INTRODUCTION
According to the National Institutes of Health, chemotherapy-induced nausea and vomiting (CINV) is a debilitating adverse event caused by cancer treatments that has a significant impact on a patient’s quality of life if not prevented or controlled adequately. CINV can be defined as acute, delayed, or anticipatory. Acute CINV occurs within 24 hours after chemotherapy. Delayed CINV begins 24 hours or more after chemotherapy and can last up to several days after the treatment is complete. Delayed nausea is more common than acute nausea, and it is more severe and harder to treat. Anticipatory CINV can occur in up to 25% of patients as a result of conditioning from stimuli associated with chemotherapy, usually occurring within 12 hours prior to treatment administration.

The emetogenic potential of chemotherapeutic agents varies in severity (Table 1). Highly emetogenic chemotherapy (HEC) regimens have a greater than 90% incidence of CINV. Moderately emetogenic chemotherapy (MEC) and low emetogenic chemotherapy (LEC) regimens have a 30% to 90% and 10% to 30% incidence of CINV, respectively.

It is theorized that CINV is triggered by the release of neurotransmitters, namely serotonin and substance P, from one of several pathways that activate the vomiting center in the medulla. The two pathways thought to influence CINV include one in the gastrointestinal (GI) tract and another in the chemoreceptor trigger zone. Nausea is not always followed by vomiting; other clinical manifestations that may accompany nausea include tachycardia, perspiration, light-headedness, dizziness, pallor, excess salivation, anorexia, and weakness. Many therapies are available to prevent and treat CINV via the oral (Table 2), intravenous, and transdermal routes. To prevent acute CINV, 5-hydroxytryptamine 3 (5-HT3) serotonin receptor antagonists are often administered; neurokinin-1 (NK1) receptor antagonists are used for both acute and delayed CINV. Corticosteroids, specifically methylprednisolone or dexamethasone, can be used as single agents or in combination with 5-HT3 receptor antagonists and/or NK1 receptor antagonists. Metoclopramide, chlorpromamide, and cannabinoids are recommended only when a patient is experiencing CINV that is refractory to 5-HT3 and/or NK1 receptor antagonists. Benzodiazepines may be beneficial in patients experiencing anticipatory nausea.

Table 1  Emetogenic Potential of Select Chemotherapeutic Agents

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
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<tbody>
<tr>
<td>Cisplatin</td>
<td>Oxaliplatin</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td>Cytarabine (&gt; 1 g/m²)</td>
<td>Docetaxel</td>
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<tr>
<td>Streptozocin</td>
<td>Carboplatin</td>
<td>Mitoxantrone</td>
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<tr>
<td>Cyclophosphamide (&gt; 1,500 mg/m²)</td>
<td>Irinotecan</td>
<td>Pemetrexed</td>
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<tr>
<td></td>
<td>Ifosfamide</td>
<td>Trastuzumab</td>
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<td></td>
<td>Doxorubicin</td>
<td>Methotrexate</td>
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<tr>
<td></td>
<td>Daunorubicin</td>
<td>Mitomycin C</td>
</tr>
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<td></td>
<td>Epirubicin</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td></td>
<td>Idarubicin</td>
<td>Cytarabine (&lt; 100 mg/m²)</td>
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Table 1 Emetogenic Potential of Select Chemotherapeutic Agents

The most recent National Comprehensive Cancer Network (NCCN) guidelines for antiemesis recommend the administration of a 5-HT3 antagonist in combination with an NK1 antagonist for the prevention of CINV due to HEC regimens. For the prevention of CINV due to MEC regimens, a 5-HT3 antagonist with or without an NK1 antagonist is recommended by the same guidelines.

The Food and Drug Administration (FDA) approved the first substance P/NK1 receptor antagonist, aprepitant (Emend capsules or oral suspension, Merck Sharp & Dohme Corp.), in 2003. A combination substance P/NK1 antagonist–5-HT3 antagonist (netupitant/palonosetron [Akyneze, Eisai]) was approved by the FDA in 2014. Most recently, the FDA approved the 5-HT3 antagonist rolapitant (Varubi, Tesaro) in 2015. This Drug Forecast will focus on rolapitant.

INDICATION
Rlapitant 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, HEC.
### Table 2  A Comparison of Select Treatments for CINV (Tablet/Capsule Formulations)

<table>
<thead>
<tr>
<th>Drug (Brand Name, Manufacturer)</th>
<th>Initial Approval</th>
<th>Indication(s)</th>
<th>Recommended Dosage</th>
<th>AWP per Unit$</th>
</tr>
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<tbody>
<tr>
<td><strong>Substance P/NK1 Receptor Antagonists</strong></td>
<td></td>
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</tbody>
</table>
| Aprepitanta (Emend capsules, Merck Sharp & Dohme Corp.) | 2003 | In combination with other antiemetic agents in patients 12 years of age and older for prevention of:  
- Acute and delayed nausea and vomiting associated with initial and repeat courses of HEC, including high-dose cisplatin  
- Nausea and vomiting associated with initial and repeat courses of MEC  
Also for prevention of PONV in adults only | 125 mg administered within one hour before chemotherapy on day 1  
80 mg on days 2 and 3 | $129 per 40-mg capsule  
$239 per 80-mg capsule  
$373 per 125-mg capsule |
| Rolapitant (Varubi tablets, Tesaro) | 2015 | In combination with other antiemetic agents in adults for prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC | 180 mg administered approximately one to two hours prior to chemotherapy on day 1 | $337 per 90-mg tablet |
| **5-HT\textsubscript{3} Antagonists** |                 |                                                                                |                                                                                    |               |
| Dolasetronsb (Anzemet tablets, Sanofi-Aventis) | 1997 | In adults and children 2 years of age and older for prevention of nausea and vomiting associated with MEC, including initial and repeat courses | Adults = 100 mg  
Patients 2–16 years of age = 1.8 mg/kg (maximum 100 mg)  
Administer within one hour before chemotherapy | $86 per 50-mg tablet  
$115 per 100-mg tablet |
| Granisetronc (generic tablets, multiple manufacturers) | 1995 | In adults for:  
- Nausea and vomiting associated with initial and repeat courses of emetogenic cancer therapy, including high-dose cisplatin  
- Nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation | See prescribing information of concomitant drugs for dosage and administration instructions | $7 per 1-mg tablet |
| Ondansetrond (generic tablets, multiple manufacturers) | 1992 | In patients 4 years of age and older for:  
- Nausea and vomiting associated with HEC, including cisplatin greater than or equal to 50 mg/m\textsuperscript{2}  
- Nausea and vomiting associated with initial and repeat courses of MEC  
- Nausea and vomiting associated with radiotherapy in patients receiving either total body irradiation, single high-dose fraction to the abdomen, or daily fractions to the abdomen  
- PONV | See ondansetron prescribing information for dosage and administration instructions | $25 per 4-mg tablet  
$41 per 8-mg tablet |
| **Combination Substance P/NK1 Receptor Antagonist With 5-HT\textsubscript{3} Antagonist** |                 |                                                                                |                                                                                    |               |
| Netupitant/palonosetron (Akynzeo capsules, Eisai, Inc.) | 2014 | In adults for acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC | One 300-mg netupitant/0.5-mg palonosetron capsule administered approximately one hour prior to the start of chemotherapy | $659 per capsule |

$a$ Also available in oral suspension and IV formulations  
$b$ Also available in IV formulation  
$c$ Also available in IV, ER transdermal film, and ER subcutaneous injection formulations  
$d$ Also available in oral solution, orally disintegrating tablet, oral soluble film, and IV formulations  

5-HT\textsubscript{3} = 5-hydroxytryptamine 3; AWP = average wholesale price; CINV = chemotherapy-induced nausea and vomiting; ER = extended-release; HEC = highly emetogenic chemotherapy; IV = intravenous; MEC = moderately emetogenic chemotherapy; NK1 = neurokinin-1; PONV = postoperative nausea and vomiting
MECHANISM OF ACTION
Rolapitant is a selective and competitive antagonist of human substance P/NK1 receptors with antiemetic activity. Rolapitant crosses the blood–brain barrier and occupies NK1 receptors in the brain. Substance P and NK1 receptors are present in the brain stem (medulla) centers that control the emetic reflex. Substance P is a peptide that increases the contractions of smooth GI muscles and leads to vasodilation. NK1 receptors are present on motor neurons in the stomach that are responsible for the physiological and pathological behaviors of the stomach, such as gastric relaxation, emesis, or stasis. Rolapitant does not have significant affinity for the NK2 or NK3 receptors or for a battery of other receptors, transporters, enzymes, and ion channels.

PHARMACOKINETICS
Rolapitant, which is eliminated primarily through the liver, is metabolized by cytochrome P450 (CYP) 3A4 to form the major circulating active metabolite C4-pyrrolidine-hydroxylated rolapitant (M19).

Excretion studies have shown that six weeks after a single dose of rolapitant, 14.2% and 73% of the dose was found in the urine and feces, respectively. Administration of rolapitant with a high-fat meal did not significantly affect absorption. Elimination studies revealed the half-life of rolapitant to be approximately seven days.

Age, gender, or race do not have an effect on the pharmacokinetic profile of rolapitant.

DOSAGE AND ADMINISTRATION
The recommended dosage of rolapitant is 180 mg (two 90-mg tablets) administered orally as a single dose one to two hours prior to chemotherapy. Rolapitant is indicated for use in combination with a corticosteroid (i.e., dexamethasone) and a 5-HT3 antagonist. Granisetron was the 5-HT3 antagonist utilized in all of the clinical trials of rolapitant. Rolapitant should not be given more than once every 14 days.

No dosage adjustment is necessary for patients with mild or moderate renal or hepatic impairment; however, patients with severe renal or hepatic impairment should avoid rolapitant or be closely monitored for adverse reactions.

DRUG INTERACTIONS
Based upon pharmacokinetic studies, rolapitant is a CYP3A4 substrate and a moderate inhibitor of CYP2D6, breast cancer resistance protein (BCRP) transporter, and P-glycoprotein (P-gp) transporter. Use of rolapitant should be avoided in patients taking pimozide (Orap, Teva) or thioridazine due to potential QT prolongation, which may result in torsades de pointes, a potentially fatal complication.

The CYP2D6 inhibition of rolapitant lasts at least seven days; however, it is possible that this activity lasts beyond that time frame. If CYP2D6 inhibitors cannot be avoided, patients need to be monitored for QT prolongation and adverse reactions caused by the substrate drug. The lowest effective dose of BCRP substrates (i.e., methotrexate, topotecan, rosuvastatin) and P-gp substrates (i.e., digoxin) are recommended when coadministered with rolapitant. Strong CYP3A4 inducers (i.e., rifampin) may significantly reduce the plasma concentration of rolapitant and, therefore, coadministration of rolapitant with such agents should be avoided.

ADVERSE EVENTS
Although rolapitant is well tolerated, constipation, headache, fatigue, dizziness, dyspepsia, hiccups, and neutropenia have been observed in treated patients. However, the percentage of patients reporting adverse effects in phase 3 trials did not differ significantly in the study groups compared with the control groups. One phase 3 trial reported that only 4% of patients receiving HEC discontinued rolapitant due to side effects compared with 5% in the control group. Patients receiving MEC had the same discontinuation rate when comparing the rolapitant group (2%) with the control group (2%).

The severity of neutropenia was evaluated in all phase 3 trials using a grading scale ranging from mild (grade 1) to fatal (grade 5). In patients receiving MEC or HEC and rolapitant, no grade 5 neutropenia was reported, and the percentage of patients reporting grade 3 and grade 4 neutropenia did not differ significantly between the study and control groups.

A recent retrospective meta-analysis reviewed antiemetic regimens with aprepitant, rolapitant, and netupitant/palonosetron plus a steroid and a 5-HT3 antagonist. Compared with the aprepitant regimen, rolapitant had the lowest incidence of constipation (23.9% for aprepitant versus 0.4% for rolapitant) and hiccups (35.5% versus 0.6%, respectively). There were insufficient data on the incidence of adverse effects for netupitant/palonosetron and rolapitant to make a comparative analysis.

CLINICAL TRIALS
Rolapitant’s FDA approval was based on three pivotal phase 3 clinical trials (Table 3). The primary endpoint in all three studies was complete response to therapy, defined as no emetic episodes and no need for rescue medication in the delayed phase after the initiation of chemotherapy (more than 24 hours to 120 hours). The primary endpoint results were similar in all three studies and demonstrated the statistically significant superiority of the rolapitant regimen over control therapy. Each study also had two key secondary endpoints in common: 1) the proportion of patients with complete responses in the acute phase after chemotherapy (0 to 24 hours) and 2) overall response after chemotherapy (0 to 120 hours).

HEC 1 and HEC 2 Trials
In two global, multicenter, randomized, double-blind, active-controlled clinical studies (HEC 1 and HEC 2), a rolapitant regimen (180 mg rolapitant plus granisetron and dexamethasone) was compared with control therapy (placebo plus granisetron and dexamethasone) in patients receiving a cisplatin-based chemotherapy regimen. All regimens were administered one to two hours prior to chemotherapy.

The HEC 1 study enrolled a total of 532 patients who were randomized to receive a rolapitant-containing regimen (n = 266) or control therapy (n = 266) for up to five cycles of chemotherapy. The intention to treat (ITT) efficacy evaluation included 526 patients. In this study, 82% of the patients received a concomitant chemotherapeutic agent in addition to the protocol-mandated cisplatin. Common concomitant chemotherapeutic agents included gemcitabine (17%), paclitaxel (12%), fluorouracil (11%), and docetaxel (11%).
and etoposide (10%). The mean cisplatin dose was 77 mg/m².\textsuperscript{16}

The HEC 2 trial enrolled a total of 555 patients who were randomized to either a rolapitant-containing regimen (n = 278) or control therapy (n = 277). A total of 544 patients were included in the ITT efficacy analysis. During this study, 85% of patients received a concomitant chemotherapeutic agent in addition to protocol-mandated cisplatin, including vinorelbine (16%), gemcitabine (15%), fluorouracil (12%), and etoposide (11%). The mean cisplatin dose was 76 mg/m².\textsuperscript{16}

In the pooled analysis for the HEC 1 and 2 studies, 71% of patients in the rolapitant regimen achieved the primary endpoint versus 60% for the control therapy group (odds ratio [OR], 1.6; 95% confidence interval [CI], 1.1–2.1; \( P = 0.0001 \)). In addition, in the pooled data analysis, the rolapitant regimen demonstrated superiority in both of the secondary endpoints versus control therapy (acute phase: OR, 1.6; 95% CI, 1.1–2.1; \( P = 0.0045 \); overall: OR, 1.6; 95% CI 1.2–2.0; \( P = 0.0005 \)).\textsuperscript{16}

**MEC Trial**

This multicenter, randomized, double-blind, parallel-group, active-controlled clinical study in MEC evaluated a rolapitant regimen (rolapitant plus granisetron and dexamethasone) compared with control therapy (placebo plus granisetron and dexamethasone) in patients receiving an MEC regimen that included at least 50% of patients receiving a combination of anthracycline and cyclophosphamide. A total of 1,369 patients were randomized to either the rolapitant regimen (n = 684) or control therapy (n = 685). A total of 1,332 patients were included in the ITT efficacy evaluation.\textsuperscript{15}

In the MEC study, the rolapitant regimen outperformed control therapy, with 71% of patients achieving the primary endpoint versus 62% in the control therapy arm (OR 1.6; 95% CI, 1.2–2; \( P = 0.0002 \)). The proportion of patients achieving the secondary endpoints was higher in the rolapitant therapy arm compared with the control therapy arm; however, the rolapitant therapy arm demonstrated a statistically significant difference only in overall response versus the control arm (acute phase: OR, 1.2; 95% CI, 0.9–1.6; \( P = 0.1425 \); overall: OR, 1.6; 95% CI 1.3–2.0; \( P = 0.0001 \)).\textsuperscript{15}

**COST**\textsuperscript{10}

The average wholesale prices (AWPs) per unit for rolapitant and other oral antiemetics for CINV are listed in Table 2. Rola...
and it is supplied in a two-tablet blister pack. Therefore, the recommended 180-mg dose administered to the patient on day 1 of chemotherapy results in an AWP of $674 for a single treatment. Rolapitant must be administered in conjunction with dexamethasone and a 5-HT3 antagonist, which will add minimal additional cost. Rolapitant may be administered at the start of each chemotherapy cycle.

There are two comparator agents for CINV within the same therapeutic class as rolapitant: aprepitant and netupitant/palonosetron. Each treatment may be utilized for repeat courses of chemotherapy. Aprepitant is recommended on day 1 of chemotherapy at a dosage of 125 mg (AWP $373 per capsule), and then at a dosage of 80 mg (AWP $239 per capsule) on days 2 and 3 for a total AWP of $851 per chemotherapy cycle. Like rolapitant, it is administered along with dexamethasone and a 5-HT3 antagonist. Netupitant/palonosetron is administered as a single dose on day 1 of chemotherapy and is priced comparatively with rolapitant at an AWP of $859 per capsule. It is also given along with dexamethasone.

P&T COMMITTEE CONSIDERATIONS

The discovery of substance P/NK1 receptor antagonists has led to a significant patient care breakthrough that decreases CINV incidence to less than 16% when used in combination with 5-HT3 antagonists and dexamethasone.11 Based on the NCCN Clinical Practice Guidelines in Oncology,2 rolapitant could be considered for acute-phase treatment for MEC in a combination regimen with a 5-HT3 antagonist and dexamethasone.18 Historically, 5-HT3 receptor antagonists were able to prevent emesis in approximately 50% of patients. The addition of dexamethasone to 5-HT3 receptor antagonist increased this percentage to approximately 70%.37 Compared to other substance P/NK1 receptor antagonists, rolapitant may offer additional safety benefits because it has the lowest incidence of adverse effects. This better tolerance may, in turn, enhance overall patient compliance with the regimen. Another advantage of rolapitant is that it is not an inhibitor or an inducer of CYP3A4, thereby reducing the risk of clinically significant drug–drug interactions. Because it is administered in one dose, rolapitant may offer the advantages of enhanced compliance and improved quality of life. Given the aforementioned benefits of rolapitant and its comparative pricing to other agents in the class, P&T committees should give rolapitant favorable consideration for formulary addition.

CONCLUSION

Rolapitant has demonstrated an excellent efficacy and safety profile in three phase 3 clinical trials. Additional comparative studies will be beneficial to determine the benefits of the drugs within the NK1 receptor antagonist class. A trial comparing rolapitant and the shorter-acting NK1 receptor antagonists will further help to solidify its place in therapy.

REFERENCES