	Varubi®	placebo	p value
Study 1			
Complete Response	72.7%	58.4%	<0.001
Study 2			

Complete Response	70.1%	61.9%	0.043

(**GHS Comments**: The calculated NNT for complete response with the Varubi® regimen as compared with the control regimen was 7 for study 1, and was 13 for study 2.)

Study 3 was a double-blind, parallel-group study that included adults (N=1369) who were receiving a moderately emetogenic chemotherapy (MEC) regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide and who were randomized to the Varubi® regimen (as above) or the control regimen as described above (with the exception that the granisetron dose was administered as an oral dose in this study, not as an IV dose). The primary endpoint was complete response, defined as above. Results, obtained from the prescribing information, are included in the table below.

Primary Endpoint	Varubi®	placebo	p value
Study 3			
Complete Response	71.3%	61.6%	<0.001

(**GHS Comments**: The calculated NNT for complete response with the Varubi® regimen as compared with the control regimen for study 3 was 11.)

Place in Therapy: The American Society of Clinical Oncology (ASCO) guidelines for antiemetic use in oncology were last updated in November 2015 (published in 2016) to include an updated recommendation on antiemetic use with a HEC regimen. While the guidelines do not include Varubi®, the newest antagonist of human substance P/neurokinin 1 (NK1) receptors, they do include a new recommendation for chemotherapy-induced nausea and vomiting associated with HEC and the remaining 2011 guideline recommendations are unchanged. For HEC, a three-drug regimen is recommended, which includes an NK1 receptor antagonist, a 5HT3 receptor antagonist, and dexamethasone. The guideline adds that the combination of netupitant and palonosetron plus dexamethasone is an additional treatment option. For MEC, a two drug regimen of palonosetron and dexamethasone is recommended.[2] (Note that if palonosetron is not available, a first-generation 5HT3 receptor antagonist may be substituted, but preferably granisetron or ondansetron.[4]) One noted reference indicates rolapitant is an acceptable alternative to the other NK1 receptor antagonists (e.g. aprepitant, fosaprepitant IV, or netupitant in combination with palonosetron).[3]

There is no evidence at this time to support that Varubi® is safer or more effective than the currently available, more cost effective medications. It is therefore recommended that Varubi® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred with Conditions**

References

[1] Varubi [package insert]. Waltham, MA: Tesaro; 2015.
[2] Hesketh PJ, Bohlke K, Lyman GH, et al. Antiemetics: American Society of Clinical Oncology Focused Guideline Update. *J Clin Oncol*. 2016; 34(4): 381-6.
[3] UpToDate desktop reference. Prevention and treatment of chemotherapy-induced nausea and vomiting. Accessed June 2016.
[4] Basch E, Prestrudd AA, Hesketh PJ, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2011; 29(31): 4189-98.