New Drugs 2016 PART 3

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THIS ARTICLE REVIEWS 23 drugs recently approved by the FDA, including:

- a medication approved to treat both men and women for irritable bowel syndrome characterized by diarrhea.
- an antiemetic indicated to prevent delayed nausea and vomiting associated with cancer chemotherapy.
- 14 newly marketed antineoplastic drugs.
- 3 drugs approved for rare disorders.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the package insert, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions for all these drugs.

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DRUG FOR IBS WITH DIARRHEA

Eluxadoline

Indicated for both men and women with IBS-D

Irritable bowel syndrome (IBS) is estimated to affect about 1.4 million Americans, most of whom are diagnosed before age 30.[1] Some patients with IBS experience diarrhea as the most common manifestation (IBS-D); in others, constipation is the most common manifestation (IBS-C).

A functional bowel disorder, IBS-D is characterized by chronic abdominal pain and frequent diarrhea (loose or watery stools at least 25% of the time). Although loperamide may help control diarrhea, it doesn't adequately relieve symptoms in many patients.

Until recently, the serotonin subtype 3 receptor antagonist alosetron was the only available drug with a labeled indication for treatment of IBS-D. However, it's indicated only for the treatment of women with severe IBS-D and is available only under the provisions of a risk management program because of its potential to cause serious gastrointestinal (GI) adverse reactions such as ischemic colitis and serious complications of constipation.

Eluxadoline (*Viberzi*, Allergan) is a mu-opioid receptor agonist that also acts as an agonist at kappa-opioid receptors and as an antagonist at delta-opioid receptors. It's indicated for the treatment of adults with IBS-D. Unlike alosetron, eluxadoline is indicated for use in men as well as women.[2]

On the same day that eluxadoline was approved, the FDA also approved rifaximin to treat adults with IBS-D. Rifaximin, which has a different mechanism of action, had previously been approved to treat travelers' diarrhea caused by noninvasive strains of *Escherichia coli* and to reduce the risk of overt hepatic encephalopathy recurrence.

The mu-opioid receptor agonist action of eluxadoline may increase the risk of spasm in the sphincter of Oddi, the smooth muscle that surrounds the end portion of the common bile duct and pancreatic duct. Patients without a gallbladder are at increased risk for this response, and some patients also experienced pancreatitis. However, fewer than 1% of the patients in the clinical trials experienced sphincter of Oddi spasm and less than 1% experienced pancreatitis.

In two abuse potential studies of eluxadoline in recreational opioid-experienced individuals, euphoria was reported at a rate of 14% to 28%. These data suggest that the drug may produce psychological dependence. It's included in Schedule IV under the provisions of the Controlled Substances Act.

Precautions: (1) Contraindicated in patients with known or suspected biliary duct obstruction or sphincter of Oddi disease, a history of pancreatic disease, or severe hepatic impairment, and in patients who consume large quantities of alcoholic beverages; for example, those who abuse alcohol or who drink more than three alcoholic beverages a day. (2) Monitor patients without a gallbladder for new or worsening abdominal pain or acute biliary pain with liver or pancreatic enzyme elevations. If such signs or symptoms develop, patients should discontinue the use of eluxadoline and seek medical attention. (3) Contraindicated in patients with known or suspected mechanical GI obstruction, or a history of chronic or severe constipation or complications from constipation. (4) Avoid concurrent use with opioid analgesics, anticholinergic agents, or other drugs that may cause constipation. (5) Loperamide may be used occasionally for the acute management of severe diarrhea but it shouldn't be used on a continuing basis. Loperamide should be immediately discontinued if constipation occurs. (6) Eluxadoline is an inhibitor of organic anion-transporter polypeptide 1B1 (OATP1B1). If an OATP1B1 inhibitor such as cyclosporine or gemfibrozil is used concurrently, the action of eluxadoline may be increased and the dosage should be reduced. (7) Along with OATP1B1, eluxadoline also inhibits breast cancer resistance protein and may increase the action of drugs such as rosuvastatin that are substrates of these transporters. If used concurrently with eluxadoline, the lowest effective dose of rosuvastatin should be used. (8) The concurrent use of a strong CYP inhibitor (such as clarithromycin, paroxetine, fluconazole, gemfibrozil, and ciprofloxacin) may increase the action of eluxadoline; patients should be monitored for possible impairment of mental or physical abilities needed to perform potentially hazardous activities such as driving. (9) Eluxadoline may increase the action of drugs that are CYP3A substrates and have a narrow therapeutic index, such as cyclosporine and fentanyl. Concurrent use should be closely monitored.

Adverse reactions: constipation, abdominal pain, nausea

Supplied as: 75 mg and 100 mg tablets

Dosage: 100 mg twice a day with food. The dosage should be reduced to 75 mg twice a day with food in patients who don't have a gallbladder, have mild or moderate hepatic

impairment, are concurrently taking an OATP1B1 inhibitor, or who can't tolerate the 100 mg dose.

Nursing considerations: (1) Tell patients to take one tablet twice a day with food, or as otherwise prescribed. (2) Warn patients with liver impairment to avoid driving and other potentially hazardous activities until they learn how the drug affects them. (3) Instruct patients to discontinue the drug and contact their healthcare provider if they experience severe constipation for more than 4 days. (4) If a dose is missed, the next dose should be taken at the regular time, but warn patients not to take a double dose. (5) Warn patients using loperamide to manage diarrhea to avoid prolonged use and to discontinue it immediately if they become constipated. (6) Tell patients to limit or avoid alcohol use, which increases the risk of pancreatitis. (7) Warn patients about the drug's abuse potential and tell them to keep it in a safe place to protect against theft.

REFERENCES

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2. Viberzi (eluxadoline) tablets, for oral use. Prescribing information. www.allergan.com/assets/pdf/viberzi_pi.

ANTIEMETIC

Rolapitant hydrochloride

Prevention of nausea and vomiting following cancer chemotherapy

Many of the antineoplastic agents included in cancer chemotherapy regimens are associated with nausea and vomiting. Antiemetic regimens prescribed to prevent or manage these adverse reactions often include a serotonin subtype 3 (5-HT_3) receptor antagonist such as ondansetron, granisetron, or palonosetron; a substance P/neurokinin 1 (NK_1) receptor antagonist such as aprepitant or netupitant (included with palonosetron in the combination product Akynzeo); and dexamethasone. The 5-HT_3 antagonists prevent nausea and vomiting during the acute phase after cancer chemotherapy, and aprepitant and netupitant prevent nausea and vomiting during both the acute and delayed phases. Dexamethasone adds to the regimen's effectiveness.

Rolapitant hydrochloride (*Varubi*, Tesaro) is the third substance P/NK_1 receptor antagonist to be marketed in the United States. It's indicated for use in combination with other antiemetics in adults to prevent delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including (but not limited to) highly emetogenic chemotherapy such as cisplatin-based regimens. Rolapitant has a longer duration of action than aprepitant and netupitant, and its primary benefit is prevention of delayed nausea and vomiting.

The new drug's effectiveness was demonstrated in three studies in which a regimen of rolapitant, granisetron, and dexamethasone was compared with a control therapy that included granisetron, dexamethasone, and placebo. The primary endpoint in the studies was a complete response (defined as no emetic episodes and no rescue medication) in the delayed phase (25 to 120 hours) of chemotherapy-induced nausea and vomiting. Approximately 70% of the patients treated with the regimen that included rolapitant experienced a complete response, compared with about 60% of those receiving the control regimen. Rolapitant hasn't been directly compared with aprepitant or netupitant in clinical studies.

The labeled indication for rolapitant, prevention of delayed nausea and vomiting, is more limited than the indications for aprepitant and netupitant, which are indicated to prevent both acute and delayed nausea and vomiting. Aprepitant is also indicated for prevention of postoperative nausea and vomiting.

Precautions: (1) Contraindicated in patients receiving thioridazine, a CYP2D6 substrate. Rolapitant is a moderate inhibitor of the CYP2D6 metabolic pathway and a single dose may inhibit the CYP2D6 pathway for at least 7 days. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and torsades de pointes. (2) Avoid concurrent use with other CYP2D6 substrates with a narrow therapeutic index, such as pimozide. (3) Rolapitant is also an inhibitor of breast cancer resistance protein (BCRP) and an inhibitor of P-glycoprotein (P-gp). The use of rolapitant in patients treated with a BCRP substrate with a narrow therapeutic index (such as methotrexate, irinotecan, or topotecan) is best avoided, and rosuvastatin should be used in the lowest effective dosage. If rolapitant is used concurrently with a P-gp substrate with a narrow therapeutic index (such as digoxin), the patient should be closely monitored during treatment. (4) Strong CYP3A4 inducers such as rifampin significantly reduce rolapitant's plasma concentration. Avoid use of rolapitant in patients who require chronic administration of such drugs.

Adverse reactions: *In patients treated with cisplatin-based highly emetogenic chemotherapy (cycle 1):* neutropenia, hiccups. *In patients receiving moderately emetogenic chemotherapy and a combination of an anthracycline and cyclophosphamide:* anorexia, neutropenia, dizziness.

Supplied as: 90 mg film-coated tablets

Dosage: 180 mg as a single dose approximately 1 to 2 hours before chemotherapy on Day 1. Consult the prescribing information for dosage guidelines for other drugs in the antiemetic regimen based on the prescribed type and day of chemotherapy. The antiemetic regimen should be administered before the initiation of each chemotherapy cycle but at no less than 2-week intervals.

Selected drugs for rare disorders marketed in 2015[1-3]

Drug name (*trade name,* manufacturer), description	Route	Indications
Asfotase alfa (*Strensiq,* Alexion) A tissue nonspecific alkaline phosphatase	Subcutaneous	Treatment of perinatal/infantile- and juvenile-onset hypophosphatasia
Cholic acid (*Cholbam,* Asklepion) A bile acid	Oral	Treatment of bile acid synthesis disorders due to single enzyme defects; also indicated for adjunctive treatment of peroxisomal disorders including Zellweger spectrum disorders in patients who exhibit manifestations of liver disease, steatorrhea, or complications from decreased fat-soluble vitamin absorption
Sebelipase alfa (*Kanuma,* Alexion) A hydrolytic lysosomal cholesteryl ester and triacylglycerol-specific enzyme	I.V.	Treatment of patients with lysosomal acid lipase deficiency

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1. Strensiq (asfotase alfa) injection, for subcutaneous use. Prescribing information. www.strensiq.com/images/Strensiq_PRESCRIBING_INFORMATION.pdf.
2. Cholbam (cholic acid) capsules, for oral use. Prescribing information. www.cholbam.com/pdf/Cholbam-PI.pdf.
3. Kanuma (sebelipase alfa) injection, for intravenous use. Prescribing information. http://kanuma.com/docs/full-prescribing-information.pdf.

Nursing considerations: (1) Teach patients to take two tablets of rolapitant 1 to 2 hours before Day 1 of their chemotherapy regimen, as directed. Rolapitant can be taken without regard to food. (2) Warn patients not to take rolapitant more than once in 14 days. If they take too much, they should immediately contact their healthcare provider or go to a hospital ED. (3) Because rolapitant interacts with many drugs, remind patients to inform their healthcare provider about all medications they take or that they stop taking, including over-the-counter products, herbal remedies, vitamins, and dietary supplements.

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ANTIPLATELET DRUG

Cangrelor

The first $P2Y_{12}$ platelet inhibitor to be administered I.V.

In the United States, approximately 500,000 people undergo percutaneous coronary intervention (PCI) each year.[1] This procedure opens an occluded or stenotic coronary artery to improve blood flow to the myocardium; it's usually followed by endovascular stent placement to maintain coronary artery patency. However, the procedure is associated with a risk of platelet aggregation and thrombosis that may result in complications such as myocardial infarction (MI) and stent thrombosis.

Cangrelor (*Kengreal*, The Medicines Company) is an antiplatelet drug with activity that's most similar to that of clopidogrel, prasugrel, and ticagrelor. These drugs are all $P2Y_{12}$ platelet receptor inhibitors that block adenosine diphosphate–induced platelet activation and aggregation.

Cangrelor is the first $P2Y_{12}$ platelet inhibitor to be administered I.V. It's indicated as an adjunct to PCI to reduce the risk of periprocedural MI, repeat coronary revascularization, and stent thrombosis in patients who've not been treated with a $P2Y_{12}$ platelet inhibitor and who aren't being given a glycoprotein IIb/IIIa inhibitor such as eptifibatide or tirofiban.[2]

When cangrelor is administered as an I.V. bolus followed by an I.V. infusion, platelet inhibition occurs within 2 minutes. Following discontinuation of the infusion, the antiplatelet effect decreases rapidly and platelet function returns to normal within 1 hour. The use of cangrelor is followed with the use of an oral $P2Y_{12}$ inhibitor.

The effectiveness of cangrelor was demonstrated in a study in which it was compared with clopidogrel in more than 10,000 patients undergoing PCI who hadn't been previously treated with antiplatelet therapy other than aspirin. The primary outcome measure was the first occurrence of any one of the composite endpoint of all-cause mortality, MI, stent thrombosis, and ischemia-driven revascularization within 48 hours of randomization. Cangrelor significantly reduced the occurrence of primary composite endpoint events compared with clopidogrel (4.7% and 5.9%, respectively), representing a relative risk reduction of 22%. Most of the effect was a reduction in postprocedural MIs. However, cangrelor didn't reduce the risk of death, which was 0.3% in both groups.

Bleeding is the most important risk associated with cangrelor. Bleeding events occurred in 15.5% of the patients treated with the new drug in the clinical trial. These events occurred more often than in patients treated with clopidogrel, in whom the corresponding incidence was 10.9%.

Precautions: (1) Contraindicated in patients with significant active bleeding. (2) Contraindicated in patients with hypersensitivity to cangrelor or any component of the product.

Adverse reaction: bleeding

Supplied as: a lyophilized powder in single-use vials containing 50 mg of the drug

Dosage: 30 mcg/kg as an I.V. bolus administered in less than a minute, administered prior to the start of the PCI. The I.V. bolus should be followed immediately with a 4 mcg/kg/minute I.V. infusion continuing for at least 2 hours or for the duration of the PCI, whichever is longer.

Nursing considerations: (1) Reconstitute vial contents with 5 mL of Sterile Water for Injection. Immediately dilute the reconstituted solution further by withdrawing the vial contents and adding to a 250 mL bag of 0.9% Sodium Chloride or 5% Dextrose Injection. Mix thoroughly and inspect the bag for particles. (2) Rapidly administer the bolus volume from the diluted bag via manual I.V. push or pump. The bolus should be completely administered before the start of PCI, and the infusion should be started immediately after discontinuation of the bolus. (3) Following discontinuation of the I.V. infusion of cangrelor, administer an oral $P2Y_{12}$ platelet inhibitor, as prescribed, to maintain platelet inhibition. Although ticagrelor may be administered at any time during the cangrelor infusion or immediately following discontinuation, clopidogrel and prasugrel will have no effect if given during the cangrelor infusion and must not be administered until the infusion is discontinued.

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ANTIASTHMATIC DRUG

Mepolizumab

Add-on maintenance therapy for some patients with severe asthma

Many patients with asthma don't respond adequately to conventional therapy; in the United States, more than 400,000 asthma-related hospitalizations occur each year.[1] Patients with asthma and an eosinophilic phenotype typically have severe disease characterized by high concentrations of eosinophils in the blood and sputum. Multiple cell types, including eosinophils, and mediators such as cytokines are involved in the inflammatory process that occurs in pulmonary airways. Interleukin-5 (IL-5) is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils.

Mepolizumab (*Nucala*, GlaxoSmithKline) is an IL-5 antagonist monoclonal antibody that reduces the production and survival of eosinophils. Given subcutaneously, it's indicated for the add-on maintenance treatment of patients age 12 and older with severe asthma and an eosinophilic phenotype.

The effectiveness of mepolizumab was demonstrated in three placebo-controlled studies in which either the new drug or placebo was added to an existing treatment regimen (such as oral and/or inhaled corticosteroids). In one of the studies, the primary endpoint was the percent reduction of the oral corticosteroid dose during weeks 20 to 24 compared with the baseline dose, while maintaining asthma control. Twenty-three percent of the patients treated with mepolizumab had a 90% to 100% reduction in their oral corticosteroid dose, compared with 11% in the placebo group. Additionally, 54% of patients treated with the new drug achieved at least a 50% reduction in the daily corticosteroid dose compared with 33% of those receiving placebo. However, mepolizumab didn't provide consistent improvements in mean change from baseline in mean forced expiratory volume in one second (FEV_1).

Information on the use of mepolizumab in pregnant women is very limited although no evidence of fetal harm was found in animal studies. A pregnancy exposure registry has been established (1-877-311-8972) to monitor pregnancy outcomes in women exposed to the drug during pregnancy.

Precautions: (1) Contraindicated in patients with a history of hypersensitivity to mepolizumab or excipients in the formulation. (2) Not indicated to treat acute bronchospasm or status asthmaticus, or to treat other eosinophilic conditions. (3) In clinical trials, some patients experienced hypersensitivity reactions (rash, pruritus, angioedema, bronchospasm); discontinue treatment if such responses occur. (4) Treatment with a systemic or inhaled corticosteroid shouldn't be discontinued abruptly upon initiation of therapy with mepolizumab. A reduction in corticosteroid dosage, which should be gradual, may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy. (5) In clinical trials, two patients treated with mepolizumab experienced serious herpes zoster reactions compared with none in the placebo group. If appropriate, varicella vaccination should be considered before therapy begins. (6) Preexisting helminth parasitic infections should be treated before initiating therapy with the new drug. Because eosinophils may be involved in the immunologic response to some helminth infections, patients with known parasitic infections were excluded from participation in the clinical trials and it's not known whether mepolizumab will influence a patient's response to a parasitic infection. If a helminth infection occurs during treatment with mepolizumab and doesn't respond to treatment, mepolizumab should be discontinued until the infection resolves.

Adverse reactions: headache, injection site reactions, back pain, fatigue

Supplied as: single-dose vials containing 100 mg of lyophilized powder for reconstitution

Dosage: 100 mg once every 4 weeks by subcutaneous injection into the upper arm, thigh, or abdomen

Nursing considerations: (1) The drug should be reconstituted and administered by a healthcare professional. Reconstitute vial contents with 1.2 mL of Sterile Water for Injection. Swirl (but don't shake) the vial for 10 seconds with a circular motion at 15-second intervals until the powder is dissolved. Reconstitution usually takes less than 5 minutes, but more time is sometimes required for complete dissolution. (2) Administer the solution in the upper arm, thigh, or abdomen within 8 hours of reconstitution. (3) Store the drug in its original packaging to protect it from light. (4) Teach patients to recognize and report signs and symptoms of possible adverse reactions to mepolizumab, such as hypersensitivity reactions and opportunistic herpes zoster infection. (5) Warn patients not to stop taking any corticosteroid abruptly; if indicated, it should be discontinued gradually as directed by the healthcare provider.

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DRUGS FOR CYSTIC FIBROSIS

Lumacaftor/ivacaftor

Combination product treats patients with a common mutation in the CFTR gene

Usually diagnosed during infancy or childhood, cystic fibrosis is a progressive genetic disease that affects approximately 30,000 people in the United States and is the most common fatal genetic disease among White Americans.[1,2] It's caused by a gene mutation resulting in defective and/or missing cystic fibrosis transmembrane conductance regulator (CFTR) protein, which regulates chloride and water transport throughout the body, including the lungs, sweat glands, GI tract, and pancreas. Because of the defect in chloride and water transport, thick mucus forms and builds up in the lungs, digestive tract, and other areas. Manifestations of the disease include chronic cough and persistent lung and sinus infections, pancreatic insufficiency, and other severe digestive problems.

More than 1,900 mutations in the CFTR gene have been identified, with the F508del mutation being the most common cause of cystic fibrosis. Patients who are homozygous for this mutation, meaning they've inherited two copies of this mutation, one from each parent, account for about half of patients with cystic fibrosis in the United States.

In 2012, ivacaftor was marketed as the first treatment for cystic fibrosis that targets the underlying cause of the disease. Acting as a *CFTR potentiator*, it facilitates increased chloride transport. It was initially approved for patients age 6 or older who have a G551D mutation in the CFTR gene. However, only about 4% of patients with cystic fibrosis have this mutation. The labeled indications were subsequently expanded to cover additional genetic mutations, but when used alone, ivacaftor isn't effective in patients who are homozygous for the F508del mutation.

Lumacaftor/ivacaftor (*Orkambi*, Vertex) is a fixed-dose combination of ivacaftor and the new drug lumacaftor. It's been approved to treat cystic fibrosis in patients age 12 and older who are homozygous for the F508del mutation in the CFTR gene.[3] Lumacaftor improves the stability of F508del-CFTR and increases the quantity of mature protein that reaches the cell surface. It's designated as a *CFTR corrector*. The combination formulation was evaluated in two 24-week placebo-controlled studies that demonstrated improved lung function and a reduction in pulmonary exacerbations in patients taking the new drug.

The effectiveness and safety of lumacaftor/ivacaftor haven't been established in patients with cystic fibrosis other than those who are homozygous for the F508del mutation. If a patient's genotype isn't known, an FDA-cleared cystic fibrosis mutation test should be performed before this treatment is prescribed.

Lumacaftor is a strong inducer of CYP3A and its use in combination with ivacaftor, a sensitive CYP3A substrate, reduces the exposure of the latter drug by approximately 80%. Accordingly, the dose of ivacaftor when used in the combination formulation (250 mg) is higher than when it's used alone (150 mg).

Precautions: (1) Use lumacaftor/ivacaftor with caution in patients with advanced liver disease. In patients with moderate or severe hepatic impairment, the dosage should be reduced. Determine serum transaminases and bilirubin before initiating therapy, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring may be indicated in patients with a history of liver function test elevations. Treatment should be interrupted if a patient experiences elevations in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to greater than 5 times (x) the upper limit of normal (ULN), or ALT or AST greater than 3 x ULN with bilirubin greater than 2 x ULN. (2) In patients whose percent predicted forced expiratory volume in 1 second ($ppFEV_1$) is less than 40, additional monitoring is recommended. In clinical trials, respiratory adverse reactions were more common during the initiation of treatment. (3) Periodically monitor BP during therapy. Some patients taking the new drug have experienced increased BP. (4) Baseline and follow-up ophthalmologic examinations are recommended in

Antineoplastic drugs marketed in 2015[1-14]

Drug (*trade name*, manufacturer), description	Route	Indications
Daratumumab (*Darzalex,* Janssen Biotech) A human monoclonal antibody against CD38 antigen, a transmembrane glycoprotein expressed on the surface of hematopoietic cells	I.V.	To treat multiple myeloma in patients who've received at least three prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent
Elotuzumab (*Empliciti,* Bristol-Myers Squibb) A human monoclonal antibody directed to signaling lymphocytic activation molecule family 7 (SLAMF7) protein, a cell surface glycoprotein	I.V.	Administered in a combination regimen with lenalidomide and dexamethasone for treatment of patients with multiple myeloma who've received one to three prior therapies
Ixazomib citrate (*Ninlaro,* Takeda) A reversible proteasome inhibitor	Oral	Administered in combination with lenalidomide and dexamethasone for treatment of patients with multiple myeloma who've received at least one prior therapy
Panobinostat lactate (*Farydak,* Novartis) A histone deacetylase inhibitor	Oral	Administered in combination with bortezomib and dexamethasone for treatment of patients with multiple myeloma who've received at least two prior regimens including bortezomib and an immunomodulatory agent
Necitumumab (*Portrazza,* Lilly) A human monoclonal antibody that's an epidermal growth factor receptor (EGFR) antagonist	I.V.	Administered in a combination regimen with gemcitabine and cisplatin for first-line treatment of patients with metastatic squamous non–small cell lung cancer
Osimertinib mesylate (*Tagrisso,* AstraZeneca) A kinase inhibitor of EGFR	Oral	Treatment of patients with metastatic EGFR T790M mutation-positive non–small cell lung cancer, as detected by an FDA-approved test, who've progressed on or after EGFR tyrosine kinase inhibitor therapy
Palbociclib (*Ibrance,* Pfizer) A kinase inhibitor	Oral	In combination with letrozole for treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease
Lenvatinib mesylate (*Lenvima,* Eisai) A receptor tyrosine kinase inhibitor that inhibits the kinase activities of vascular endothelial growth factor receptors (VEGFRs)	Oral	Locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and renal cell cancer (RCC) in combination with everolimus for patients with advanced RCC following one prior anti-angiogenic therapy
Tipiracil hydrochloride/trifluridine (*Lonsurf,* Taiho Oncology) A thymidine phosphorylase inhibitor that increases the exposure of trifluridine, a thymidine-based nucleoside analogue, by inhibiting its metabolism by thymidine phosphorylase	Oral	Treatment of patients with metastatic colorectal cancer who've been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy
Cobimetinib fumarate (*Cotellic,* Genentech) A reversible inhibitor of mitogen-activated protein kinase/extracellular signal regulated kinase 1 (MEK1) and MEK2	Oral	Administered in combination with vemurafenib for the treatment of patients with unresectable or metastatic melanoma with a BRAF V600E or V600K mutation
Talimogene laherparepvec (*Imlygic,* Amgen) A genetically modified oncolytic viral therapy	Intra-lesional injection	Administered for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery
Sonidegib phosphate (*Odomzo,* Novartis) A Smoothened antagonist that inhibits the Hedgehog signaling pathway	Oral	Treatment of patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, and for those who aren't candidates for surgery or radiation therapy
Trabectedin (*Yondelis,* Janssen Biotech) An alkylating agent	I.V.	Unresectable or metastatic liposarcoma or leiomyosarcoma in patients who've received a prior anthracycline-containing regimen
Dinutuximab (*Unituxin,* United Therapeutics) A chimeric monoclonal antibody that binds to the glycolipid GD2	I.V.	Administered in a combination regimen with granulocyte-macrophage colony-stimulating factor, interleukin-2, and 13-cis-retinoic acid for the treatment of pediatric patients with high-risk neuroblastoma who achieved at least a partial response to prior first-line multiagent, multimodality therapy

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pediatric patients. Noncongenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor. (5) Because lumacaftor/ivacaftor may reduce the exposure and activity of other sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index, concurrent use with midazolam, triazolam, cyclosporine, everolimus, sirolimus, or tacrolimus isn't recommended. (6) Also avoid concurrent use with itraconazole, ketoconazole, posaconazole, or voriconazole because their effectiveness in the treatment of fungal infections may be compromised. (7) Lumacaftor/ivacaftor may reduce the activity of hormonal contraceptives. (8) Lumacaftor/ivacaftor may alter the activity of many other commonly prescribed drugs, including digoxin, warfarin, and some antidiabetic drugs, and many common drugs can affect the action of lumacaftor/ivacaftor (for example, prednisone, clarithromycin, ibuprofen, and citalopram). Consult the prescribing information for a full list of potential drug interactions and detailed recommendations.

Adverse reactions: dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory infection, fatigue, abnormal respiration, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, influenza

Supplied as: tablets containing 200 mg of lumacaftor and 125 mg of ivacaftor

Dosage: two tablets every 12 hours with fat-containing food. *In patients with moderate hepatic impairment:* reduce the dosage to two tablets in the morning and one tablet in the evening. *In patients with severe hepatic impairment:* the maximum recommended dosage is one tablet in the morning and one tablet in the evening. Consult the prescribing information for recommended dosage modifications for patients taking a strong CYP3A inhibitor concurrently.

Nursing considerations: (1) Tell the patient to take each dose with food containing fat, such as eggs, nuts, butter, peanut butter, cheese pizza, whole milk, and whole-milk dairy products such as yogurt. Doses should be taken in the morning and evening, 12 hours apart. (2) If the patient misses a dose and remembers it within 6 hours, the dose should be taken at that time. If more than 6 hours have elapsed after the usual dosing time, that dose should be skipped and the normal schedule resumed for the following dose. (3) Tell female patients that this drug reduces the effectiveness of hormonal contraceptives, which shouldn't be relied upon as an effective method of contraception when they use lumacaftor/ivacaftor concurrently. (4) Caution patients to avoid driving and other activities requiring alertness until they learn how the drug affects them. (5) Educate patients about the importance of keeping follow-up appointments as directed to monitor liver function and BP.

REFERENCES

1. Food and Drug Administration. FDA approves new treatment for cystic fibrosis. News release. July 2, 2015.
2. Cystic Fibrosis Foundation. About cystic fibrosis. https://www.cff.org/What-is-CF/About-Cystic-Fibrosis.
3. Orkambi (lumacaftor/ivacaftor) tablets, for oral use. Prescribing information. http://pi.vrtx.com/files/uspi_lumacaftor_ivacaftor.pdf.

CYTOLYTIC DRUG

Deoxycholic acid

A new profile for double chins

Endogenous deoxycholic acid, a bile acid, is a product of cholesterol metabolism. It solubilizes dietary fat in the GI tract and facilitates fat absorption. This new drug, a synthetic form of deoxycholic acid (*Kybella*, Allergan), is identical to endogenous bile acid. Administered subcutaneously, it's the first drug indicated for use in adults for improvement in the appearance of moderate-to-severe convexity or fullness associated with submental fat (double chin). When injected into subcutaneous fat, deoxycholic acid exhibits a cytolytic action that destroys the cell membrane, causing lysis. The inflammatory response that occurs contributes to the clearing of cell debris.

The effectiveness of deoxycholic acid was evaluated in two placebo-controlled studies in adults with submental fat (grade 2 or 3 on a grading scale in which 0 = none and 4 = extreme), as judged by both clinician and patient ratings. The efficacy assessments were based on at least 2-grade and at least 1-grade improvements on the composite of clinician-reported and patient-reported ratings of submental fat 12 weeks after the final treatment. In the two trials, a 2-grade improvement occurred in 13% and 19% of patients treated with the drug, compared with 0% and 3% of those receiving placebo. A 1-grade improvement occurred in 70% and 67% of those treated with deoxycholic acid, compared with 19% and 22% of those receiving placebo.

In a subset of patients, changes in submental fat volume were evaluated using magnetic resonance imaging. Forty-three percent of patients treated with deoxycholic acid had at least a 10% reduction in submental fat volume compared with 5% of those receiving placebo.

The overall patient-reported satisfaction and self-perceived visual attributes showed greater improvement in the deoxycholic acid group than in the placebo group.

The effectiveness and safety of using deoxycholic acid for treating subcutaneous fat in areas other than below the chin haven't been established and isn't recommended.

The effective and safe use of deoxycholic acid depends on the use of the correct number and locations for injections, proper needle placement, and administration techniques. Treatments should be administered by qualified healthcare providers who should consult the product labeling for information regarding administration and injection technique. The use of ice/cold packs and or topical and/or

an injectable local anesthetic such as lidocaine may enhance patient comfort.

Precautions: (1) Contraindicated in the presence of infection at the injection sites. (2) Use caution in patients with bleeding abnormalities and in those who are currently being treated with anticoagulant or antiplatelet therapy because of the risk of excessive bleeding or bruising in the treatment area. (3) To avoid nerve injury, the drug shouldn't be injected into or in close proximity to the marginal mandibular branch of the facial nerve. Some patients in the clinical studies experienced marginal mandibular nerve injury, manifested as an asymmetric smile or facial muscle weakness. (4) Deoxycholic acid also shouldn't be injected into or in close proximity to salivary glands, lymph nodes, and muscles to avoid tissue damage. (5) Deoxycholic acid shouldn't be used in patients with dysphagia or a history of dysphagia, as the condition may be exacerbated. (6) Deoxycholic acid should be used with caution in patients with excessive skin laxity, prominent platysmal bands, or other conditions for which reduction of submental fat may result in an aesthetically undesirable outcome. (7) Caution must also be exercised in patients who've had prior surgical or aesthetic treatment of the submental area because changes in anatomy/landmarks or the presence of scar tissue may impact the clinician's ability to safely administer deoxycholic acid or obtain the desired aesthetic result.

Adverse reactions: injection site reactions (edema, hematoma/ecchymoses, pain, numbness, erythema, induration)

Supplied as: a concentration of 10 mg/mL in vials containing 2 mL of sterile solution intended for single-patient use

Dosage: injected into subcutaneous fat in the submental area using an area-adjusted dose of 2 mg/cm^2. A single treatment consists of up to a maximum of 50 injections, 0.2 mL each (up to a total of 10 mL), spaced 1-cm apart. Up to 6 single treatments may be administered at intervals no less than 1 month apart.

Nursing considerations: (1) Assess patients for bleeding disorders or use of anticoagulant or antiplatelet drugs, including over-the-counter products, which increase the risk of ecchymoses and bleeding complications. (2) Provide local anesthesia and/or ice packs for patient comfort as directed. (3) Following a treatment, discard any vials containing unused solution. ■

REFERENCE

Kybella (deoxycholic acid) injection, for subcutaneous use. Prescribing information. http://consumers.mykybella.com/~/media/Unique%20Sites/Kybella/Documents/KYBELLA-Combined-FINAL-Labeling.ashx.

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