critical part of care planning for patients with cancer is the prevention and management of chemotherapy-induced nausea and vomiting (CINV), one of the most feared side effects of chemotherapy. Overall, 70% to 80% of patients with cancer experience CINV in the absence of appropriate CINV prophylaxis.1,2 There are 3 main types of CINV3:

• Acute-onset CINV, which occurs within a few minutes to several hours of the initial administration of chemotherapy
• Delayed-onset CINV, which occurs more than 24 hours after the initial chemotherapy treatment
• Anticipatory CINV, which occurs before the administration of chemotherapy and is triggered by senses, thoughts, or anxiety associated with previous chemotherapy.

In addition to engendering significant emotional and physical distress, CINV has multiple clinical consequences for patients, their families, and the healthcare system, including noncompliance with cancer treatment; early discontinuation of cancer treatment; problems with appetite and eating, which can result in nutritional deficits; impaired daily functioning; a decline in performance status; impaired health-related quality of life; increased physician office visits; emergency department admissions; and increased direct and indirect costs of care.2,4

CINV is associated with significant economic costs.4 One study showed that the estimated monthly medical costs associated with uncontrolled CINV for working-aged patients were approximately $1300 higher than that of patients without uncontrolled CINV. In addition, the estimated monthly indirect costs (eg, lost work time) for patients with uncontrolled CINV were more than $400 higher than for patients without uncontrolled CINV.4

The incidence and severity of CINV are influenced by multiple factors. The primary risk factor for CINV is the chemotherapy regimen, including the agents used and the dosages. Patient-related factors that increase the risk for CINV include sex and age. For example, women report CINV and other chemotherapy-associated adverse events more often than men do, and elderly patients report fewer side effects than younger patients with cancer.5 A history of CINV, emesis during pregnancy, motion sickness, alcohol use, tumor burden, anxiety, concomitant medication and medical conditions, and inadequate hydration are also significant contributors to CINV.2

The National Comprehensive Cancer Network (NCCN), the Multinational Association of Supportive Care in Cancer (MASCC), the American Society of Clinical Oncology, and the European Society for Medical Oncology (ESMO) have published antiemetic guidelines for patients with cancer.3,7,8

For acute-onset emesis associated with highly emetogenic chemotherapy (including anthracycline and cyclophosphamide combinations), the antiemesis guidelines recommend triple therapy with a 5-hydroxytryptamine (5-HT3) receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor antagonist.3,7,8

For acute-onset CINV that is associated with moderately emetogenic chemotherapy regimens, the MASCC/
ESMO guidelines recommend double therapy with a 5-HT3 receptor antagonist and dexamethasone. For low-risk chemotherapy agents, dexamethasone monotherapy is adequate. For minimally emetogenic chemotherapy, prophylaxis for acute emesis is not recommended.

For delayed-onset CINV associated with highly emetogenic chemotherapy, the MASCC/ESMO guidelines recommend the combination of dexamethasone and an NK1 receptor antagonist. NK1 monotherapy is appropriate for anthracycline plus cyclophosphamide-based regimens. Dexamethasone or a 5-HT3 receptor antagonist (assuming the latter was not part of the primary prophylactic treatment) are preferred for other moderately emetogenic chemotherapy regimens. No prophylaxis for delayed emesis is needed for low and minimally emetogenic chemotherapy.

The current NCCN guidelines for the management of CINV focus on the emetogenic potential of the chemotherapy drug, and divide chemotherapy agents into 4 risk groups, including high, moderate, low, and minimal (Table 1).

Antiemetic agents that are available in the United States are summarized in Table 2.

Because maintaining the dose intensity of chemotherapy is important, particularly in early-stage disease, recommendations for highly emetogenic chemotherapy should be followed if nausea and vomiting are not controlled by guideline recommendations for moderately emetogenic chemotherapy.

Improved adherence to treatment guidelines, as well as more effective antiemetic agents are needed. A significant number of patients undergoing treatment with moderately emetogenic chemotherapy and highly emetogenic chemotherapy continue to experience nausea and vomiting.

Rolapitant Approved for Delayed-Onset CINV

On September 2, 2015, the US Food and Drug Administration (FDA) approved rolapitant (Varubi; Tesaro), an oral NK1 receptor antagonist, in combination with dexamethasone and a 5-HT3 receptor antagonist, for the prevention of delayed nausea and vomiting associated with initial and repeated courses of cancer chemotherapy in adults, including, but not limited to, highly emetogenic chemotherapy.

The efficacy of rolapitant was demonstrated in 3 randomized, double-blind clinical trials involving approximately 2800 patients who received highly emetogenic or moderately emetogenic chemotherapy. In these studies, antiemetic treatment with rolapitant combined with granisetron and dexamethasone was compared with placebo, granisetron, and dexamethasone.

According to Amy Egan, MD, MPH, Deputy Director of the FDA’s Office of Drug Evaluation III, “Chemotherapy-induced nausea and vomiting remains a major issue that can disrupt patients’ lives and sometimes their therapy. Today’s approval provides cancer patients with another treatment option for the prevention of delayed nausea and vomiting.”

### Table 1

<table>
<thead>
<tr>
<th>Emetogenic Risk Level Associated with Chemotherapy Agents</th>
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<tbody>
<tr>
<td><strong>Emetogenic risk</strong></td>
</tr>
<tr>
<td>High</td>
</tr>
<tr>
<td>Moderate</td>
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<tr>
<td>Low</td>
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<td>Minimal</td>
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### Table 2

<table>
<thead>
<tr>
<th>Antiemetic Drugs</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT3 receptor antagonists</td>
<td>Dolasetron, Granisetron, Ondansetron, Palonosetron, Tropisetron</td>
</tr>
<tr>
<td>Neurokinin-1 receptor antagonists</td>
<td>Aprepitant capsules, Fosaprepitant dimeglumine for injection, Netupitant</td>
</tr>
<tr>
<td>Various</td>
<td>Benzodiazipines, Butyrophenones, Cannabinoids (nabilone, dronabinol), Dexamethasone, Metoclopramide, Olanzapine, Phenothiazines</td>
</tr>
</tbody>
</table>

5-HT3 indicates 5-hydroxytryptamine.

of the delayed phase of nausea and vomiting caused by chemotherapy.”

**Mechanism of Action**

Rolapitant is a selective and competitive antagonist of human substance P and NK₁ receptors. These receptors are broadly distributed in the central and peripheral nervous systems. The activation of NK₁ receptors plays a central role in CINV, particularly in delayed-onset CINV.

**Dosage and Administration**

The recommended dosage of rolapitant is 180 mg (two 90-mg tablets) administered orally approximately 1 to 2 hours before the administration of chemotherapy.

Similar to the results from Study 1, Study 2 demonstrated that the rolapitant-containing antiemetic regimen significantly improved the complete response rates compared with the control regimen in patients with delayed-onset CINV.

Patients receiving highly emetogenic chemotherapy should take rolapitant in combination with dexamethasone (20 mg orally) 30 minutes before starting chemotherapy and a 5-HT₃ receptor antagonist dosed according to the manufacturer’s prescribing information. Dexamethasone should be administered at a dose of 8 mg orally twice daily on days 2 to 4 after receiving highly emetogenic chemotherapy.

Patients receiving moderately emetogenic chemotherapy should take rolapitant in combination with dexamethasone (20 mg orally) 30 minutes before chemotherapy, and a 5-HT₃ receptor antagonist dosed according to the manufacturer’s prescribing information. The 5-HT₃ receptor antagonist taken on days 2 to 4 after receiving moderately emetogenic chemotherapy should be used in accordance with the approved labeling.

Rolapitant should not be taken more than once every 14 days. It can be taken with or without food. No dosage adjustment for dexamethasone, a cytochrome (CY) P3A4 substrate, is necessary.

**Clinical Studies**

The efficacy and safety of rolapitant in combination with granisetron and dexamethasone were evaluated in 3 randomized, multicenter clinical trials. Overall, 2 of these clinical trials were conducted with patients receiving highly emetogenic chemotherapy, and 1 clinical trial was conducted with patients receiving moderately emetogenic chemotherapy.

The primary end point in all 3 studies was complete response rate, defined as no emetic episodes and no use of rescue medications in the delayed phase of CINV—25 to 120 hours after chemotherapy.

**Highly Emetogenic Chemotherapy**

The 2 studies in patients receiving highly emetogenic chemotherapy—Study 1 and Study 2—were multicenter, randomized, controlled, blinded clinical trials. Patients undergoing their first cycle of chemotherapy received a rolapitant-containing antiemetic regimen (rolapitant, intravenous granisetron, and oral dexamethasone) or a control regimen (placebo, intravenous granisetron, and oral dexamethasone).

Study 1 enrolled 532 patients with cancer who were receiving cisplatin-based chemotherapy (mean dose, 77 mg/m²). The majority of patients were male (58%) and white (67%). The patients’ ages ranged from 20 to 90 years (mean, 57 years). In this study, 82% of patients received a concomitant chemotherapeutic agent in addition to cisplatin, including gemcitabine (17%), paclitaxel (12%), fluorouracil (11%), and etoposide (10%).

The results from Study 1 showed that the rolapitant-based antiemetic regimen demonstrated significant improvements in the complete response rates compared with the control regimen in patients with delayed-onset CINV (73% vs 58%, respectively; P < .001).

Study 2 enrolled 555 patients with cancer who were receiving cisplatin-based chemotherapy (mean dose, 76 mg/m²). The majority of patients were male (68%) and white (81%). The patients’ ages ranged from 18 to 83 years (mean, 58 years). Overall, 85% of patients received a concomitant chemotherapeutic agent in addition to cisplatin, including vinorelbine (16%), gemcitabine (15%), fluorouracil (12%), and etoposide (11%).

Similar to the results from Study 1, Study 2 demonstrated that the rolapitant-containing antiemetic regimen significantly improved the complete response rates compared with the control regimen in patients with delayed-onset CINV (70% vs 62%, respectively; P = .043).

**Moderately Emetogenic Chemotherapy**

Study 3 was a multicenter, randomized, double-blind, parallel-group, controlled clinical trial in patients undergoing moderately emetogenic chemotherapy, including anthracycline plus cyclophosphamide. In this clinical
trial, the rolapitant-containing antiemetic regimen (rolapitant, oral granisetron, and dexamethasone) was compared with a control regimen (placebo, oral granisetron, and dexamethasone). Of the 1369 patients who were randomized to receive the rolapitant-containing regimen or the control regimen in Study 3, a total of 1332 patients were included in the efficacy evaluation. The majority of patients were female (80%) and white (77%). Patients in this study ranged in age from 22 to 88 years (mean, 57 years). At least 50% of patients received anthracycline plus cyclophosphamide, and 30% of patients received carboplatin in their first cycle of chemotherapy.

The rolapitant-containing antiemetic regimen demonstrated significant improvements in the complete response rates versus the control regimen in patients with delayed-onset CINV (71% vs 62%, respectively; P < .001).

### Multiple-Cycle Extension Study

Patients who participated in the 3 rolapitant clinical trials were able to enroll in a multiple-cycle extension study. Six to 8 days after chemotherapy administration, patients were asked to recall any episode of vomiting, retching, or nausea that interfered with their normal daily life. More than 70% of patients who received the rolapitant-containing antiemetic regimen in all 3 studies reported no delayed nausea and no delayed emesis during subsequent chemotherapy cycles.

### Adverse Reactions

The safety of rolapitant was evaluated in approximately 2800 patients with cancer who were receiving emetogenic chemotherapy in 4 clinical trials. In all of the clinical trials, rolapitant was administered in combination with a 5-HT3 receptor antagonist and dexamethasone. More than 1560 patients received the rolapitant-containing antiemetic regimen on the first day of their first cycle of chemotherapy. Nearly 1200 of these patients enrolled in the optional multiple-cycle extension study for up to 6 cycles of chemotherapy. The median number of rolapitant doses (180 mg) was 4.

After receiving their first cycle of highly emetogenic chemotherapy, 7% of patients who received the rolapitant-containing regimen reported adverse reactions compared with 6% of those in the control arm. The most common adverse reactions (incidence of ≥3% and more than with control) associated with the rolapitant regimen in patients receiving highly emetogenic chemotherapy included neutropenia (9%), hiccups (5%), and abdominal pain (3%).

The most common adverse reactions (incidence of ≥3% and more than with control) reported with the rolapitant-containing regimen by patients receiving their first cycle of moderately emetogenic chemotherapy, including anthracycline plus cyclophosphamide, included anorexia (9%), neutropenia (7%), dizziness (6%), urinary tract infection (4%), dyspepsia (4%), stomatitis (4%), and anemia (3%).

### Warnings and Precautions

**Interaction with CYP2D6 substrates with a narrow therapeutic index.** The inhibitory effect of rolapitant on the liver enzyme CYP2D6 persists for at least 7 days. The use of rolapitant should be avoided in patients who are taking the antipsychotic agent pimozide, a CYP2D6 substrate. QT prolongation can result from an increase in the plasma concentrations of pimozide. Patients should be monitored for adverse reactions if the concomitant use of rolapitant and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

**Use in Specific Populations**

**Pregnancy.** There are no adequate and well-controlled studies of rolapitant in pregnant women.

**Nursing mothers.** There are no data on the presence of rolapitant in human milk, its effects on the breast-fed infant, or its effects on milk production.

**Pediatric use.** The safety and effectiveness of rolapitant have not been established in pediatric patients.
Geriatric use. Among the 1294 adults who received rolapitant in clinical studies, 25% were aged ≥65 years, and 5% were aged ≥75 years. Rolapitant’s efficacy and safety were similar between the age cohorts.12

Renal impairment. Patients with mild or moderate renal impairment do not require dosage adjustment of rolapitant. Data are insufficient regarding the use of rolapitant in patients with severe renal impairment or end-stage renal disease that requires hemodialysis.12

Hepatic impairment. No dosage adjustment of rolapitant is recommended for patients with mild or moderate hepatic impairment. The use of rolapitant is not recommended for patients with severe liver impairment.12

Conclusion

Three randomized controlled clinical trials have demonstrated that the combination of rolapitant, an orally administered NK1 receptor antagonist; granisetron, a 5-HT3 receptor antagonist; and dexamethasone safely and effectively reduces the risk for delayed-onset CINV in patients with cancer who are undergoing initial and repeat courses of emetogenic chemotherapy, including highly emetogenic chemotherapy regimens. These findings reinforce the substantial body of literature documenting the adjunctive value of NK1 receptor antagonists in reducing CINV.16 With its approval by the FDA, rolapitant became the third NK1 receptor antagonist available in the United States for patients with cancer who are receiving moderately or highly emetogenic chemotherapy.17

References