Formulary Drug Reviews
Rolapitant

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Each month, subscribers to The Formulary Monograph Service receive 5 to 6 well-documented monographs on drugs that are newly released or are in late phase 3 trials. The monographs are targeted to Pharmacy & Therapeutics Committees. Subscribers also receive monthly 1-page summary monographs on agents that are useful for agendas and pharmacy/nursing in-services. A comprehensive target drug utilization evaluation/medication use evaluation (DUE/MUE) is also provided each month. With a subscription, the monographs are sent in print and are also available on-line. Monographs can be customized to meet the needs of a facility. A drug class review is now published monthly with The Formulary Monograph Service. Through the cooperation of The Formulary, Hospital Pharmacy publishes selected reviews in this column. For more information about The Formulary Monograph Service, contact Wolters Kluwer customer service at 866-397-3433. The February 2016 monograph topics are mepolizumab, cobimetinib, glycopyrrolate, indacaterol/glycopyrrolate, and coagulation factor X (human). The Safety MUE is on mepolizumab.

Generic Name: Rolapitant
Proprietary Name: Varubi (Tesaro, Inc.)
Approval Rating: 1S
Therapeutic Class: Substance P/Neurokinin-1 Receptor Antagonists
Similar Drugs: Aprepitant, Fosaprepitant, Netupitant/Palonosetron
Sound- or Look-Alike Names: Varibar products, Varivax, Varizig

INDICATIONS
Rolapitant (formally SCH 619734) is a substance P/neurokinin-1 (NK₁) receptor antagonist approved by the US Food and Drug Administration (FDA) in 2015 for use in combination with other antiemetic agents for the prevention of delayed nausea and vomiting associated with initial and repeat doses of emetogenic chemotherapy. Rolapitant has been studied in combination with highly emetogenic cancer chemotherapy combinations that include cisplatin and with moderately emetogenic regimens that include an anthracycline and/or cyclophosphamide. See Table 1 for a comparison of oral substance P/NK₁ receptor antagonists.

Rolapitant is thought to have a longer half-life, better affinity for the NK₁ receptor, and less drug-drug interactions than other NK₁ receptor antagonists because it does not induce or inhibit the CYP3A4 enzyme. Rolapitant has also been studied for the prevention of postoperative nausea and vomiting with promising results.

Chemotherapy-induced nausea and vomiting is more common in female patients, younger patients, and patients with a high pretreatment expectation of experiencing severe nausea; treatment-related factors, such as the specific agent used and the dosage of the antineoplastic medication, are also causes to consider. Agents with the highest risk of nausea and vomiting include cisplatin and high doses of cyclophosphamide, while lower doses of cyclophosphamide and carboplatin, among others, are considered

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Agents used in the treatment of chemotherapy-induced nausea and vomiting include 5-HT<sub>3</sub> receptor antagonists (eg, ondansetron), NK<sub>1</sub> receptor antagonists (eg, rolapitant), corticosteroids (eg, dexamethasone), dopamine receptor antagonists (eg, metoclopramide, prochlorperazine, olanzapine), and cannabinoids (eg, dronabinol, nabilone), as well as multiple other agents, including first-generation antihistamines.\textsuperscript{11-14}

### CLINICAL PHARMACOLOGY

Rolaapitant is a small molecule that can cross the blood-brain barrier and shows a strong affinity for the substance P/NK<sub>1</sub> receptor when compared to the NK<sub>2</sub> and NK<sub>3</sub> receptors; rolapitant did not show affinity for any other receptor, transporter, enzyme, and/or ion channel tested.\textsuperscript{1,15}

### PHARMACOKINETICS

Following a single oral dose of rolapitant 180 mg while fasting, measurable concentrations were observed 30 minutes post dose and maximum concentration (C<sub>max</sub>) of 968 ng/mL was reached 4 hours post dose; administration with a high-fat meal did not affect rolapitant pharmacokinetics. The area under the curve (AUC) and C<sub>max</sub> were both noted to increase in a dose-proportional manner after doses of 4.5 to 180 mg were tested. After multiple doses of rolapitant (9 to 45 mg), accumulation was approximately 5-fold.\textsuperscript{1}

Rolaapitant is 99.8\% bound to human plasma, with an apparent volume of distribution of 387 L in patients with cancer. The apparent volume of distribution for healthy patients is 460 L.\textsuperscript{1}

Rolaapitant is metabolized by the cytochrome P450 (CYP-450) 3A4 pathway to the active metabolite M19. The formation of M19 is delayed, with a time to maximum concentration (T<sub>max</sub>) of approximately 120 hours (range, 24 to 168 hours). The half-life of rolapitant is 169 to 183 hours and the half-life of M19 is 158 hours. Rolaapitant’s clearance is 0.96 L/h in patients with cancer.\textsuperscript{1}

### Table 1. Comparison of orally administered substance P/NK<sub>1</sub> receptor antagonists

<table>
<thead>
<tr>
<th>Brand name (manufacturer)</th>
<th>Rolapitant&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Aprepitant&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Netupitant/Palonosetron&lt;sup&gt;4&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Varubi (Tesaro, Inc.)</td>
<td>Prevention of delayed nausea and vomiting associated with the use of cancer chemotherapy agents, used in combination with other antiemetic agents</td>
<td>Prevention of acute and delayed chemotherapy-induced nausea and vomiting, used in combination with other antiemetic agents</td>
<td>Prevention of postoperative nausea and vomiting</td>
</tr>
<tr>
<td>Emend (Merck Sharp &amp; Dohme)</td>
<td>180 mg administered 1 to 2 hours prior to chemotherapy (with dexamethasone or a 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist)</td>
<td>125 mg on day 1 administered 1 hour prior to chemotherapy, followed by 80 mg on days 2 and 3 (with dexamethasone and a 5-HT&lt;sub&gt;3&lt;/sub&gt; receptor antagonist administered on day 1, and dexamethasone administered on days 2, 3, and 4); if no chemotherapy is given on days 2 and 3, aprepitant should be administered in the morning</td>
<td>Netupitant 300 mg/palonosetron 0.5 mg fixed-dose combination capsule administered 1 hour prior to chemotherapy (with dexamethasone)</td>
</tr>
<tr>
<td>Akynzeo (Eisai, Inc.)</td>
<td>Prevention of delayed nausea and vomiting associated with emetogenic cancer chemotherapy agents</td>
<td>Prevention of acute and delayed nausea and vomiting associated with emetogenic cancer chemotherapy agents</td>
<td></td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>169 to 183 hours</td>
<td>9 to 13 hours</td>
<td>96 hours</td>
</tr>
<tr>
<td><strong>Mean NK&lt;sub&gt;1&lt;/sub&gt; receptor occupancy</strong></td>
<td>73% at 120 hours after administration of a single dose of 180 mg</td>
<td>&gt; 95% at 24 hours, with a serum concentration of 500 ng/mL</td>
<td>76% at 96 hours after administration of a single dose of netupitant 300 mg</td>
</tr>
</tbody>
</table>

\textsuperscript{1}to have moderate emetogenic potential.\textsuperscript{11}
Elimination of rolapitant is primarily through the hepatobiliary tract, with 14.2% and 73% excreted unchanged in the urine and feces, respectively, over 6 weeks.\(^1\)

Age, gender, and race do not significantly influence the pharmacokinetics of rolapitant. No major pharmacokinetic differences were noted in patients with mild to moderate hepatic and/or renal dysfunction, but pharmacokinetics were not studied in patients with severe impairment.\(^1\)

Rolaipitant inhibits the calcium efflux induced by GR73632, a tachykinin NK\(_1\) receptor agonist, and has no effect on basal calcium flux in ferrets.\(^15\)

**COMPARATIVE EFFICACY**

**Indications: Chemotherapy-Induced Nausea and Vomiting**

**Guideline**

**Guideline:** Antiemetics: American Society of Clinical Oncology clinical practice guideline update

**Reference:** Basch, et al, 2011\(^13\)

**Comments:** The optimal regimen of antiemetic agents (a 5-HT\(_3\) receptor antagonist on day 1 only, an NK\(_1\) receptor antagonist on day 1 or days 1 through 3 [depending on the specific NK\(_1\) receptor antagonist selected], and dexamethasone on days 1 through 3 or days 1 through 4) should be coadministered with highly emetogenic chemotherapy. Moderately emetogenic chemotherapy should be preceded by a drug combination consisting of palonosetron on day 1 and dexamethasone on days 1 through 3; if palonosetron is not available, a first-generation 5-HT\(_3\) receptor antagonist, preferably granisetron or ondansetron, can be substituted. Patients at low emetic risk due to their chemotherapy regimens should be administered a single dose of dexamethasone before receiving antineoplastic medication. An antiemetic is not required for patients administered chemotherapy of minimal emetogenic risk. Lorazepam and diphenhydramine are used as adjuncts in chemotherapy-induced nausea and vomiting but are not recommended as single-agent antiemetics. If these agents are unsuccessful in treating nausea and vomiting, the addition of lorazepam or alprazolam may be considered; substituting high-dose intravenous (IV) metoclopramide for the 5-HT\(_3\) antagonist or adding olanzapine or a dopamine-blocking agent to the regimen may also be considered.

**Guideline:** Guideline update for Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) in the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting: Results of the Perugia Consensus

**Reference:** Roila F, et al, 2010\(^12\)

**Comments:** Patients undergoing treatment with highly emetogenic cancer chemotherapy should be treated with the following antiemetic regimen: a 5-HT\(_3\) receptor antagonist (eg, ondansetron, granisetron, tropisetron, dolasetron) on day 1, an NK\(_1\) receptor antagonist (eg, aprepitant, IV fosaprepitant) on days 1 through 3, and dexamethasone on days 1 through 4. Patients receiving moderately emetogenic cancer chemotherapy consisting of an anthracycline with cyclophosphamide should be treated with a 5-HT\(_3\) receptor antagonist with dexamethasone on day 1 and an NK\(_1\) receptor antagonist on days 1 through 3; in patients receiving non-anthracycline plus cyclophosphamide–based regimens, the 5-HT\(_3\) receptor antagonist palonosetron should be given on day 1, with dexamethasone administered on days 1 through 3. Patients receiving chemotherapy with low emetogenic potential should be treated with a single antiemetic, such as dexamethasone, a 5-HT\(_3\) receptor antagonist, or a dopamine receptor antagonist on day 1. Cancer chemotherapy with minimal emetogenic potential requires no regular treatment unless desired by the patient.

**Guideline:** Nausea and vomiting – for health professionals (Physician Data Query [PDQ])

**Reference:** National Cancer Institute\(^14\)

**Comments:** Many agents have been proven effective in the treatment of chemotherapy-induced nausea and vomiting. Many modulate their effects via the dopamine receptor, including phenothiazines (eg, prochlorperazine), butyrophenones (eg, droperidol), and dopamine D\(_2\) receptor antagonists (eg, metoclopramide, olanzapine). In addition, 5-HT\(_3\) receptor antagonists (eg, ondansetron, granisetron, dolasetron, palonosetron) are effective in controlling chemotherapy-induced nausea and vomiting. Dexamethasone is often the treatment of choice for chemotherapy-induced nausea and vomiting. Substance P/NK\(_1\) receptor antagonists (eg, aprepitant), have been effective as add-on therapy to 5-HT\(_3\) receptor antagonists and/or dexamethasone. Other
agents with data supporting their use as adjuvants include the benzodiazepine lorazepam and cannabinoids (eg, dronabinol, nabilone). There are also unsubstantiated claims of ginger helping to control chemotherapy-induced nausea and vomiting.

**Studies**

**Drug:** Rolapitant vs Placebo  
**Reference:** Rapoport B, et al, 2015

**Study Design:** Randomized, double-blind, placebo-/active-controlled pivotal dose-ranging phase 2 trial  
**Study Funding:** Schering-Plough & Tesaro, Inc.

**Patients:** Adults (older than 18 years) with a Karnofsky performance status score of 60 or greater and life expectancy of 3 months or longer. Patients also were required to have adequate kidney and liver function. Patients were scheduled to receive highly emetogenic cisplatin-based chemotherapy (at least 70 mg/m²). Exclusions included previous use of cisplatin-based chemotherapy, a 5-HT₃ receptor antagonist, or an NK₁-receptor antagonist; or current long-term use of glucocorticoids (ie, prednisone 10 mg/day or more) or any other medication that could interfere with the study results. Other exclusions included systemic glucocorticoid use within 72 hours of day 1 of the study period, except when used as premedication for taxane-based chemotherapy. Individuals scheduled to receive radiation therapy to the abdomen or pelvis on days 5 or 6 were not included. A total of 454 patients were randomized, with 416 completing cycle 1.

**Intervention:** Patients were randomized to receive rolapitant 9 mg (n = 91), 22.5 mg (n = 91), 90 mg (n = 91), or 180 mg (n = 90) or placebo (n = 91) 2 hours prior to their first dose of chemotherapy. All patients also received IV ondansetron 32 mg plus oral dexamethasone 20 mg 30 minutes prior to treatment (active control). Dexamethasone 8 mg orally twice daily was also administered to patients on days 2, 3, and 4. Patients were allowed to continue their antiemetic treatment regimen for a total of 5 cycles of chemotherapy. Rescue medication was allowed at the discretion of the investigator; if the patient required rescue medication during the first cycle, they were considered to have a failed complete response but were allowed to continue the trial. Patient diaries were used to record individual visual analog scale scores for nausea and vomiting during cycle 1, and the Functional Living Index-Emesis (FLIE) questionnaire was used to measure quality of life.

**Results**

**Primary Endpoint(s)**
- Complete response during cycle 1 of chemotherapy: Rolapitant 180 mg (62.5%) resulted in more complete responses than the active control plus placebo arm (46.7%) (P = .032; number needed to treat [NNT] = 6.3).

**Secondary Endpoint(s)**
- Complete response during the acute phase of cycle 1 of chemotherapy: Rolapitant 180 mg (87.6%) resulted in more complete responses than active control plus placebo (66.7%) (P = .001; NNT = 4.8).
- Complete response during the delayed phase of cycle 1 of chemotherapy: Rolapitant 180 mg resulted in more complete responses (63.6%) than active control plus placebo (48.9%) (P = .045; NNT = 6.8).

**Endpoint(s)**
- No emesis in the overall, acute, and delayed phases: Rolapitant 90 mg had an impact on overall and delayed phases, while the 180 mg dose had an impact on all 3 phases compared with active control plus placebo.
- No nausea in the overall, acute, and delayed phases: Rolapitant 180 mg had an impact on all 3 time frames tested compared with the active control plus placebo arm.
- Time to first emetic episode or rescue medication: There was a longer time to emesis or needed rescue medication in the rolapitant 180 mg arm compared with the active control plus placebo arm. The Kaplan-Meier curves for the 2 arms separated at 6 hours.
- Complete protection (no emesis, no use of rescue medication, and no significant nausea): A greater number of patients had complete protection in the 180 mg arm compared with the active control plus placebo arm.
- Patient-reported quality of life: Rolapitant 90 and 180 mg demonstrated improvements compared with the active control plus placebo arm.
- Impact on daily life: Rolapitant 90 and 180 mg arms had a positive effect compared with the active control plus placebo arm.

**Comments:** The effects of rolapitant plus active control medications were better than those of active control medications plus placebo. The study
was stratified by gender and concurrent emetogenic chemotherapy. The authors analyzed these data via a modified intention-to-treat (mITT) analysis of randomized patients who had received at least 1 cycle of chemotherapeutic medication plus 1 dose of study medication (either rolapitant or placebo); patients were also required to have 1 posttreatment data point for inclusion. Treatment-related adverse events were generally mild, including constipation, headache, fatigue, and dizziness; serious adverse events were related to chemotherapy or disease progression. The analysis was made using a stepwise approach, moving from primary to secondary and other endpoints; only the 180 mg dose was significant for the primary outcome, so other dosages were reported for informational use only.

Limitations: The trial used a mITT, rather than ITT, approach for analysis.

Drug: Rolapitant 180 mg vs Placebo


Study Design: Two randomized, double-blind, placebo-controlled, multicenter, multinational, phase 3 studies

Study Funding: Tesaro, Inc.

Patients: 1,087 patients 18 years and older with a Karnofsky performance score of 60 or higher and a predicted life expectancy of 4 months or longer. Patients were required to have adequate bone marrow, kidney, and liver function. All patients naive to cisplatin therapy were scheduled to receive a cisplatin-based cancer chemotherapy regimen (dose of 60 mg/m2 or greater). Women of childbearing potential were required to use a medically accepted contraceptive method before treatment and for up to 30 days after study completion. Patients were excluded if they were currently on a cancer chemotherapy regimen; had a medical history of any uncontrolled disorder other than the malignant disease; had a contraindication to the use of cisplatin, dexamethasone, or granisetron; or were receiving multiple days of cisplatin or had previously used cisplatin. Patients scheduled to receive highly emetogenic chemotherapy, other than on day 1, were excluded, as were those scheduled to receive radiation therapy on the abdomen or pelvis. Female patients who were pregnant or breastfeeding were also not included. Other exclusion criteria included nausea, vomiting, and/or retching before treatment began; central nervous system (CNS) metastatic disease; use of an investigational product within 30 days of randomization; and participation in another clinical trial. In the HEC-1 trial, 532 patients were randomized to treatment, with an mITT population of 526 patients (rolapitant, n = 264; active control plus placebo, n = 262); in the HEC-2 trial, 555 patients were randomized, with an mITT population of 544 patients (rolapitant, n = 271; active control plus placebo, n = 273). Patients were recruited from North, Central, and South America; Europe; Asia; and Africa.

Intervention: Patients were randomized to rolapitant plus active control, or placebo plus active control in a 1:1 ratio, with stratification by gender. Patients were administered rolapitant 180 mg or placebo 1 to 2 hours prior to receiving chemotherapy on day 1; dexamethasone 8 mg orally twice daily was administered on days 2 through 4, while in patients also receiving taxanes, dexamethasone was dosed according to the prescribing information. Chemotherapy cycles lasted at least 14 days; the investigator could order rescue medication at any time or withdraw the patient and allow him or her to use aprepitant. Patients could be included for up to 5 additional cycles regardless of their outcome after cycle 1. Medications prohibited within 48 hours of starting treatment included other 5-HT3 receptor antagonists (palonosetron was not allowed within 7 days of treatment), phenothiazines, benzamides, domperidone, cannabinoids, other NK1 receptor antagonists, and benzodiazepines. Systemic glucocorticoids or sedative antihistamines were not allowed within 72 hours of day 1 of chemotherapy, except as needed as premedication for the antineoplastic medication(s).

Results

Primary Endpoint(s)

• Proportion of patients achieving a complete response in the delayed phase: A significantly greater proportion of patients receiving rolapitant had a complete response compared with placebo.

○ HEC-1: 73% in the rolapitant arm and 58% in the placebo arm (odds ratio [OR], 1.9; 95% confidence interval [CI], 1.3 to 2.7; P < .001; NNT = 6.7).
• HEC-2: 70% in the rolapitant arm and 62% in the placebo group (OR, 1.4; 95% CI, 1 to 2.1; \( P = .0426 \); NNT = 12.5).
• Pooled: 71% in the rolapitant arm compared with 60% in the placebo group (OR, 1.6; 95% CI, 1.3 to 2.1; \( P < .001 \); NNT = 9.1).

Secondary Endpoint(s)
• Proportion of patients achieving complete response in the overall phase: In the HEC-1 and pooled studies, more patients achieved a complete response with rolapitant compared with placebo.
• Proportion of patients achieving complete response in the acute phase: In the HEC-1 and pooled data analysis, more patients in the rolapitant arm had a complete response compared with placebo.
• No emesis in the acute, delayed, and overall phases (120-hour period): In the HEC-1 and pooled studies, more patients did not experience vomiting in the rolapitant arm compared with the placebo arm.
• No clinically significant nausea in the overall phase: More patients did not experience significant nausea when administered rolapitant compared with placebo.
• Time to first emesis: There was a delay in the group receiving rolapitant, starting in the acute phase and carryng over to the delayed phase.
• Time to first rescue medication: There was a delay with rolapitant, starting in the acute phase and carrying over to the delayed phase.

Endpoint(s)
• No clinically significant nausea in the acute and delayed phases: In the HEC-1 and pooled studies, more patients in the rolapitant arm did not have significant nausea compared with placebo.
• Complete protection: In the HEC-1 study, as well as the pooled trials, more patients experienced complete protection with rolapitant compared with placebo.

Comments: The protocol was designed in 2010 prior to the change in the guidelines that suggested addition of an NK\(_3\) receptor antagonist to a 5-HT\(_3\) receptor antagonist and dexamethasone. HEC-1 enrolled a higher percentage of subjects from North America and patients with ovarian cancer than did HEC-2, which included higher proportions of lung and gastric cancers. More males than females were included in both trials (63%), and the most common tumor site was the lung. The use of taxanes was evenly distributed between the rolapitant and placebo groups, while the median follow-up time was 2 versus 3 cycles for rolapitant and placebo, respectively, in the HEC-1 trial, and 3 cycles for both rolapitant and placebo in the HEC-2 trial. In the rolapitant arm, more patients experiencing a response in the acute phase continued to respond in the delayed phase compared with those administered placebo (HEC-1, NNT = 14.3; HEC-2, NNT = 20). Also, more patients in the rolapitant arm who did not have a response in the acute phase experienced a response in the delayed phase (HEC-1 and HEC-2, NNT = 11.1) compared with those receiving placebo. No differences in quality of life were reported. The most common adverse events included dyspepsia, headache, constipation, and hiccups.

Limitations: The difference in results between the 2 studies may be related to gender, tumor site, chemotherapy regimen, and when and/or where the studies were conducted. The study did not report differences in patient quality of life with rolapitant.


Study Design: Randomized, double-blind, placebo-controlled, multicenter, multinational phase 3 study

Study Funding: Tesaro, Inc.

Patients: 1,369 patients 18 years and older with a Karnofsky performance score of at least 60 and a life expectancy of 4 months or longer. Patients also needed to have adequate bone marrow, liver, and kidney function. Patients were scheduled to receive IV cyclophosphamide, doxorubicin, epirubicin, idarubicin, carboplatin, ifosfamide, irinotecan, daunorubicin, or IV cytarabine. Patients were excluded if they had received moderately to highly emetogenic cancer chemotherapy in the past. Other key exclusion criteria included history of uncontrolled disorder of any kind other than the malignant disease; contraindications to chemotherapy, granisetron, or dexamethasone; pregnancy and/or breast-feeding; CNS metastasis; ongoing nausea, retching, or anticipatory nausea and/or vomiting; use of any investigational medication within 30 days of randomization; or participation in another clinical trial. Patients were randomized to rolapitant \((n = 684)\) or placebo \((n = 685)\), both with active control. The mITT population consisted of 666 patients in both arms.

Intervention: Patients were randomized in a 1:1 ratio to receive rolapitant 180 mg or a matching placebo 1 to 2 hours prior to the first dose of moderately
emetogenic chemotherapy (cycle 1). All patients also received granisetron 2 mg orally and dexamethasone 20 mg orally about 30 minutes prior to the chemotherapy dose, then granisetron 2 mg orally once daily on days 2 and 3. Patients scheduled to receive a taxane-based chemotherapy regimen received dexamethasone (dosing based on the taxane product labeling). Rescue medication could be used at any time or patients could be withdrawn from the study if medically necessary. All cycles of chemotherapy had to be at least 14 days and could be continued for up to 5 additional cycles. Medications prohibited for 48 hours prior to chemotherapy included other 5-HT₃ receptor antagonists (except palonosetron, which was not allowed within 7 days), other NK₁ receptor antagonists, phenothiazines, benzamides, domperidone, cannabinoids, and benzodiazepines. Systemic corticosteroids or sedative antihistamines were not allowed within 72 hours except as premedication for chemotherapy.

Results

Primary Endpoint(s)
- Proportion of patients achieving complete response in the delayed phase: 71% of patients assigned to the rolapitant arm compared with 62% in the placebo arm (OR, 1.6; 95% CI, 1.2 to 2; P < .001; NNT = 11.1).

Secondary Endpoint(s)
- Proportion of patients achieving complete response in the acute phase: No difference was noted between patients using rolapitant and those receiving placebo.
- Proportion of patients achieving complete response in the overall phase: 69% in the rolapitant arm compared with 58% in the placebo arm (OR, 1.6; 95% CI, 1.3 to 2; P < .001; NNT = 9.1).
- No emesis in the acute, delayed, or overall phases: More patients in the rolapitant arm did not experience emesis compared with those in the placebo arm (NNT = 7.1).
- Time to first emesis or use of rescue medication: Via Kaplan-Meier curves, differences were evident between the 2 groups, favoring rolapitant, in both the acute phase (12 to 24 hours) and delayed phase (24 to 120 hours) (P < .001 for between-group comparison).

Endpoint(s)
- Complete protection: More patients in the rolapitant arm than those in the placebo had complete protection (NNT = 11.1).

Comments: Study sites included North, Central, and South America; Europe; Asia; and Africa. All endpoints were evaluated in a stepwise manner; after a nonsignificant finding, all information was used for informational purposes. Most patients included in the study were women, with breast cancer being the most common cancer. The use of taxane-based chemotherapy was evenly spread throughout the groups and very few of the patients had developed nausea and/or vomiting with their previous regimen. Patients in the rolapitant arm who did not receive rescue medications by 48 hours were less likely to need any compared with those administered placebo. More patients in the rolapitant arm than the placebo arm reported that chemotherapy had no impact on their daily life (NNT = 16.7).

Limitations: Multiple endpoints were not addressed and are not included in the Clinicaltrials.gov report for this study. Improvement in patient quality of life was also not reported.

CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS

Contraindications

Use is contraindicated in patients taking thioridazine; CYP2D6 inhibition can cause an unsafe increase in thioridazine plasma concentrations, which may result in prolongation of the QT interval as well as torsades de pointes.¹ Though not stated in the product labeling, previous hypersensitivity reactions to rolapitant or any of its inactive ingredients should be considered (lactose monohydrate, pregelatinized starch, microcrystalline cellulose, povidone, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, FD&C Blue No. 2, Indigo Carmine Lake, and polysorbate 80).¹

Warnings and Precautions

Rolaipant should be used with caution in patients taking a medication metabolized by the CYP2D6 pathway that may have a narrow therapeutic window (eg, pimozide).¹ Concurrent use with pimozide can lead to QT segment prolongation and possibly torsades de pointes; thus this combination should be avoided.¹

There are no data regarding the use of rolapitant during pregnancy. However, when used in rats and
rabbits at dosages 1.2 to 2.9 times the recommended human dose, there was no evidence of teratogenicity or other embryofetal effects. Rolapitant should be used with caution during pregnancy and only if the benefits outweigh the risks.  

There are no data regarding the presence of rolapitant in human breast milk, but rolapitant was present in the milk of lactating rats. Use in breastfeeding women is not recommended.

The safety and effectiveness of rolapitant in pediatric patients has not been established. Required pediatric studies are not due until August 2026.

In clinical studies, 25% of subjects were older than 65 years, while 5% were 75 years of age or older. There were no differences in the safety and/or efficacy of the medication, so no change in dose is warranted, but a greater sensitivity in this population cannot be ruled out.

See Table 2 for a comparison of contraindications, warnings, and precautions associated with substance P/NK₁-receptor antagonists.

**ADVERSE REACTIONS**

In patients undergoing highly emetogenic chemotherapy, the most common adverse reactions seen in more than 3% of the rolapitant study population and at a higher rate than placebo included neutropenia (9%), hiccups (5%), and abdominal pain (3%). Those receiving moderately emetogenic chemotherapy and rolapitant experienced decreased appetite (9%), neutropenia (7%), dizziness (6%), dyspepsia (4%), urinary tract infections (4%), stomatitis (4%), and anemia (3%).

### Table 2. Comparison of contraindications, warnings, and precautions associated with substance P/NK₁ receptor antagonists

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Rolapitant¹</th>
<th>Aprepitant²</th>
<th>Netupitant/Palonosetron³</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hypersensitivity to drug or other product ingredients</td>
<td>X²</td>
<td>X</td>
<td>X¹</td>
</tr>
<tr>
<td>Coadministration with pimozide</td>
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<tr>
<td>Coadministration with thioridazine</td>
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<table>
<thead>
<tr>
<th>Warnings and precautions</th>
<th>Rolapitant¹</th>
<th>Aprepitant²</th>
<th>Netupitant/Palonosetron³</th>
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</thead>
<tbody>
<tr>
<td>Coadministration with CYP2D6 substrates with a narrow therapeutic index</td>
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<td></td>
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<tr>
<td>Coadministration with pimozide</td>
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<td></td>
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<tr>
<td>Hypersensitivity to other 5-HT₁ receptor antagonists</td>
<td>X¹</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Serotonin syndrome</td>
<td>X¹</td>
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<td>X</td>
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<tr>
<td>Coadministration with CYP3A4 substrates</td>
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</tr>
<tr>
<td>Coadministration with CYP3A4 inhibitors (eg, ketoconazole, diltiazem)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coadministration with CYP3A4 inducers (eg, rifampin)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coadministration with warfarin</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Coadministration with hormonal contraceptives</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pediatric patients</td>
<td>Not established</td>
<td>Safety and effectiveness established for patients 6 months of age and older</td>
<td>Not established</td>
</tr>
</tbody>
</table>

*Note: NK₁ = neurokinin-1.*

¹Contraindications, warnings, and precautions of other drugs used in combination with these drugs should also be considered.

²Not contained in the product labeling, but should be considered.

³Used in combination with a 5-HT₁ receptor antagonist.
A comparison of the adverse reactions associated with the various substance P/NK₁ receptor antagonists is not possible because of differences (e.g., diseases, drug therapies) in the study populations.

**DRUG INTERACTIONS**

Rolapitant is a moderate CYP2D6 inhibitor and an inhibitor of P-glycoprotein (P-gp) and BCRP.¹

A 3-fold increase in dextromethorphan exposure was observed 7 days after administration of a single dose of rolapitant with dextromethorphan (a CYP2D6 substrate). Concurrent use of thioridazine or pimozide with rolapitant is not recommended because of the increased risk of QT segment prolongation. All CYP2D6 substrates administered with rolapitant should be monitored.¹

Digoxin (a P-gp substrate) levels should be monitored when given concurrently with rolapitant.¹

All BCRP substrates, such as methotrexate, topotecan, and irinotecan, should be monitored when given concomitantly with rolapitant. The lowest effective dosage of rosuvastatin should be used when coadministered with rolapitant.¹

Strong CYP3A4 inducers, such as rifampin, significantly reduce the plasma concentrations of rolapitant and may decrease its efficacy; rolapitant should be avoided in patients who require chronic CYP3A4 inducers.¹

See Table 3 for a comparison of the drug interactions associated with substance P/NK₁ receptor antagonists.¹,²,³

**RECOMMENDED MONITORING**

There is no recommended monitoring for rolapitant.¹

**DOsing**

Rolapitant should be administered with a 5-HT₃ receptor antagonist and dexamethasone (see Table 4) approximately 1 to 2 hours prior to chemotherapy.¹ The dose can be given without regard to meals.¹

There is no dosage adjustment required for patients with mild or moderate hepatic disease (Child-Pugh class A or B). Rolapitant should only be used in patients with severe hepatic dysfunction (Child-Pugh class C) if no other options exist and under closely monitored parameters. Patients with

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**Table 3. Comparison of the drug interactions** associated with substance P/NK₁ receptor antagonists

<table>
<thead>
<tr>
<th>Substances</th>
<th>Rolapitant¹</th>
<th>Aprepitant⁷</th>
<th>Netupitant/Palonosetron⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCRP substrates (e.g., methotrexate, irinotecan, topotecan)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP2D6 substrates</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Strong CYP3A4 inducers (rifampin)</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CYP3A4 inhibitors (e.g., ketoconazole, diltiazem)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYP3A4 substrates (e.g., midazolam, alprazolam, triazolam, docetaxel, paclitaxel, etoposide, irinotecan, cyclophosphamide, ifosfamide, imatinib, vinorelbine, vinblastine, vincristine)</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Digoxin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-gp substrates</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pimozide</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonergic drugs</td>
<td>X²</td>
<td>X³</td>
<td>X</td>
</tr>
<tr>
<td>Thioridazine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

Note: NK₁ = neurokinin-1.

¹Drug interactions with other drugs used in combination with these drugs should be considered.
moderate hepatic dysfunction had a 25% reduction in C\textsubscript{max} while the T\textsubscript{max} for M19 was delayed 204 hours compared with 168 hours in healthy subjects.\textsuperscript{1}

No changes in dosing are needed in patients with mild to moderate renal dysfunction, although rolapitant was not studied in individuals with a creatinine clearance of less than 30 mL/min.\textsuperscript{1}

**PRODUCT AVAILABILITY**

Roplapitant was approved by the FDA on September 1, 2015.\textsuperscript{2} It is available as a 90 mg film-coated blue tablet with “T0101” imprinted on one side and “100” on the other.\textsuperscript{1} The product is packaged as a single-dose foil blister pack containing 2 tablets as one set of twinned blisters.\textsuperscript{1}

The product should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted to between 15°C and 30°C (59°F and 86°F).\textsuperscript{1}

**DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS)**

No REMS is required for rolapitant.\textsuperscript{2}

**CONCLUSION**

Roplapitant appears to be a useful agent in treating the delayed phase of chemotherapy-induced nausea and/or vomiting. Roplapitant is taken once on day 1 of chemotherapy and then repeated on day 1 of treatment with additional cycles. Comparable agents in this class of drugs require multiple days of dosing or use a fixed-dose combination capsule with a 5-HT\textsubscript{3} receptor antagonist. Roplapitant’s half-life, affinity for the NK\textsubscript{1} receptor, and dosing schedule make it a useful option, but its narrow indication and required use in combination with 2 other medications make it less convenient.

**REFERENCES**


7. Emend (aprepitant) [prescribing information]. Whitehouse Station, NJ: Merck & Dohme; August 2015.


Continuing Education Case Study Quiz

Goal—The goal of this activity is to educate pharmacists about the use of rolapitant in the treatment of patients with chemotherapy-induced nausea and vomiting.

Objectives—At the completion of this activity, the reader will be able to:
1. Describe the pharmacology and pharmacokinetics of rolapitant.
2. Discuss the risks associated with the use of rolapitant.
3. Discuss the potential benefit of rolapitant for an individual patient.
4. Apply the information on the use of rolapitant to a case study.

Key Words—rolapitant, chemotherapy-induced nausea and vomiting, new drugs

This CE activity is jointly provided by ProCE, Inc. and Hospital Pharmacy. ProCE, Inc. is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. ACPE Universal Activity Number 0221-9999-16-003-H01-P has been assigned to this knowledge-based home-study CE activity (initial release date 02-01-2016). This CE activity is approved for 1.5 contact hours (0.15 CEUs) in states that recognize ACPE providers. This CE activity is provided at no cost to participants. Completion of the evaluation and the post-test with a score of 70% or higher are required to receive CE credit. No partial credit will be given.

Faculty: Dennis J. Cada, PharmD, FASHP, FASCP (Editor), Founder and Contributing Editor, The Formulary; Ross Bindler, PharmD, Drug Information Resident, College of Pharmacy, Washington State University, and Danial E. Baker, PharmD, FASHP, FASCP, Director, Drug Information Center, and Professor of Pharmacy Practice, College of Pharmacy, Washington State University. The authors indicate no relationships that could be perceived as a conflict of interest. This activity is self-funded by Hospital Pharmacy.

Release Date: February 1, 2016
Expiration Date: February 1, 2018

Continuing Education for this activity is processed through the ProCE online CE Center. To receive CE credit, please go to:

1. Rolapitant is an antiemetic that was approved by the US Food and Drug Administration (FDA) for the prevention of which phase of chemotherapy-induced nausea and vomiting?
   A. Initial phase
   B. Delayed phase
   C. Initial and delayed phases
   D. Initial, delayed and latent phases

2. Which one of the following receptors located within the blood-brain barrier does rolapitant have the strongest affinity for?
   A. Serotonin3-receptor
   B. Neurokinin1-receptor
   C. Neurokinin2-receptor
   D. Neurokinin3-receptor

3. Which one of the following compounds is the active metabolite of rolapitant?
   A. M19
   B. M20
   C. GR73632
   D. Rolapitant does not have an active metabolite.
Case History

O.G. is a 67-year-old male who weighs 87.9 kg and has been diagnosed with a solid cell malignant tumor in his lung; after histological evaluation, it is discovered to be a combined small cell lung cancer (cSCLC). He is currently cisplatin-naïve, but is scheduled to receive a cisplatin-based highly emetogenic regimen starting tomorrow morning. He will be receiving 60 mg/m$^2$ of cisplatin on day 1 plus 60 mg/m$^2$ of irinotecan on days 1, 8, and 15. His Karnofsky performance score is above 60 and his life expectancy is longer than 4 months, making him a candidate for treatment with rolapitant. Currently he is taking hydrocodone/acetaminophen and over-the-counter (OTC) ibuprofen for his intense pain and also has standing orders entered for ondansetron and dexamethasone for prophylaxis of nausea and vomiting. He has not been able to quit smoking and has a total of 33 pack years.

4. What is the most common adverse reaction observed during use of rolapitant in patients undergoing highly emetogenic cancer chemotherapy?
   A. Decreased appetite
   B. Dizziness
   C. Abdominal pain
   D. Neutropenia

5. Which one of the following medications should be used with caution while utilizing rolapitant?
   A. Alprazolam
   B. Diltiazem
   C. Digoxin
   D. Dexamethasone

6. Which of the following is considered a contraindication to the use of rolapitant?
   A. Concurrent use of pimozide
   B. Concurrent use of thioridazine
   C. Concurrent use of CYP3A4 inhibitors
   D. Concurrent use of CYP3A4 substrates

7. What is the recommended starting dose and schedule for initiating rolapitant therapy in a patient undergoing cancer chemotherapy with a highly emetogenic regimen including cisplatin?
   A. One 180 mg tablet by mouth 1 to 2 hours prior to the start of chemotherapy on day 1 of treatment
   B. Two 90 mg tablets by mouth 1 to 2 hours prior to the start of chemotherapy on day 1 of treatment
   C. One 180 mg tablet by mouth 1 to 2 hours prior to the start of chemotherapy on days 1, 2, and 3 of treatment
   D. Two 90 mg tablets by mouth 1 to 2 hours prior to the start of chemotherapy on days 1, 2, and 3 of treatment

8. Which of the following is NOT an advantage of rolapitant when compared to other NK$_1$-receptor antagonists?
   A. Being highly protein bound in human plasma
   B. Having greater affinity for the NK$_1$-receptor than other agents
   C. Having a longer half-life than other NK$_1$-receptor antagonists
   D. Having fewer drug-drug interactions due to CYP3A4 effects

9. Which one of the following is the correct dose of dexamethasone that O.G. should receive with rolapitant based on his chemotherapeutic regimen?
   A. 8 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
   B. 16 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
   C. 20 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
   D. 20 mg by mouth 30 minutes prior to chemotherapy on day 1 and 8 mg on days 2, 3, and 4

10. Due to O.G.’s older age, he is worried about how the medication will affect his body. What are the pharmacokinetic differences of rolapitant when compared to a person under the age of 65 years old?
    A. The area under the curve of rolapitant will be higher in O.G. than a younger patient.
    B. The maximum concentration of rolapitant will be higher in O.G.
    C. The time to maximum concentration of rolapitant will be longer in O.G.
    D. There were no age-related differences in the pharmacokinetics of rolapitant.

11. O.G. is scheduled to receive irinotecan. What pharmacokinetic interactions would result after rolapitant is added to his antineoplastic regimen?
A. Rolapitant inhibits the BCRP altering serum concentrations of irinotecan.
B. Irinotecan inhibits the BCRP resulting in altered concentrations of rolapitant.
C. Rolapitant inhibits the P-gp, which results in an altered serum concentration of irinotecan.
D. Irinotecan has variable effects on different patients, so the effect on rolapitant is unknown.

12. O.G. begins to complain about what he calls “athlete’s foot” and is then prescribed griseofulvin (a strong CYP3A4 inducer) by his primary care provider as a treatment for the irritating condition. What pharmacokinetic effects can griseofulvin have on rolapitant?
A. No pharmacokinetic interaction will occur and the serum concentration will remain consistent.
B. The metabolism of rolapitant will slow, leading to an increased plasma concentration of rolapitant.
C. The metabolism of rolapitant will increase, leading to a decreased plasma concentration of rolapitant.
D. The plasma concentration of rolapitant will remain consistent despite the potential interaction.

Case History
M.K. is a 34-year-old female who weighs 62.8 kg and has been diagnosed with node-negative breast cancer. She is currently scheduled to receive cyclophosphamide, doxorubicin, and 5-fluorouracil. Her Karnofsky performance score is above 60 and her life expectancy is longer than 4 months, which makes her candidate for treatment with rolapitant to prevent the delayed stage of chemotherapy-induced nausea and vomiting. She is currently receiving OTC ibuprofen and acetaminophen for her moderate pain and also has orders entered for granisetron and dexamethasone for the prophylaxis of nausea and vomiting.

13. What dose of rolapitant should M.K. receive?
A. One 180 mg tablet by mouth 1 to 2 hours prior to the start of chemotherapy on day 1 of treatment
B. Two 90 mg tablets by mouth 1 to 2 hours prior to the start of chemotherapy on day 1 of treatment
C. One 180 mg tablet by mouth 1 to 2 hours prior to the start of chemotherapy on days 1, 2, and 3 of treatment
D. Two 90 mg tablets by mouth 1 to 2 hours prior to the start of chemotherapy on days 1, 2, and 3 of treatment

14. What dose of dexamethasone should M.K. receive concurrently with her rolapitant and granisetron?
A. 8 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
B. 16 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
C. 20 mg by mouth 30 minutes prior to chemotherapy on day 1 of the current cycle
D. 20 mg by mouth 30 minutes prior to chemotherapy on day 1 and 8 mg on days 2, 3, and 4

15. M.K has now developed a cold and has decided to take an OTC cough suppressant that contains dextromethorphan. Taking dextromethorphan concurrently with rolapitant can cause what pharmacokinetic interaction?
A. An increase in the plasma level of rolapitant
B. An increase in the plasma level of dextromethorphan
C. A decrease in the plasma level of rolapitant
D. A decrease in the plasma level of dextromethorphan