One of the most fear-inducing side effects of chemotherapy is nausea and vomiting. Without appropriate antiemetic prophylaxis, 70% to 80% of all patients with cancer who receive chemotherapy experience nausea and/or vomiting. Consequently, preventing and managing chemotherapy-induced nausea and vomiting (CINV) is a crucial part of care planning for patients with cancer.

In addition to being a distressing side effect of cancer treatment, CINV has multiple clinical consequences for patients, their families, and the healthcare system, including:

- Nonadherence to chemotherapy treatment
- Early treatment discontinuation
- Problems with appetite and eating, which can lead to nutritional deficits
- Impaired daily functioning
- Performance status decline
- Impaired health-related quality of life, as assessed by the Functional Living Index—Emesis
- More frequent office visits and emergency department admissions, and higher direct and indirect costs of care compared with patients without CINV.

The economic costs associated with CINV are significant. In a study of working-aged adults who were receiving highly or moderately emetogenic chemotherapy, uncontrolled CINV was associated with higher costs; that is, the monthly medical costs for patients with uncontrolled CINV were $1300 higher than the costs for patients without uncontrolled CINV. In addition, the monthly indirect costs, such as lost work time, were $400 higher for patients with uncontrolled CINV than for patients without uncontrolled CINV. Given the many potential negative effects of CINV, the use of effective antiemetic therapy is an essential part of treatment planning for patients undergoing chemotherapy and should be initiated at the start of cancer treatment.

Several factors influence the incidence and severity of CINV. The primary risk factor for CINV is the chemotherapy regimen, including the type of chemotherapy agent, the route of administration, and the treatment dosage. Patient-related factors that influence CINV include sex and age. For example, women report CINV and other chemotherapy-associated adverse events more often than do men, and elderly patients report fewer side effects than younger patients. 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.

In practice, CINV is classified into 3 categories—acute onset occurs within 24 hours of the initial administration of chemotherapy; delayed onset occurs 24 hours to several days after the initial treatment; and anticipatory CINV is triggered by senses, thoughts, or anxiety that patients associate with previous chemotherapy.

Current emesis-related management guidelines focus on the emetogenic potential of chemotherapy drugs and divide agents into 4 risk groups, including high, moderate, low, and minimal. Table 1 summarizes the classification of chemotherapy drugs according to the National Comprehensive Cancer Network (NCCN) guidelines, and provides examples of agents in each risk group.

Supportive care for patients receiving chemotherapy has dramatically improved during the past 20 years, with combination antiemetic regimens emerging as the standard of care for CINV control.

Four groups—the NCCN, the Multinational Association of Supportive Care in Cancer (MASCC), the European Society for Medical Oncology (ESMO), and the American Society of Clinical Oncology—have published antiemetic guidelines. These groups broadly agree on the majority of key issues regarding the management of CINV.

For acute emesis associated with highly emetogenic chemotherapy, as well as with the combination use of anthracycline and cyclophosphamide, antiemetic guidelines recommend triple therapy with a 5-hydroxytryptamine (5-HT3) receptor antagonist, dexamethasone, and a neurokinin 1 (NK1) receptor agonist. For acute emesis associated with moderately emetogenic regimens, the MASCC/ESMO guidelines recommend double ther-
apy with a 5-HT\textsubscript{3} receptor antagonist (ideally, palonosetron) and dexamethasone. For low emetogenic chemotherapy, dexamethasone monotherapy is adequate, but for minimal emetogenic chemotherapy, prophylaxis for acute emesis is not recommended.\textsuperscript{6,7}

For delayed emesis associated with highly emetogenic chemotherapy, the MASCC/ESMO guidelines recommend the combination of dexamethasone and an NK\textsubscript{1} receptor agonist. For delayed emesis associated with moderately emetogenic chemotherapy, such as anthracycline and cyclophosphamide–based regimens, the guidelines recommend aprepitant monotherapy. In other moderately emetogenic regimens, dexamethasone or a 5-HT\textsubscript{3} receptor antagonist (presuming the latter was not part of the primary prophylactic treatment) are the preferred agents. For low- and minimal-emetogenic chemotherapy, no prophylaxis for delayed emesis is needed.\textsuperscript{6,7}

Because maintaining dose intensity of chemotherapy is important, particularly in early-stage disease, recommendations for highly emetogenic chemotherapy should be followed when nausea and vomiting are not reduced by the recommended therapy for moderately emetogenic chemotherapy.\textsuperscript{5}

Although the majority of patients with cancer are protected from CINV with these current therapies, other patients still experience nausea and vomiting associated with chemotherapy. Consequently, there remains a need for greater adherence to treatment guidelines and for more effective antiemetic agents.\textsuperscript{2,5}

**Mechanism of Action**

Palonosetron has a strong binding affinity for 5-HT\textsubscript{3} receptors, acting as a 5-HT\textsubscript{3} antagonist. Acute emesis is known to depend on serotonin and its 5-HT\textsubscript{3} receptors.\textsuperscript{10}

Netupitant is a selective antagonist of human substance P and NK\textsubscript{1} receptors. These receptors are broadly distributed in the central and the peripheral nervous systems. Delayed emesis is associated with the activation of NK\textsubscript{1} receptors by substance P. In vitro and in vivo studies demonstrated that netupitant inhibits substance P–mediated responses.\textsuperscript{10}

**Dosing and Administration**

Netupitant plus palonosetron is a fixed-dose combination capsule containing netupitant (300 mg) and palonosetron (0.5 mg).\textsuperscript{10} For patients undergoing highly emetogenic chemotherapy, including cisplatin-based chemotherapy, the recommended dosage of netupitant plus palonosetron is 1 capsule given approximately 1 hour before starting chemotherapy, with oral dexamethasone 12 mg administered 30 minutes before the start of chemotherapy on days 1 and dexamethasone 8 mg once daily on days 2 to 4.\textsuperscript{10}

For patients receiving anthracycline and cyclophosphamide or other chemotherapy that is not considered highly emetogenic, the recommended dosage of the new combination is 1 capsule approximately 1 hour before the start of chemotherapy, with dexamethasone 12 mg administered 30 minutes before the start of chemothera-

### FDA Approves a Novel Combination Therapy for CINV

On October 10, 2014, the US Food and Drug Administration (FDA) approved the combination of netupitant plus palonosetron (Akynzeo; Eisai) for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy in patients with cancer.\textsuperscript{9,10} The fixed combination capsule of netupitant plus palonosetron contains 300 mg of netupitant and 0.5 mg of palonosetron.\textsuperscript{10}

Oral palonosetron was initially approved as a single agent in 2008 for the prevention of acute and delayed nausea and vomiting associated with initial and repeated courses of moderately emetogenic chemotherapy in patients with cancer.\textsuperscript{9,11} Palonosetron prevents nausea and vomiting during the acute phase. Netupitant is a new drug that prevents nausea and vomiting during the acute and the delayed phases after the start of chemotherapy.\textsuperscript{9,10}

“Supportive care products, such as Akynzeo, help ease the nausea and vomiting patients may experience as a side effect of cancer chemotherapy,” said Julie Beitz, MD, Director of the Office of Drug Evaluation III in the FDA’s Center for Drug Evaluation and Research.\textsuperscript{9}

### Table 1 Classification of Emetogenic Risk Associated with Some Chemotherapy Agents

<table>
<thead>
<tr>
<th>Emetogenic risk</th>
<th>Proportion of patients experiencing acute emesis without prophylaxis, %</th>
<th>Examples of IV chemotherapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>&gt;90</td>
<td>Cisplatin, high-dose cyclophosphamide, dacarbazine</td>
</tr>
<tr>
<td>Moderate</td>
<td>30-90</td>
<td>Carboplatin, high-dose cytarabine, doxorubicin, trinitotecan, oxaliplatin</td>
</tr>
<tr>
<td>Low</td>
<td>10-30</td>
<td>Cabazitaxel, docetaxel, floxuridine, gemcitabine, pemetrexed, temsirolimus, topotecan</td>
</tr>
<tr>
<td>Minimal</td>
<td>&lt;10</td>
<td>Bevacizumab, ifosfamide, vincristine, vinorelbine</td>
</tr>
</tbody>
</table>

IV indicates intravenous.

Clinical Trials

The efficacy and safety of fixed-dose netupitant plus palonosetron in combination with dexamethasone were evaluated in 2 randomized, parallel, double-blind, multicenter, controlled clinical trials—1 clinical trial in participants receiving highly emetogenic chemotherapy and 1 clinical trial in patients receiving moderately emetogenic chemotherapy.10

Study 1: Highly Emetogenic Chemotherapy

This multicenter, randomized, parallel, double-blind study enrolled 694 chemotherapy-naive patients with cancer who were receiving cisplatin-based chemotherapy (median dose, 75 mg/m²).10,12 This trial evaluated 3 oral doses of netupitant (100 mg, 200 mg, and 300 mg) combined with oral palonosetron 0.5 mg and compared it with oral palonosetron 0.5 mg alone, all administered on day 1.10,12 A standard 3-day aprepitant and intravenous ondansetron regimen were included as an exploratory arm. All patients received oral dexamethasone on days 1 through 4.12 Of the 694 patients who enrolled in this clinical trial, 135 patients received netupitant plus palonosetron (netupitant 300 mg and palonosetron 0.5 mg), and 136 patients received oral palonosetron 0.5 mg alone.10 The majority of patients who received netupitant plus palonosetron were male (57%) and white (100%); the patients’ median age was 53 years (range, 19-77 years).10 During the study, 86% of patients who received netupitant plus palonosetron also received a concomitant chemotherapeutic agent in addition to cisplatin, including cyclophosphamide (34%), fluorouracil (24%), etoposide (21%), and doxorubicin (16%).10

The key efficacy end points were the complete response rates (defined as no emetic episode and no use of rescue medication) 0 to 24 hours after cisplatin treatment (acute phase), 25 to 120 hours after cisplatin treatment (delayed phase), and within 120 hours after cisplatin treatment (overall phase).10,12 Table 2 summarizes the efficacy data for netupitant plus palonosetron versus palonosetron alone, which show that the netupitant plus palonosetron combination offers clinically significant improvements in the complete response rates over palonosetron alone.10,12

Study 2: Moderately Emetogenic Chemotherapy

In this multicenter, randomized, parallel, double-blind, active-control superiority study, the efficacy and safety of a single oral dose of netupitant plus palonosetron were compared with a single oral dose of palonosetron 0.5 mg in 1450 chemotherapy-naive patients with cancer who were scheduled to receive anthracycline and cyclophosphamide.10,13 Patients in this clinical trial also received a single oral dose of dexamethasone. After completing their first cycle of anthracycline and cyclophosphamide, patients could participate in a multiple-cycle extension in which they continued the same antiemetic treatment as assigned in cycle 1.10 A total of 725 patients received netupitant plus palonosetron, and 725 patients received palonosetron alone.10,13 Overall, 1438 patients completed cycle 1 of chemotherapy, and the majority (88%) of patients continued treatment in the multiple-cycle extension. A total of 907 (62%) patients finished the multiple-cycle extension for a maximum of 8 treatment cycles.10

The majority of patients who received the netupitant plus palonosetron combination were female (98%) and white (79%); the patients’ median age was 54 years (range, 22-79 years).10 Overall, nearly all patients (99.9%) received cyclophosphamide and an anthracycline; in addition, all patients received either doxorubicin (68%) or epirubicin (32%).10 During the first cycle of chemotherapy, 32% of patients who received netupitant plus palonosetron also received a concomitant chemotherapeutic agent in addition to the protocol-mandated regimens, including fluorouracil (28%) and docetaxel (3%).10

The efficacy end points included the complete response rates for the acute phase, the delayed phase, and the overall phase after chemotherapy with an anthracycline plus cyclophosphamide.10,13 Table 3 summarizes the efficacy data for netupitant plus palonosetron versus palonosetron alone.

Table 2

<table>
<thead>
<tr>
<th>Phase after cisplatin chemotherapy</th>
<th>Netupitant 300 mg + palonosetron (N = 135)</th>
<th>Palonosetron 0.5 mg, % (N = 136)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute phase†</td>
<td>98.5</td>
<td>89.7</td>
<td>.002</td>
</tr>
<tr>
<td>Delayed phase‡</td>
<td>90.4</td>
<td>80.1</td>
<td>.032</td>
</tr>
<tr>
<td>Overall†</td>
<td>89.6</td>
<td>76.5</td>
<td>.003</td>
</tr>
</tbody>
</table>

†0-24 hours after treatment.
‡25-120 hours after treatment.
*0-120 hours after treatment.
Source: Akynzeo (netupitant and palonosetron) capsules prescribing information; October 2014.
palonosetron monotherapy, which show that the combination of netupitant plus palonosetron offers significant improvements in complete response rate over palonosetron monotherapy.\textsuperscript{10,13}

Among the patients who participated in the multiple-cycle extension of the study, the antiemetic activity of netupitant plus palonosetron was maintained throughout the repeated cycles of chemotherapy.\textsuperscript{10}

### Adverse Reactions

The safety of netupitant plus palonosetron was evaluated in clinical trials that included more than 1500 healthy volunteers and patients with cancer.\textsuperscript{10} More than 1150 patients with cancer have been exposed to netupitant plus palonosetron, receiving at least 1 cycle of cancer chemotherapy in 1 of 3 active-controlled clinical trials, including 782 patients who were exposed to netupitant plus palonosetron for at least 4 cycles, and 321 patients who were exposed to netupitant plus palonosetron for at least 6 cycles, up to a maximum of 12 cycles of chemotherapy.\textsuperscript{10}

All patients received a single oral dose of netupitant plus palonosetron 1 hour before the start of each chemotherapy cycle. In all the studies, dexamethasone was co-administered with netupitant plus palonosetron.\textsuperscript{10}

### Cisplatin-Based Highly Emetogenic Chemotherapy

In a single-cycle study of patients who received cisplatin-based highly emetogenic chemotherapy, 136 patients received netupitant plus palonosetron.\textsuperscript{10} Adverse reactions that were reported at an incidence rate of at least 3% and for which the rate with netupitant plus palonosetron exceeded the rate with palonosetron alone included dyspepsia (4%), fatigue (4%), constipation (3%), and erythema (3%).\textsuperscript{10}

### Anthracycline and Cyclophosphamide-Based Moderately Emetogenic Chemotherapy

In a study of patients who received moderately emetogenic chemotherapy, 725 patients received netupitant plus palonosetron durin the first cycle, and 635 of these patients continued for up to 8 cycles in a multiple-cycle extension.\textsuperscript{10} The adverse reactions that were reported at an incidence rate of at least 3% and for which the rate with netupitant plus palonosetron exceeded the rate with palonosetron alone included headache (9%), asthenia (8%), and fatigue (7%).\textsuperscript{10} The adverse reactions associated with netupitant plus palonosetron during subsequent cycles of anthracycline and cyclophosphamide were similar to those observed in the first cycle.\textsuperscript{10}

In both treatment arms of the clinical trials that compared netupitant plus palonosetron with oral palonosetron monotherapy, concomitant elevations of total bilirubin and transaminase levels of more than 3 times the upper limit of normal were reported, and the frequency of these elevations was similar with both treatments.\textsuperscript{10}

The combination of netupitant plus palonosetron has no contraindications.\textsuperscript{10}

### Drug Interactions

Netupitant plus palonosetron should be used with caution in patients receiving cytochrome (CY) P3A4 substrates (eg, tacrolimus, imatinib, anastrozole, paclitaxel); inhibition of CYP3A4 can result in increased plasma concentrations of the concomitant drug that can last for 4 days or more. The concomitant use of netupitant plus palonosetron with CYP3A4 inducers (eg, rifampin, carbamazepine, phenobarbital, pioglitazone) should be avoided.\textsuperscript{10,14}

### Warnings and Precautions

#### Hypersensitivity

Hypersensitivity reactions, including anaphylaxis, have been reported after the use of other 5-HT\textsubscript{3} receptor antagonists.\textsuperscript{10} Patients experiencing anaphylaxis may or may not have a known hypersensitivity to 5-HT\textsubscript{3} receptor antagonists. Patients taking netupitant plus palonosetron should seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur.\textsuperscript{10}

#### Serotonin syndrome

The development of serotonin syndrome has been reported with 5-HT\textsubscript{1} receptor antagonists, most often when serotonergic drugs (eg, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, mirtazapine, fentanyl, lithium, tramadol) were used concomitantly; several of the cases were fatal.\textsuperscript{10}
The symptoms associated with serotonin syndrome can include mental status changes (eg, agitation, hallucinations, delirium, coma); autonomic instability (eg, tachycardia, labile blood pressure, dizziness, diaphoresis, flushing, hyperthermia); neuromuscular symptoms (eg, tremor, rigidity, myoclonus, hyperreflexia, incoordination); and seizures, with or without gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). If symptoms of serotonin syndrome occur, netupitant/palonosetron should be discontinued and supportive treatment should be initiated.10

Use in Specific Populations

**Pregnancy.** Netupitant plus palonosetron is listed as pregnancy category C; there are no adequate and well-controlled studies with this combination in pregnant women. Netupitant plus palonosetron should only be used during pregnancy if the potential benefit outweighs the potential risk to the fetus.10

**Nursing mothers.** It is not known whether the components of netupitant plus palonosetron are present in human breast milk. Nursing or netupitant plus palonosetron therapy should be discontinued on the basis of the importance of the drug to the mother.10

**Pediatric use.** The safety and efficacy of netupitant plus palonosetron have not been established in pediatric patients aged <18 years.10

**Geriatric use.** Of the 1169 patients with cancer who received netupitant plus palonosetron in clinical trials, 18% were aged ≥65 years, and 2% were aged ≥75 years.10 The nature and the frequency of adverse events were similar between elderly patients and younger patients. In general, caution should be used when administering netupitant plus palonosetron to elderly patients, because of their higher risk for hepatic, renal, and/or cardiac dysfunction, as well as concomitant diseases and multiple medications.10

**Renal impairment.** Patients with mild or moderate renal impairment do not require dose adjustment of netupitant plus palonosetron.10 Patients with severe renal impairment or end-stage renal disease should not receive netupitant plus palonosetron.10

**Hepatic impairment.** No dosage adjustment of netupitant plus palonosetron is recommended for patients with mild or with moderate hepatic impairment. Netupitant plus palonosetron is not recommended for use in patients with severe hepatic impairment.10

**Conclusion**

The new fixed-dose combination agent that targets 2 antiemetic pathways, netupitant plus palonosetron offers an effective and safe alternative for patients undergoing initial and repeated courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. This novel dual-acting prophylactic therapy is an important option for patients receiving chemotherapy, in part because adherence to antiemetic therapy is more important for patients receiving chemotherapy, in part because adherence to antiemetic consensus guidelines remains low. As an oral single capsule, the use of netupitant plus palonosetron combination therapy may improve the management of patients with cancer who are at high risk for CINV.

**References**