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New Drugs: Akynzeo, Blincyto, Harvoni, and Movantik

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Goal. The goal of this lesson is to provide information on four new drugs: blinatumomab (Blincyto™), ledipasvir/sofosbuvir (Harvoni®), naloxegol (Movantik™), and netupitant/palonosetron (Akynzeo®).

Objectives. At the completion of this activity, the participant will be able to:

1. recognize signs and symptoms, and key features of targeted pathologies including information on their prevalence in the population;
2. recognize important therapeutic uses for these drugs;
3. select the indications, pharmacologic actions, clinical applications, dosing regimens, mode of administration, and availability for each drug;
4. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions reported for each agent; and
5. list important counseling advice to convey to patients and/or their caregivers.

The four new-molecular entity drugs discussed in this lesson are approved to treat a wide variety of pathologies (Table 1). Two of the new drugs are combined with previously-approved drugs. This lesson provides a brief introduction to the therapeutic agents, and neither depth nor expanse is intended to extend beyond an overview of the topic. The reader is, therefore, encouraged to consult the products' full Prescribing Information leaflet (package insert), FDA-approved *Medication Guide* when available, and other published sources and websites for detailed descriptions.

Blinatumomab (Blincyto)

FDA granted Blincyto (blin-SYE-toe) breakthrough therapy designation, priority review, and orphan product designation. The drug's sponsor demonstrated through preliminary clinical evidence that the drug may offer substantial improvement over available therapies to treat a form of leukemia; that it had the potential at the time the application was submitted to be a significant improvement in safety or effectiveness in treatment of a serious condition; and that the drug was intended to treat a rare disease. Blincyto was approved under the FDA's accelerated approval program, which permits approval of a drug to treat a serious or life-threatening disease based on clinical data showing the drug has an effect on a surrogate endpoint reasonably likely to predict clinical benefit to patients. This program provides earlier patient access to promising new drugs while the company conducts confirmatory clinical trials.

Indications and Use. Blincyto is indicated for treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). As this indication was approved under accelerated approval, continued approval may be contingent on verification of clinical benefit in subsequent trials.

Precursor B-cell ALL. This is a rapidly growing cancer in which the bone marrow makes too many B-cell lymphoblasts, an immature type of white blood cell. The Philadelphia chromosome is an abnormality that sometimes occurs in the bone marrow cells of leukemia patients. Most cases of ALL occur in children, with the highest risk for development in children younger than five years of age. However, the most deaths from ALL (approximately four out of five) occur in adults. Among children and teens, ALL is the most common leukemia, accounting for 75 percent of cases. The National Cancer Institute estimates that 6,250 Americans will be diagnosed with ALL and 1,450 will die from the disease in 2015.

Mechanism of Action. Blinatumomab is an example of immunotherapy, a treatment that uses certain parts of a person's immune system to fight disease. It is a novel bispecific CD19-directed CD3 T-cell engager (BiTE) that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the

Table 1
Selected new drugs

Generic (Trade Name)	Distributor	Indication	Dose*	Dosage Form	Most Common Side Effects	Medication Guide‡
Blinatumomab (Blincyto)	Amgen	acute lymphoblastic leukemia (ALL)	9 mcg/day Days 1-7; 28 mcg/day Days 8-28	single-use vial for IV infusion, 35 mcg	(≥20%): pyrexia, headache, peripheral edema, febrile neutropenia, nausea, tremor, hypokalemia, rash, constipation	Yes
Ledipasvir/ sofosbuvir (Harvoni)	Gilead Sciences	chronic hepatitis C (CHC)	one tablet daily	tablet (90 mg ledipasvir, 400 mg sofosbuvir§)	(≥10%): fatigue, headache	No
Naloxegol (Movantik)	AstraZeneca	opioid-induced constipation	25 mg once daily	tablet 12.5 mg, 25 mg	(≥3%): abdominal pain, diarrhea, nausea, vomiting, flatulence, headache	Yes
Netupitant/ palonosetron (Akynzeo)	Eisai	acute & delayed nausea & vomiting with initial & repeat courses of chemotherapy	one capsule prior to chemotherapy	capsule (300 mg netupitant, 0.5 mg palonosetron§)	(≥3%): headache, asthenia, dyspepsia, fatigue, constipation, erythema	No

*Recommended dose for most patients ‡Availability at the time of publication of this lesson §Sofosbuvir (Sovaldi) approved in 2013
§Palonosetron (Aloxi) approved in 2008

T-cell receptor complex with CD19 on benign and malignant B cells. Blinatumomab mediates formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells. In essence, it acts as a connector between protein CD19 on B cells and CD3 on T cells which engages the T cells to destroy the malignant B cells. This is immunotherapy at its best since autologous effector cells are brought into direct contact with the target and nothing else.

Efficacy and Safety. Safety and effectiveness were evaluated in a clinical study involving 185 adult patients with Philadelphia chromosome-negative relapsed or refractory precursor B-cell ALL. All participants were treated with the new drug for at least four weeks via infusion. Results confirmed that 32 percent of subjects experienced no evidence of disease (complete remission) for approximately 6.7 months.

The drug's label contains a *Boxed Warning* alerting patients and healthcare professionals of the following potential toxicities: the cytokine release syndrome (CRS) and neurological toxicities. The most common adverse reactions noted in these preclinical trials were fever, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, rash, constipation, and tremor.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Cytokine Release Syndrome*: Serious reactions that may be associated with CRS include pyrexia, headache, nausea, asthenia (loss of strength), hypotension, and increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin. Disseminated intravascular coagulation, capillary leak syndrome, and hemophagocytic lymphohistiocytosis/ macrophage activation syndrome have been reported in the setting of CRS. The most highly elevated cytokines in patients who develop cytokine release syndrome after blinatumomab are interleukin (IL)-6, IL-10, and interferon-γ. Reactions may be life-threatening or fatal. Interrupt or discontinue Blincyto as recommended.

• *Neurological toxicities:* occurred in approximately 50 percent of patients with a median time to onset of seven days. These include encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders. Reactions may be severe, life-threatening, or fatal. Interrupt or discontinue Blincyto as recommended.

• *Infections*: Sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections have been observed, some of which were life-threatening or fatal. Monitor patients for signs or symptoms and treat appropriately.

• *Tumor lysis syndrom*e: This may be life-threatening or fatal. Monitor for signs or symptoms.

Temporary interruption or discontinuation of the drug may be necessary.

• *Neutropenia and febrile neutropenia*: Monitor laboratory parameters including, but not limited to, white blood cell count and absolute neutrophil count. Interrupt Blincyto if prolonged neutropenia occurs.

• *Elevated liver enzymes*: Monitor ALT, AST, gamma-glutamyl transferase (GGT), and total blood bilirubin prior to the start of and during Blincyto treatment. Interrupt Blincyto therapy if the transaminases rise to greater than five times the upper limit of normal or if bilirubin rises to more than three times the upper limit of normal.

• *Preparation and administration errors*: Strictly follow instructions for preparation (including admixing) and administration.

• *Effects on ability to drive and use machines*: Advise patients to refrain from driving and operating machinery while receiving Blincyto due to potential for neurologic events.

• *Leukoencephalopathy*: has been observed on MRI in some patients. The clinical significance is unknown.

Known hypersensitivity to blinatumomab or to any component of the product formulation is the only **contraindication** listed.

Drug Interactions. No formal drug interaction studies have been conducted with Blincyto. The highest drug-drug interaction risk is during the first nine days of the first cycle and the first two days of the second cycle in patients receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index.

Administration, Dosing, and Availability. For patients weighing at least 45 kg, administer blinatumomab 9 mcg/day on Days 1-7, and 28 mcg/day on Days 8-28. For subsequent cycles, administer 28 mcg/day on Days 1-28. A treatment course consists of up to two cycles of blinatumomab for induction, followed by three additional cycles for consolidation treatment (up to a total of five cycles). A single cycle of treatment consists of four weeks of continuous intravenous infusion, followed by a two-week treatment-free interval. Hospitalization is recommended for the first nine days of the first cycle, and the first two days of the second cycle. For all subsequent cycle starts and reinitiation (i.e., if treatment is interrupted for four or more hours), supervision by a healthcare professional or hospitalization is recommended. Premedicate with dexamethasone 20 mg intravenously one hour prior to the first dose of blinatumomab of each cycle, prior to a step dose (e.g., such as Cycle 1 Day 8), or when restarting an infusion after an interruption of four or more hours. Blincyto should be infused over 24 to 48 hours. Blincyto for injection is supplied as a single-use vial containing 35 mcg of blinatumomab for reconstitution, and a single-use vial containing IV Solution Stabilizer.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each infusion of Blincyto. Specific points for counseling are summarized in Table 2.

Table 2
Patient information for Blincyto*

Inform patients:
• to read the FDA-approved *Medication Guide* each time they receive this drug;
• to contact a healthcare professional for any of the following: signs and symptoms that may be associated with cytokine release syndrome and infusion reactions including pyrexia, fatigue, nausea, vomiting, chills, hypotension, rash, and wheezing; signs and symptoms of neurological toxicities including convulsions, speech disorders and confusion; signs and symptoms of infections including pneumonia;
• to refrain from driving and engaging in hazardous occupations or activities such as operating heavy or potentially dangerous machinery while Blincyto is being administered;
• that it is very important to keep the area around the intravenous catheter clean to reduce the risk of infection;
• to not adjust the setting on the infusion pump. If there is a problem with the infusion pump or the pump alarms, patients should contact their doctor or nurse immediately.

*A complete list of information is available in the product's *Medication Guide*.

Ledipasvir (ingredient in Harvoni)

Although treatment of patients infected with chronic hepatitis C virus (HCV) has evolved greatly in recent years, newly approved regimens to treat patients with HCV genotype infection still include weekly injections of recombinant human interferon alfa and ribavirin. Before Harvoni's (har-VOE-nee) approval, the only interferon-free option for treatment of HCV genotype 1 infection was sofosbuvir (Sovaldi) and ribavirin for patients ineligible to receive interferon; the reported response was 68 percent.

Harvoni is the first fixed-dose combination product (ledipasvir plus sofosbuvir) approved to treat chronic HCV genotype 1 infection. It is also the first approved regimen that does not require administration with interferon or ribavirin. Harvoni was the third drug approved by FDA to treat chronic HCV infection. Its approval was preceded by Olysio (simeprevir) in November 2013 and Sovaldi in December 2013.

Harvoni was approved in 2014 with breakthrough therapy designation. It was reviewed under the FDA's priority review program, which provides for an expedited review of drugs that treat serious conditions and, if approved, would provide significant improvement in safety or effectiveness.

Indications and Use. Harvoni is indicated for treatment of chronic hepatitis C virus genotype 1 infection in adults. Approximately 70 percent of Americans infected with HCV have genotype 1 infection.

Chronic Hepatitis C Virus Genotype 1 Infection. Hepatitis C is a viral infection that incites inflammation of the liver, which

can lead to diminished hepatic function or failure. Most people infected with HCV experience no symptoms until liver damage becomes apparent, which may take decades.

There are six known genotypes of HCV. The most common in the United States are genotype 1 (subtypes 1a and 1b), genotype 2, and genotype 3. Together, these comprise 97 percent of all HCV infections. Although there is no difference in the risk of cirrhosis according to genotype, genotype 3 is associated with a higher rate of hepatitis steatosis (fatty degeneration) and genotype 1b is associated with a higher rate of hepatocellular carcinoma. The prevalence of hepatitis C is especially high in subpopulations of homeless people, incarcerated people, veterans, and persons infected with human immunodeficiency virus (HIV).

Some patients with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as hemorrhage, yellowish eyes or skin (jaundice), abdominal edema, infections and liver cancer. More than 185 million individuals worldwide are infected with HCV. According to the U.S. Centers for Disease Control and Prevention, about 3.2 million Americans are infected with chronic HCV, and without proper treatment, 15 to 20 percent of these persons will go on to develop cirrhosis over a period of 20 to 30 years. Hepatitis C virus is the primary cause of liver transplantation in the United States.

Mechanism of Action. Both components of Harvoni interfere with enzymes required for viral replication of the hepatitis C virus. Ledipasvir is an inhibitor of the HCV NS5A protein, which is required for viral replication. Sofosbuvir is an inhibitor of the HCV NS5B RNA-dependent RNA polymerase.

Efficacy and Safety. Harvoni's efficacy and safety were evaluated in three clinical trials enrolling 1,518 participants who had not previously received treatment for their infection (treatment-naïve) or had not responded to previous treatment (treatment-experienced), including persons with cirrhosis. Participants were randomly assigned to receive Harvoni with or without ribavirin. The trials were designed to measure whether the hepatitis C virus was no longer detected in the blood at least 12 weeks after completing treatment (sustained virologic response, or SVR), indicating that a participant's HCV infection had been cured.

In the first trial, comprised of treatment-naïve participants, 94 percent of those who received Harvoni for eight weeks and 96 percent who received the drug for 12 weeks achieved SVR. The second trial showed 99 percent of such participants with and without cirrhosis achieved SVR after 12 weeks. In the third trial, which examined Harvoni's efficacy in treatment-experienced participants with and without cirrhosis, 94 percent of those who received the drug for 12 weeks and 99 percent of those who received it for 24 weeks achieved SVR. In all trials, ribavirin did not increase response rates in the participants. The most common adverse effects reported in clinical trial participants were fatigue and headache.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Serious symptomatic bradycardia when coadministered with amiodarone*. (See Drug Interactions below.)
- *Risk of reduced therapeutic effect due to P-glycoprotein (P-gp) inducers*. (See Drug Interactions below.)
- *Use with other drugs containing sofosbuvir, including Sovaldi, is not recommended*.

No **contraindications** are listed.

Drug Interactions. Since Harvoni contains both ledipasvir and sofosbuvir, any interactions that have been identified with these agents individually may occur with Harvoni.

After oral administration of Harvoni, sofosbuvir is rapidly absorbed and subject to extensive first-pass hepatic extraction. Ledipasvir is an inhibitor of the drug transporters P-gp and breast cancer resistance protein (BCRP) and may increase intestinal absorption of coadministered substrates for these transporters.

Postmarketing cases of severe bradycardia, including cases which were fatal or required pacemaker interventions, have been reported when amiodarone is coadministered with Harvoni. Coadministration of Harvoni plus amiodarone is not recommended. If there is no alternative or if amiodarone is discontinued just prior to starting Harvoni, daily cardiac monitoring should occur for at least two weeks and patients should be counseled of the risk.

Table 3
Patient information for Harvoni*

Inform patients:
- that they should read the FDA-approved Prescribing Information leaflet;
- that Harvoni may interact with other drugs; thus, advise patients to report to their healthcare provider the use of any other prescription or nonprescription medication or herbal products including St. John's wort;
- that the effect of treatment of hepatitis C infection on virus transmission is not known, and that appropriate precautions to prevent transmission of the hepatitis C virus during treatment or in the event of treatment failure should be taken;
- to take Harvoni once daily on a regular dosing schedule with or without food. If a dose is not taken at the regular time, it should be taken as soon as the patient remembers it on the same day. Then, the usual dosing schedule should be resumed the next day;
- to not take more than one tablet of Harvoni in a day;
- to not use if the seal over the bottle opening is broken or missing.

*A complete list of information is available in the product's Prescribing Information leaflet.

Ledipasvir and sofosbuvir are substrates of drug transporters P-gp and BCRP. P-gp inducers (e.g., rifampin or St. John's wort) may decrease ledipasvir and sofosbuvir plasma concentrations, leading to reduced therapeutic effect of Harvoni. The use of P-gp inducers is not recommended with Harvoni. The drug's Prescribing Information leaflet contains an extensive list of established and potentially significant drug interactions. The concomitant use of Harvoni with other products containing sofosbuvir is not recommended.

Administration, Dosing, and Availability. The recommended daily dosage is one tablet taken orally with or without food. Therapy should continue for 12 or 24 weeks, depending on whether the patient is treatment-naïve and with or without cirrhosis. Harvoni tablets contain 90 mg ledipasvir and 400 mg sofosbuvir. The product should be dispensed in its original container and not used if the seal over the bottle opening is broken or missing.

Patient Counseling. Specific points for patient counseling are summarized in Table 3.

Naloxegol (Movantik)

A common problem with opioid use is that they reduce the gastrointestinal tract's motility, making bowel movements difficult and causing patients to strain, have hard or lumpy stools, or experience a sensation of incomplete evacuation. Movantik (mo-VAN-tic) is used to decrease these side effects. It is a C-II controlled substance; the approved labeling indicates no risk of abuse or dependency.

Indications and Use. Movantik is indicated for treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Opioids and Constipation. Opioids play a critical role in management of acute and chronic pain. More than 240 million opioid prescriptions are dispensed each year in the United States, the majority for non-cancer pain such as musculoskeletal ailments.

Opioids can incite bothersome gastrointestinal side effects, which can adversely affect adherence to pain-medication regimens and quality of life. OIC results from binding of opioid agonists to μ-opioid receptors located in the enteric nervous system. This binding leads to increased nonpropulsive contractions with inhibition of water and electrolyte secretion into the intestinal lumen. Opioid-agonist binding to these receptors also inhibits gastric emptying, causes an increase in pyloric tone, delays transit throughout the small and large intestine, increases resting anal-sphincter pressure, as well as causes a concurrent increase in the net absorption of luminal fluid. Constipation may be debilitating among those who require chronic analgesia; OIC affected an average of 41 percent of patients taking an oral opioid for up to eight weeks in a meta-analysis of 11 placebo-controlled, randomized studies in non-malignant pain. Patients may discontinue treatment due to constipation despite their established need for long-term pain relief.

Dietary modifications, lifestyle changes, and laxatives are used to treat OIC, but their efficacy is limited. An alternative approach is to administer a peripherally acting μ-opioid receptor agonist such as naloxegol to limit the effects of opioids on the gastrointestinal tract while preserving centrally mediated analgesia.

Mechanism of Action. Naloxegol is an antagonist of opioid binding at the μ-opioid receptor in tissues such as the gastrointestinal tract, thereby decreasing the constipating effects of opioids. The drug is a polymer conjugate of the opioid antagonist naloxone (i.e., a PEGylated derivative of naloxone). The polyethylene glycol moiety limits naloxegol movement across the blood-brain barrier; consequently, this reduced CNS penetration of naloxegol limits the potential for interference with centrally mediated opioid analgesia.

Efficacy and Safety. Safety and efficacy were established in two clinical trials of 1,352 participants who had taken opioids for at least four weeks to treat non-cancer related pain and experienced opioid-induced constipation. Participants were randomly assigned to receive 12.5 mg or 25 mg of Movantik or placebo once daily for 12 weeks. The trials were designed to measure the change in the number of bowel movements per week from the start of the study.

Results of the first trial showed that 44 percent of participants receiving 25 mg of Movantik and 41 percent of participants receiving 12.5 mg experienced an increase in bowel movements each week, compared to 29 percent of subjects receiving placebo. The second trial showed similar results. Common adverse effects included abdominal pain, diarrhea, headache, and the experience of excessive gas in the stomach or intestinal area (flatulence).

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

• *Gastrointestinal perforation*: Consider the overall risk benefit in patients with known or suspected lesions of the GI tract. Monitor for severe, persistent or worsening abdominal pain and discontinue if these symptoms develop.

• *Opioid withdrawal*: Consider the overall risk benefit in patients with disruptions to the blood-brain barrier. Monitor for symptoms of opioid withdrawal.

Three **contraindications** are included in the drug's label:

(1) patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction;

(2) concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin); and

(3) known serious or severe hypersensitivity reaction to Movantik or any of its excipients.

Drug Interactions. An extensive table showing the effect of various drugs known to interact

Table 4
Patient information for Movantik*

Inform patients:
- to read the FDA-approved *Medication Guide* prior to taking Movantik and re-read it each time the prescription is refilled, and to take the drug exactly as prescribed;
- to discontinue all maintenance laxative therapy prior to initiation of Movantik, and if there is a suboptimal response to the new drug, laxatives can be used as needed after three days;
- to take Movantik on an empty stomach at least 1 hour prior to the first meal of the day or 2 hours after the meal;
- to swallow the tablets whole, without crushing or chewing;
- to discontinue Movantik if treatment with the opioid pain medication is also discontinued;
- to avoid grapefruit or grapefruit juice during treatment with Movantik;
- that they should tell healthcare providers when they start or stop taking other medications;
- that they should discontinue Movantik and promptly seek medical attention if they develop unusually severe, persistent or worsening abdominal pain;
- that clusters of symptoms consistent with opioid withdrawal may occur while taking Movantik, including sweating, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning;
- that if they take methadone as therapy for their pain condition, they may be more likely than patients receiving other opioids to have gastrointestinal adverse reactions such as abdominal pain and diarrhea that may be related to opioid withdrawal;
- that Movantik taken during pregnancy may precipitate opioid withdrawal in a fetus;
- that females who are nursing should not breastfeed during treatment with Movantik due to the potential for opioid withdrawal in nursing infants.

*A complete list of information is available in the product's *Medication Guide*.

with naloxegol is included in the product's prescribing information. For moderate CYP3A4 inhibitors (e.g., diltiazem, erythromycin, verapamil), use with naloxegol should be avoided; if unavoidable, reduce dosage to 12.5 mg once daily and monitor for adverse reactions. For strong CYP3A4 inducers (e.g., rifampin, carbamazepine, St. John's wort), concomitant use with naloxegol can result in decreased concentrations of naloxegol. Concomitant use is not recommended.

For other opioid antagonists, there is potential for an additive effect and increased risk of opioid withdrawal. Concomitant use should be avoided.

Administration, Dosing, and Availability. The recommended dose of Movantik is 25 mg once daily in the morning. If the patient is unable to tolerate 25 mg, dosages may be reduced to 12.5 mg once daily. The drug should be taken on an empty stomach, one hour prior to the first meal of the day or two hours after the meal. Tablets should be swallowed whole. Movantik is efficacious in patients who have taken opioids for at least four weeks. Sustained exposure to opioids prior to starting Movantik may increase the patient's sensitivity to the effects of Movantik. It is not necessary to alter an analgesic dosing regimen prior to initiating Movantik. It is supplied as 12.5 mg and 25 mg tablets.

Patient Counseling. An FDA-approved *Medication Guide* must be dispensed with each new or refill prescription for Movantik. Specific counseling points are summarized in Table 4.

Netupitant (ingredient in Akynzeo)

Akynzeo (a-KIN-zee-oh) is a combination product comprised of the new drug netupitant, along with palonosetron (Aloxi) which was approved in 2008.

Indications and Use. Akynzeo is indicated for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy including, but not limited to, highly emetogenic chemotherapy.

Cancer Chemotherapy and the Gastrointestinal Tract. Chemotherapeutic agents produce nausea and vomiting by stimulating release of serotonin from the enterochromaffin cells of the small intestine. Serotonin then activates 5-HT_3 receptors located on vagal afferents to initiate the vomiting reflex. Development of acute emesis depends on serotonin, and its 5-HT_3 receptors have been demonstrated to selectively stimulate the emetic response. Delayed emesis has been largely associated with activation of tachykinin family neurokinin 1 (NK_1) receptors (widely distributed in the central and peripheral nervous systems) by substance P. Nausea and vomiting with chemotherapy are now viewed as something to be *treated* rather than *tolerated* by the patient.

Mechanism of Action. Netupitant is a selective antagonist of human substance P/NK_1 receptors. Palonosetron is a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor with little or no affinity for others. Palonosetron thus prevents nausea and vomiting during the acute phase, and netupitant prevents nausea and vomiting in both the acute and delayed phases of chemotherapy.

Efficacy and Safety. Safety and effectiveness were established in two clinical trials of 1,720 participants receiving cancer chemotherapy. Participants were randomly assigned to receive Akynzeo or oral palonosetron. The trials were designed to measure whether the study drugs prevented vomiting episodes in the acute, delayed and overall phases after the start of cancer chemotherapy.

Results of the first trial showed that 98.5 percent, 90.4 percent, and 89.6 percent of Akynzeo-treated participants did not experience vomiting or require rescue medication for nausea during the acute, delayed and overall phases, respectively. In contrast, 89.7 percent, 80.1 percent and 76.5 percent of participants treated with oral palonosetron alone did not experience vomiting or require rescue medica-

Table 5
Patient information for Akynzeo*

Inform patients:
- to read the FDA-approved Prescribing Information leaflet;
- to take Akynzeo with or without food approximately one hour prior to the start of chemotherapy;
- that hypersensitivity reactions, including anaphylaxis, have been reported in patients receiving Aloxi. Since Akynzeo contains the same ingredient as in Aloxi, hypersensitivity reactions, including anaphylaxis, may occur. Patients should seek immediate medical attention if any signs or symptoms of a hypersensitivity reaction occur while taking Akynzeo;
- to seek immediate medical attention if the following symptoms occur: changes in mental status, autonomic instability, or neuromuscular symptoms, with or without gastrointestinal symptoms.

*A complete list of information is available in the product's Prescribing Information leaflet.

tion for nausea during the acute, delayed and overall phases, respectively. The second trial showed similar results.

Common adverse effects of Akynzeo in the clinical trials were headache, asthenia, fatigue, indigestion (dyspepsia) and constipation.

Warnings, Precautions, and Contraindications. The following **warnings** and **precautions** are listed:

- *Hypersensitivity reactions, including anaphylaxis*: These outcomes have been reported in patients receiving palonosetron with or without known hypersensitivity to other 5-HT_3 receptor antagonists.
- *Serotonin syndrome*: The syndrome may include signs and symptoms of mental status changes (e.g., agitation, hallucinations), autonomic instability (e.g., tachycardia, labile blood pressure), neuromuscular instability (e.g., tremor, rigidity, incoordination), and seizures. The syndrome has been reported with 5-HT_3 receptor antagonists alone, but particularly with concomitant use of serotonergic drugs. If symptoms occur, discontinue therapy and initiate supportive treatment.

The drug's manufacturer reports that no **contraindications** are listed.

Drug Interactions. Inhibition of CYP3A4 by netupitant can result in increased plasma concentrations of the concomitant drug that can last at least four days, and may last longer after a single dose of Akynzeo. Use the two drugs together with caution.

Use with CYP3A4 inducers (e.g., rifampin) can decrease plasma concentrations of netupitant. Concomitant use should be avoided.

Serotonin syndrome (including altered mental status, autonomic instability, and neuromuscular symptoms) has been described following concomitant use of 5-HT_3 receptor antagonists and other serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs), and serotonin and norepinephrine reuptake inhibitors (SNRIs).

Administration, Dosing, and Availability. For highly emetogenic chemotherapy, including cisplatin-based chemotherapy, the recommended dosage is one capsule of Akynzeo administered approximately one hour prior to the start of chemotherapy, with dexamethasone 12 mg orally 30 minutes prior to chemotherapy on Day 1, and dexamethasone 8 mg orally once daily on Days 2 to 4. For anthracyclines and cyclophosphamide-based chemotherapy and chemotherapy not considered highly emetogenic, the recommended dose is one capsule of Akynzeo approximately one hour prior to the start of chemotherapy, with dexamethasone 12 mg administered orally 30 minutes prior to chemotherapy on Day 1. Administration of dexamethasone on Days 2 to 4 is not necessary. Akynzeo can be taken with or without food. Akynzeo is available as capsules containing 300 mg netupitant and 0.5 mg palonosetron.

Patient Counseling. Specific points for patient counseling are summarized in Table 5.

Overview and Summary

Two new drugs (Blincyto and Harvoni) detailed in this lesson have been approved to treat life-threatening conditions. Two others (Akynzeo and Movantik) have been approved to relieve specific side effects common with drug regimens used by millions of Americans. All four agents offer patients renewed hope with improved therapy, and all are welcomed additions to their respective therapeutic armamentaria.

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This lesson is a knowledge-based CPE activity and is targeted to pharmacists in all practice settings.

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continuing education quiz

New Drugs: Akynzeo, Blincyto, Harvoni, and Movantik

1. All of the following are true about acute lymphoblastic leukemia EXCEPT:
   a. it is the most common leukemia in children and teens.
   b. it accounts for 75% of leukemia in children and teens.
   c. the bone marrow makes too many B-cell lymphoblasts.
   d. most deaths occur in children under 5 years of age.

2. The *Boxed Warning* for Blincyto refers to the cytokine-releasing syndrome and:
   a. gastrointestinal perforation.
   b. neurological toxicities.
   c. thyroid cancer.
   d. serotonin syndrome.

3. Blincyto therapy should be interrupted if blood bilirubin rises to more than which of the following upper limits of normal?
   a. 3
   b. 5
   c. 8
   d. 10

4. Harvoni is the first fixed-dose combination product approved to treat chronic HCV genotype 1 infection.
   a. True
   b. False

5. Which genotype of HCV is associated with a higher rate of hepatitis steatosis?
   a. Genotype 1
   b. Genotype 2
   c. Genotype 3
   d. Genotype 4

6. HCV:
   a. is the primary cause of liver transplantation in the U.S.
   b. affects 100 million people worldwide.
   c. leads to kidney cancer.
   d. is especially prevalent in the middle class.

7. The recommended daily dose of ledipasvir with sofosbuvir is:
   a. 45 mg.
   b. 90 mg.
   c. 180 mg.
   d. 400 mg.

Completely fill in the lettered box corresponding to your answer.

1.	[a]	[b]	[c]	[d]	6.	[a]	[b]	[c]	[d]	11.	[a]	[b]	[c]	[d]
2.	[a]	[b]	[c]	[d]	7.	[a]	[b]	[c]	[d]	12.	[a]	[b]	[c]	[d]
3.	[a]	[b]	[c]	[d]	8.	[a]	[b]	[c]	[d]	13.	[a]	[b]	[c]	[d]
4.	[a]	[b]			9.	[a]	[b]	[c]	[d]	14.	[a]	[b]		
5.	[a]	[b]	[c]	[d]	10.	[a]	[b]	[c]	[d]	15.	[a]	[b]	[c]	[d]

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2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
3. Was the content balanced and without commercial bias?
   ❑ yes ❑ no If no, why?_____
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6. Comments/future topics welcome.

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8. Appropriate counseling advice for Movantik is to:
   a. warn against taking on an empty stomach.
   b. swallow the tablet whole without crushing.
   c. refrain from driving while taking Movantik.
   d. avoid sunlight and use a sunscreen with SPF 50 or higher.

9. Which of the following is not recommended to be administered with amiodarone due to severe bradycardia?
   a. Akynzeo
   b. Blincyto
   c. Movantik
   d. Harvoni

10. Naloxegol's mechanism of action is to antagonize:
   a. μ-opioid receptors.
   b. κ-opioid receptors.
   c. δ-opioid receptors.
   d. ς-opioid receptors.

11. Common adverse effects of Akynzeo in clinical trials included all of the following EXCEPT:
   a. headache.
   b. constipation.
   c. tremor.
   d. fatigue.

12. Which of the following is used concurrently with Akynzeo for emetogenic chemotherapy?
   a. Prednisone
   b. Dexamethasone
   c. Prednisolone
   d. Triamcinolone

13. Movantik is efficacious in patients who have taken opioids for at least:
   a. one day.
   b. one week.
   c. four days.
   d. four weeks.

14. Which of the following prevents nausea and vomiting in both the acute and delayed phases of chemotherapy?
   a. Netupitant
   b. Palonosetron

15. Label contraindications for Movantik include all of the following EXCEPT:
   a. GI obstruction.
   b. hypersensitivity reaction to Movantik or its excipients.
   c. moderate CYP3A4 inhibitors.
   d. concomitant use with strong CYP3A4 inhibitors.

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