



# CE PRN

PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

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## “New Drugs of 2015—A Banner Year”

September 2016

This educational program will focus on some of the newer agents that are of interest to pharmacy. The goal is to provide key information relevant to dosing guidelines, common adverse effects, contraindications and significant counseling points. **The program ID # for this lesson is 707-000-16-009-H01-P for pharmacists & 707-000-16-009-H01-T for technicians.**

**Participants completing this lesson by August 31, 2019 may receive full credit. Release date: September 1, 2016.**

**To obtain continuing education credit for this lesson,** you must answer the questions on the quiz (70% correct required), and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. Computerized records are maintained for each participant.

If you have any comments, suggestions or questions, contact us at the above address, or call 1-847-945-8050. **Please write your name, NABP eProfile (CPE Monitor®) ID Number & birthdate (MM/DD) in the indicated space on the quiz page.**

**The objectives of this lesson are such that upon completion participants will be able to:**

### Pharmacists:

1. Describe the new drugs approved by the FDA in 2015.
2. Discuss the role of these agents in therapy.
3. Summarize the adverse effects & potential drug interactions of the new agents.
4. Recommend specific counseling points that are essential when dispensing these agents to patients.

### Technicians:

1. Describe the new drugs approved by the FDA in 2015.
2. Discuss the role of these agents in therapy.
3. Summarize the adverse effects & potential drug interactions of the new agents.



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**“VALIDATION OF PRESCRIPTIONS FOR CONTROLLED SUBSTANCES” WILL BE THE TOPIC FOR OCTOBER, 2016.**

## INTRODUCTION

The Food and Drug Administration (FDA) approved a record 45 new molecular entities (NME) in 2015 (Table 1).<sup>1</sup> We list and describe the indications for all of the new 45 drugs. We discuss in detail a handful of the more significant and interesting examples. This was the highest number since 1996, when 53 new drugs were approved. This increase in the number of approvals reflects the new focus of pharmaceutical manufacturers on treating rare conditions which allows for a streamlined review process by FDA, longer patents and higher prices. The high cost of prescription drugs is a concern for patients, providers and insurers. However, the FDA is not permitted to consider drug price when approving a product.

The designation of breakthrough drug was authorized by Congress in 2012.<sup>1</sup> It is reserved for agents that treat serious or life threatening diseases or condition, or the agent provides substantial improvement over existing therapy. If a drug is designated as breakthrough therapy, FDA will expedite the review and development of these agents. **The FDA designated ten of the 2015 novel drugs (22%) as breakthrough therapies. Breakthrough status is designed to help shorten the development time of a potential new therapy.**

**The FDA approved 16 of the 45 (36%) drugs as First-in-Class, one indicator of how innovative new drugs were this year.<sup>1</sup> A drug designated as First-in-Class often has a mechanism of action that is different from existing therapies.** The rate of drugs with a First-in-Class approval designation is one reason that the drugs approved in 2015 include many innovative products. **Table 1 summarizes the new chemical entities approved as well as the new biologics.**

**Table 1 - New drugs of 2015<sup>1</sup>**

Generic Name	Brand Name	Manufacturer	Indication
1. Edoxaban	Savaysa	Daiichi Sankyo	Reduce the risk of stroke and blood clots in patients with atrial fibrillation not caused by a heart valve problem
2. Secukinumab	Cosentyx	Novartis	Treatment of moderate to severe plaque psoriasis
3. Parathyroid hormone	Natparaw	NPS Pharm	To control hypocalcemia in patients with hypoparathyroidism
4. Palbociclib*	Ibrance	Pfizer	Treatment of advanced breast cancer
5. Lenvatinib	Lenvima	Eisai	Treatment of progressive, differentiated thyroid cancer
6. Panobinostat	Fardyak	Novartis	Treatment of multiple myeloma
7. Ceftazidime-avibactam	Avycaz	Forest Labs	Treatment of complicated, intra-abdominal infections or complicated urinary tract infections including kidney infections
8. Isavuconazonium	Cresmba	Astellas Pharma	Treatment of invasive aspergillosis and invasive mucormycosis
9. Dinutuximab	Unituxin	United Therapeutics	Treatment of high-risk neuroblastoma in children
10. Cholic acid	Cholbam	Asklepion Pharm	Treatment of bile acid synthesis disorders and for patients with paroxysmal disorders
11. Ivabradine	Corlanor	Amgen	Reduce hospitalization from worsening heart failure
12. Deoxycholic acid	Kybella	Kythera Biopharm	Treatment of moderate to severe fat below the chin
13. Eluxadoline	Viberzi	Forest Pharm	Treatment of irritable bowel syndrome with diarrhea
14. Canegrelor	Kengreal	The Medicines Co	To prevent the formation of harmful blood clots in the coronary arteries for adult patients undergoing percutaneous coronary intervention
15. Lumacaftor/ivacaftor*	Orkambi	Vertex Pharm	Treatment of cystic fibrosis
16. Sacubitril/valsartan	Entresto	Novartis	Treatment of heart failure
17. Brexpiprazole	Rexulti	Otsuka America	Treatment of schizophrenia and as add-on therapy for major depressive disorder

Generic Name	Brand Name	Manufacturer	Indication
18. Alirocumab	Praluent	Sanofi-Aventis	Treatment of high cholesterol in certain patients
19. Sonidegib	Odomzo	Novartis	Treatment of locally advanced basal cell carcinoma
20. Daclatasvir	Daklinza	BMS	Treatment of Hepatitis C (genotype 3)
21. Fibanserin	Addyi	Sprout Pharm	Treatment of acquired, generalized hypoactive sexual desire disorder (HSDD) in premenopausal women
22. Evolocumab	Repatha	Amgen	Treatment of high cholesterol in certain patients
23. Rolapitant	Varubi	Tesaro	Prevention of delayed phase chemotherapy-induced nausea and vomiting
24. Uridine triacetate*	Xuriden	Wellstat Therapeutics	Treatment of hereditary orotic aciduria
25. Cariprazine	Vraylar	Actavis	Treatment of schizophrenia and bipolar disorder
26. Trifluridine and tipiracil	Lonsurf	Taiho Oncology	Treatment of advanced colorectal cancer unresponsive to other therapy
27. Insulin degludec	Tresiba	Novo Nordisk	Treatment of diabetes
28. Aripiprazole lauroxol	Aristada	Alkermes	Treatment of schizophrenia
29. Idarucizumab*	Praxbind	Boehringer Ingelheim	Reversal agent for dabigatran (Pradaxa)
30. Patiromer	Veltassa	Relypsa	Treatment of hyperkalemia
31. Trabectedin	Yondelis	Janssen Biotech	Treatment of specific soft-tissue sarcomas (liposarcoma, leiomyosarcoma)
32. Asfotase alfa*	Strensiq	Alexion	Treatment of hypophosphatasia
33. Mepolizumab	Nucala	GSK	Maintenance treatment of asthma
34. Combination tablet of elvitegravir, cobicistat, emtricitabine, and tenofovir alafenamide	Genvoya	Gilead Sciences	Treatment of HIV-1 infection
35. Cobimetinib	Cotellic	Genentech	Treatment of advanced melanoma in patients with abnormal gene (BRAF, V600E, V600K)
36. Osimertinib*	Tagrisso	AstraZeneca	Treatment of non-small cell lung cancer
37. Daratumumab*	Darzalex	Janssen Biotech	Treatment of multiple myeloma
38. Ixazomib	Ninlaro	Takeda	Treatment of multiple myeloma

Generic Name	Brand Name	Manufacturer	Indication
39. Necitumumab	Portrazza	Lilly	Treatment of advanced, squamous non-small cell lung cancer
40. Elotuzumab*	Empliciti	BMS	Treatment of multiple myeloma
41. Sebelipase alfa*	Kanuma	Alexion	Treatment of lysosomal acid lipase deficiency
42. Alectinib*	Alecensa	Genentech	Treatment of ALK-positive lung cancer
43. Sugammadex	Bridion	Merck Sharp and Dohme Corp	To reverse effects of neuromuscular blocking drugs used during surgery
44. Selexipag	Upravi	Actelion Pharmaceuticals	Treatment of pulmonary arterial hypertension
45. Lesinurad	Zurampic	AstraZeneca	Treatment of gout

\*Breakthrough status

## DRUGS FOR RARE DISEASES

Forty-seven percent of the novel new drugs approved in 2015 (21 of 45) were approved to treat rare or “orphan” diseases.<sup>1</sup> Orphan drugs are defined as drugs that are designed for diseases that affect 200,000 or fewer Americans. This is significant because patients with rare diseases often have few or no drugs available to treat their conditions. Orphan drug designation provides financial incentives, like clinical trial tax credits, user fee waivers, and eligibility for market exclusivity to promote rare disease drug development. Although each orphan disease only affects a small number of patients, collectively orphan diseases affect 25 million individuals in this country and are a serious public health concern. **Table 2 lists the orphan drug approvals of 2015.**

**Table 2- 2015 Approved Orphan Drug List<sup>1</sup>**

Generic Name	Brand Name
Alectinib	Alecensa
Cholic acid	Cholbam
Cobimetinib	Cotellic
Isavuconazonium	Cresemba
Daratumumab	Darzalex
Elotuzumab	Empliciti
Panobinostat	Farydak
Sebelipase alfa	Kanuma
Lenvatinib	Lenvima
Parathyroid hormone	Natpara
Ixazomib	Ninlaro
Lumacaftor/ivacaftor	Orkambi
Necitumumab	Portrazza
Idarucizumab	Praxbind
Evolocumab	Repatha*

Generic Name	Brand Name
Asfotase alfa	Strensiq
Osimertinib	Tagrisso
Dinutuximab	Unituxin
Selexipag	Uptravi
Uridine triacetate	Xuriden
Trabectedin	Yondelis

\* Repatha was submitted with two indications. One indication received Orphan designation while the other did not.

## Edoxaban (Savaysa)

Edoxaban was approved by the FDA on January 8, 2015.<sup>2</sup> It is the fourth oral anticoagulant to be approved for use in venous thromboembolism and atrial fibrillation. It is available as 15, 30 and 60 mg tablets.

### Pharmacology/Pharmacokinetics

Edoxaban is a factor Xa inhibitor.<sup>3</sup> It works by inhibiting free factor Xa and prothrombinase activity. It also inhibits thrombin-induced platelet aggregation. Edoxaban does not require antithrombin III for its activity.

Edoxaban is well absorbed after oral ingestion and can be taken with or without food.<sup>3</sup> There is no data on altering the tablets (crushing or chewing). This drug is 55% plasma protein bound. Edoxaban is only minimally metabolized. It is excreted as unchanged drug primarily through the kidney. The half-life of edoxaban is 10 to 12 hours.

### Indications

Edoxaban is approved to reduce the risk of stroke or embolism in patients with non-valvular atrial fibrillation.<sup>3</sup> It is also approved to treat DVT or PE in patients who have had initial therapy with parenteral anticoagulants.

### Dosing

The recommended dose for edoxaban is 60 mg once a day for both indications (DVT, atrial fibrillation).<sup>3,4</sup> The dose should be reduced to 30 mg once a day in patients with a creatinine clearance (CrCl) between 15 and 50 mL/min. The drug should not be used in patients with a CrCl < 15 mL/min or >95 mL/min. Edoxaban should be discontinued 24 hours before surgery to reduce the risk of bleeding.

### Efficacy

In a 12 month non-inferiority trial, 8,000 patients were randomized to warfarin or edoxaban to determine the incidence of recurrence of VTE.<sup>5</sup> All patients had been treated with parenteral anticoagulation prior to enrollment. This study showed edoxaban to be noninferior to warfarin in preventing recurrence of VTE, which was the primary endpoint. In addition, there were significantly less major bleeds in the edoxaban group (8.5%) compared to the warfarin group (10.3%). There were 6 fatal intracranial bleeds in the warfarin group and none in the edoxaban group.

In the ENGAGE AF-TIMI 48 trial, 21,000 patients with atrial fibrillation were randomized to edoxaban or warfarin.<sup>4</sup> After a mean duration of therapy of 2.8 years, patients receiving edoxaban had a significantly lower rate of stroke or embolism (1.18%) versus warfarin (1.50%).

The edoxaban patients also had a lower rate of major bleeding (2.75% vs.3.43%), intracranial bleed (0.39% vs. 0.85%) and cardiovascular death (2.74% vs. 3.17%).

### Contraindications/Warnings

The only contraindication to edoxaban is active bleeding.<sup>3</sup> **There are three black box warnings regarding the use of this drug (Table 3).**

**Table 3- Warnings with edoxaban<sup>3</sup>**

Warnings	Comments
Patients with CrCl > 95 ml/min	There is a reduction in efficacy in patients with non-valvular atrial fibrillation. In clinical trials there was a higher incidence of ischemic stroke in this group treated with edoxaban compared to warfarin.
Early discontinuation of edoxaban	Patients who stop this medication early are at higher risk for ischemic event. Be sure to complete therapy with edoxaban or ensure proper anticoagulation with other agents.
Risk of spinal or epidural hematoma	Edoxaban can increase the risk of spinal or epidural hematoma which can cause paralysis. Patients with epidural catheters or those receiving drugs that can affect bleeding (platelet inhibitors, NSAIDs, other anticoagulants) are at higher risk of this occurring.

In addition to the above warnings, edoxaban can cause serious bleeding that can be fatal.<sup>5</sup> Patients taking drugs that affect bleeding are at higher risk for problems with edoxaban.

### Drug Interactions

There are a few drug interactions with edoxaban.<sup>3,5</sup> Anticoagulants, thrombolytics, aspirin, and antiplatelet drugs can increase the risk of bleeding. Avoid long term co-administration with these agents. Use only as bridge therapy when required. Do not use with rifampin as it results in increased levels of edoxaban.

### Adverse Effects

The adverse effects reported with edoxaban include mild to moderate bleeding, skin rash (4.2%), abnormal liver function tests (4.8%) and anemia (9.6%).<sup>3</sup> Bleeding was the primary reason for stopping edoxaban in clinical trials and occurred in 3.9% of patients. Major bleeding occurred with edoxaban in 3.1% of patients in the ENGAGE AF-TIMI 48 trial compared to 3.1% in the warfarin group.

### Pregnancy and Lactation

Edoxaban is Pregnancy category C.<sup>3</sup> It has not been studied in pregnant women. Edoxaban should only be used if the benefits outweigh the potential risks. It is not clear if edoxaban is excreted in human breast milk. It has been shown to be excreted in milk of lactating rats. The patient and physician will need to determine if breastfeeding should be discontinued or the medication discontinued.

### Counseling the patient

When a patient begins therapy with edoxaban, the pharmacist should verify that they are not taking other anticoagulants or drugs that may affect bleeding.<sup>2,3</sup> The pharmacist should

discuss the black box warnings including the risks for bleeding and the risks from stopping the medication early. Be sure the patient understands the importance of compliance and address any specific barriers to compliance they may have.

### Role in therapy

Currently there are no direct comparisons of edoxaban to other oral anticoagulants such as Apixiban or rivaroxaban. Studies have shown edoxaban to be comparable to warfarin for the treatment of DVT and PE. In the prevention of stroke in patients with non-valvular atrial fibrillation, edoxaban was as effective as warfarin and had fewer incidences of major bleeding.

There was an increase in the incidence of ischemic stroke in patients taking edoxaban with a CrCl > 95 mL/min.

## Insulin degludec (Tresiba)

Insulin degludec is the third long-acting human insulin analogue approved by the FDA. It received approval on September 25, 2015.<sup>2</sup>

### Pharmacology/Pharmacokinetics

Insulin lowers blood glucose by stimulating glucose uptake in skeletal muscle and fat. It also inhibits production of glucose in the liver.<sup>6</sup> Insulin degludec inhibits lipolysis and proteolysis.

Like other long-acting human insulin analogues, insulin degludec has an onset of action between 1 and 9 hours.<sup>7</sup> Insulin degludec binds to circulating albumin which delays its elimination. Other long-acting insulins have a duration of action of 24-36 hours, while insulin degludec has a duration of > 42 hours. Because of the longer duration of action, insulin degludec does not need to be administered at the same time each day.

### Indications

Insulin degludec is approved for use in adults for the treatment of diabetes. It can be used in both Type I or Type II diabetes.<sup>6</sup>

### Dosing

Insulin degludec is administered subcutaneously into the thigh, upper arm or abdomen once a day.<sup>6</sup> It should not be mixed or diluted with other insulin products. The injection site should be rotated each day. **See Table 4 for dosing guidelines.**

**Table 4- Dosing guidelines for insulin degludec<sup>6</sup>**

#### Insulin Naïve Patients:

Type I Diabetes: The starting dose is one third to one half the total daily insulin dose. The remaining portion of the daily dose is given as short-acting insulin between each meal. The average initial insulin dose is 0.2 to 0.4 units/kg.

Type II Diabetes: The starting dose of insulin degludec in type 2 diabetes is 10 units once a day.

#### Patients currently receiving insulin therapy:

In patients currently receiving insulin, administer insulin degludec at the same unit dose as the total daily dose of either long or intermediate-acting insulin.

### Efficacy

There were 9 clinical trials that were submitted as part of the FDA approval process.<sup>8</sup> Eight of

the clinical trials showed that insulin degludec was non-inferior to other long-acting human insulin analogues. There was a similar reduction in hemoglobin A1C between the products, and the incidence of hypoglycemia was the same. Insulin degludec demonstrated a lower incidence of nocturnal hypoglycemia when compared to other long-acting insulins. The final clinical trial compared insulin degludec to sitagliptin 100 mg daily.<sup>7</sup> Insulin degludec was significantly more effective in lowering hemoglobin A1C, but was responsible for more episodes of hypoglycemia.

### Contraindications/Warnings

Insulin degludec should not be administered during an episode of hypoglycemia.<sup>6,7</sup> It is also contraindicated in patients allergic to insulin degludec or any of its components. Insulin degludec can cause severe hypoglycemia. Patients with renal or liver disease have a greater risk for hypoglycemia.

Hypoglycemia may occur as a result of medication errors when administering insulin products.<sup>6</sup> Patients should be instructed to always check the insulin label before injecting insulin. Insulin degludec should never be transferred from the insulin pen to a syringe. The markings on a syringe do not measure the dose correctly and can result in severe hypoglycemia.

Insulin degludec, like other insulins, may be associated with hypokalemia as a result of a shift in potassium from the extracellular to intracellular space. Patients taking thiazolidinediones (TZDs) in combination with insulin degludec can experience fluid retention which may lead to heart failure.

### Drug Interactions

There are several drug-drug interactions that have been reported with insulin products, including insulin degludec.<sup>2,6</sup> **Table 5 summarizes the clinically significant interactions.**

**Table 5- Drug interactions with insulin degludec<sup>2,6</sup>**

Effect	Drugs	Description
Drugs that increase the risk of hypoglycemia	<ul style="list-style-type: none"> <li>• ACE inhibitors</li> <li>• Angiotensin II receptor blockers</li> <li>• Fibrates</li> <li>• MAO inhibitors</li> <li>• DDP-4 inhibitors</li> <li>• SGLT-2 inhibitors</li> <li>• GLP-1 receptor agonists</li> <li>• Sulfonamide antibiotics</li> </ul>	Dose reductions of insulin degludec may be needed. Increase the frequency of blood glucose monitoring.
Drugs that decrease blood glucose lowering effect of insulin degludec	<ul style="list-style-type: none"> <li>• Atypical antipsychotics</li> <li>• Corticosteroids</li> <li>• Oral contraceptives</li> <li>• Diuretics</li> <li>• Thyroid hormones</li> <li>• Protease inhibitors</li> </ul>	Dose increases of insulin degludec may be needed. Increase the frequency of blood glucose monitoring.
Drugs that can increase or decrease blood glucose lowering effect of insulin degludec	<ul style="list-style-type: none"> <li>• Alcohol</li> <li>• Beta-blockers</li> <li>• Clonidine</li> <li>• Lithium</li> </ul>	Dose adjustments of insulin degludec may be needed. Increase the frequency of blood glucose monitoring.

Effect	Drugs	Description
Drugs that block the signs and symptoms of hypoglycemia	<ul style="list-style-type: none"> <li>• Beta-blockers</li> <li>• Clonidine</li> <li>• Guanethidine</li> <li>• Reserpine</li> </ul>	Increase the frequency of blood glucose monitoring. Educate patient about signs and symptoms of hypoglycemia.

### Adverse Effects

The most common adverse reactions observed with insulin degludec are allergic reactions including rash, itching, injection site reaction, edema and lipodystrophy.<sup>6</sup> All insulin formulations are associated with hypoglycemia and weight gain.

### Pregnancy and Lactation

Insulin degludec is pregnancy category C, which means data has shown some fetal abnormalities in animal studies but no adequate studies have been conducted in humans.<sup>6</sup> It is not known if insulin degludec is excreted in human breastmilk. Patients who are breastfeeding may require additional blood glucose monitoring and dose adjustments. Insulin degludec should be used with caution during breastfeeding.

### Counseling the patient

Patients should be properly trained to self-inject insulin degludec subcutaneously.<sup>2,6</sup> Instruct patients to never share insulin degludec pens even if the needle is changed. There is a risk of transmitting blood-borne viruses. Do not dilute or mix insulin degludec with other insulin products. Insulin degludec should not be transferred from the pen to a syringe as there is a risk of hypoglycemia due to medication error.

The pharmacist should discuss the importance of diet, weight management and exercise with the patient.<sup>2</sup> There should also be a discussion about proper methods for monitoring blood glucose. Patients should be able to describe the symptoms of hyperglycemia and hypoglycemia and how to manage them.

### Role in therapy

Insulin degludec is a new long-acting human insulin analogue that is effective in reducing hemoglobin A1C in patients with diabetes.<sup>7</sup> It is associated with fewer episodes of nocturnal hypoglycemia and does not have to be administered at the same time each day. It offers an alternative in patients who experience nocturnal hypoglycemia or who have trouble remembering when to administer the dose.

## Idarucizumab (Praxbind)

Idarucizumab is the first specific reversal agent approved for one of the new oral anticoagulants.<sup>9</sup> It received FDA approval on Oct 16, 2015.<sup>10</sup> It reverses the effects of dabigatran (Pradaxa). This drug received accelerated approval based on evidence that showed a reduction in the amount of unbound dabigatran and a normalization of coagulation parameters in healthy volunteers. Additional clinical data must be provided to the FDA post-marketing to confirm this finding.

### Pharmacology/Pharmacokinetics

Idarucizumab is a monoclonal antibody fragment (Fab) that works by binding to dabigatran

and its metabolites and neutralizes their anticoagulant effects.<sup>9</sup> Dabigatran has a higher affinity for binding to idarucizumab than thrombin. There is no evidence that indicates this drug is effective in reversing the effects of factor Xa inhibitors such as apixiban, edoxaban, or rivaroxaban.

Following intravenous administration of idarucizumab, the drug has limited extravascular distribution with a volume of distribution of 8.9 L.<sup>9</sup> It is rapidly eliminated with a terminal half-life is 10.3 hours. Approximately 32% of a dose is excreted in the urine within 6 hours, with the remainder undergoing protein catabolism in the kidneys.

### **Indications**

Idarucizumab is indicated for use in patients requiring urgent reversal of the anticoagulant effects of dabigatran.<sup>10</sup> This would include emergency surgery or life threatening bleeding.

### **Dosing**

The dose of idarucizumab is 5 grams (given as two consecutive 2.5 gram doses) intravenously.<sup>9</sup> No dose adjustment is needed in renal impairment and the drug has not been studied in patients with liver disease. Dabigatran should not be restarted for 24 hours. Idarucizumab is available as a 2.5 gram/50 mL solution. The cost of a 5 gram dose of idarucizumab is in the neighborhood of \$3,500.<sup>11</sup>

### **Efficacy**

Idarucizumab received accelerated FDA approval based on a single study, the RE-VERSE-AD trial.<sup>11</sup> This is an ongoing trial that assesses the safety and efficacy of idarucizumab in patients who developed life-threatening bleeds, or require rapid reversal for an urgent procedure. The primary endpoint is the percent reversal of anticoagulant effects at 4 hours. The FDA received data for the first 90 patients. The data showed that 89/90 patients had dabigatran levels below 20 ng/mL almost immediately after receiving idarucizumab. Dabigatran levels below 20 ng/mL have no significant anticoagulant effect. In the group of patients who underwent urgent procedures, 92% had normal coagulation during the operation.

### **Contraindications/Warnings**

There are no contraindications to the use of idarucizumab; however, there are several warnings.<sup>9</sup>

Since patients are using dabigatran for conditions that increase their risk for thromboembolism, reversing the effects of dabigatran may place the patient at high risk again. Anticoagulation should be reinstated as soon as medically feasible.

A small subset of individuals may develop a re-elevation of their coagulation factors after receiving idarucizumab.<sup>2,9</sup> In that case, a second dose of 5 grams of idarucizumab would be appropriate. Additionally, some patients may require a second procedure urgently and may have elevated coagulation levels. These patients may also require a second dose.

It is important to warn patients that there is a risk of allergic reaction.<sup>9</sup> This includes patients with a hereditary fructose intolerance due to sorbitol. There is 4 grams of fructose in a dose of idarucizumab.

### **Drug Interactions**

No data is available from clinical trials to indicate any clinically significant drug-drug interactions with idarucizumab.<sup>9</sup>

## Adverse Effects

The most common adverse effects observed with idarucizumab include headache (5%), hypokalemia (7%), constipation (7%), delirium (7%), pyrexia (6%) and pneumonia (6%).<sup>9,11</sup> Five patients (4%) reported thromboembolic events, although none of these patients were receiving anticoagulants at the time of the event. In addition, pyrexia, bronchospasm, rash and pruritus have been reported in clinical trials that indicate allergic reactions.

## Pregnancy and Lactation

No studies with idarucizumab have been conducted in pregnant or lactating women.<sup>9</sup> The FDA has not assigned a pregnancy risk category to this agent and no information about its risks in pregnancy has been reported. It should not be administered to a pregnant woman unless it is clearly needed. Since it is not known if this drug is excreted in human breastmilk, it should not be used during breastfeeding.

## Counseling the patient

This medication will be given to the patient in the hospital setting. Once the patient is stabilized, it is important to determine if the need for this antidote was from a dosing error. Was the patient taking too high of a dose of the drug or taking the drug at the wrong frequency? Medication errors or compliance errors can lead to incorrect dosing. The pharmacist should be certain the patient is taking the medication at the correct dose and time of day so that additional reversals are not required.

Physicians may ask about this product when making a decision on which new oral anticoagulant to prescribe to a patient. Be sure to explain to physicians that idarucizumab is only effective in reversing dabigatran.

## Role in therapy

Idarucizumab is the first specific reversal agent approved for the new oral anticoagulant dabigatran (Pradaxa). It rapidly reverses the anticoagulant in situations where a patient is either experiencing a life-threatening bleeding episode or requires urgent reversal of dabigatran for an emergency procedure. It is not effective for reversal of factor Xa inhibitors.

## Palbociclib (Ibrance)

Palbociclib was approved February 3, 2015 under accelerated approval because of the improvement seen in progression-free survival time (PFS) in breast cancer.<sup>2</sup> The FDA has indicated that continued approval will be based on results of a confirmatory clinical trial.

## Pharmacology/Pharmacokinetics

Palbociclib inhibits kinase 4 and 6, both of which are involved in promoting the growth of cancer cells.<sup>12</sup> It reduces cell growth of estrogen receptor positive breast cancer cell lines by blocking progression of the cell from G1 to S phase of the cell cycle. Palbociclib enhances the efficacy of cytostatic agents, such as endocrine therapy or HER2-targeted therapy, but decreases the efficacy of cytotoxic chemotherapy.

The maximum concentration of palbociclib is achieved 6 to 12 hours after an oral dose.<sup>12</sup> The elimination half-life of palbociclib was 29 hours. The absorption of palbociclib was poor (46%) when taken on an empty stomach. Absorption was improved when taken with food. Palbociclib undergoes hepatic metabolism and 75% of a dose is excreted in the feces. Seventeen percent is excreted renally. No dose reductions are needed in patients with mild to moderate hepatic or renal impairment.

## Indications

Palbociclib is approved for use in combination with letrozole for the 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 metastatic disease.<sup>12</sup>

## Dosing

The dose of palbociclib is 125 mg once a day. If the patient develops Grade 3 toxicity, the dose should be held until the toxicity improves to at least Grade 2. The drug can be restarted at 100 mg once a day. If Grade 3 toxicity occurs at the lower dose, hold the drug and restart at 75 mg once a day when the toxicity resolves. If this lower dose is not tolerated, the drug should be discontinued.

## Efficacy

There was a single clinical study (PALOMA-3) that was submitted to the FDA for approval of this drug.<sup>13</sup> It was a multicenter clinical trial of 165 women with metastatic disease who received either palbociclib and letrozole or letrozole alone. The primary measurement was progression-free survival time. Forty-three percent of patients had received prior chemotherapy and 33% received only anti-hormonal therapy. Patients who received the combination of palbociclib and letrozole had a PFS period of 20.2 months, while those receiving letrozole alone had a PFS of 10.2 months. Although the study was small, the results were significant. The FDA did grant an accelerated approval based on these findings. Additional clinical trials are required post-marketing to confirm the original findings.

## Contraindications/Warnings

There are no specific contraindications with palbociclib; however, there are several warnings.<sup>14</sup> This drug has been associated with hematologic toxicities. Grade 3 neutropenia has been reported in 57% of patients approximately 15 days after the dose. Grade 4 neutropenia occurred in 5% of patients. Patients are at greater risk of Grade 3 or 4 infections when they use palbociclib in combination with letrozole and should be monitored for signs and symptoms of infection. This combination also has a higher risk of pulmonary embolism and, therefore, patients should be monitored for this. Palbociclib is considered to cause fetal harm based on animal data. Patients should use contraception during therapy with palbociclib and for 2 weeks after stopping it.

## Drug Interactions

### *CYP3A Inducers*

Strong CYP 3A inducers, such as rifampin, decrease serum levels of palbociclib by 85%.<sup>12</sup> Moderate CYP3A inducers such as bosentan, efavirenz and modafinil can also decrease serum levels, however, not to the same degree. CYP3A inducers should not be given in combination with palbociclib.

## Adverse Effects

The most common side effects reported with palbociclib include neutropenia, thrombocytopenia, leukopenia, fatigue, anemia, stomatitis, alopecia, asthenia, epistaxis and peripheral neuropathy.<sup>12</sup> Pulmonary embolism is a serious adverse effect that has been associated with palbociclib. It is reported to occur in 5% of patients receiving palbociclib in combination with letrozole compared to letrozole alone.

## Pregnancy and Lactation

Palbociclib has been shown to be teratogenic in animal studies when given at 4 times the dose used in humans.<sup>2,12</sup> No specific data is available in humans; however, patients should be advised on the potential risks to the fetus. There is no specific data on palbociclib excretion in breastmilk; however, many drugs are excreted in human breastmilk. Patients should be warned to stop breastfeeding while taking this drug.

## Counseling the patient

The pharmacist should take time to discuss specific issues when a patient is started on palbociclib. This medication may be harmful to pregnant women. Female patients should be counseled to use effective birth control during treatment and for two weeks after stopping palbociclib.<sup>12</sup>

Since palbociclib may increase the chance for infection, discuss this risk and advise the patient to contact their doctor if they develop a fever. Since pulmonary embolism is an uncommon but serious side effect, discuss the signs and symptoms of pulmonary embolism such as shortness of breath, sharp and sudden chest pain and fast heartbeat.

If a dose is missed or vomited, do not take another dose on that day.<sup>12</sup> Tell the patient to take their next dose as scheduled. Patients should not chew, crush or open the palbociclib capsule. Grapefruit juice can increase the blood levels of palbociclib and should be avoided.

## Role in therapy

Palbociclib is approved for initial endocrine-based therapy for metastatic disease in postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer.<sup>14</sup> Clinical evidence indicates there is a significant improvement in PFS in these patients. Many practitioners will institute palbociclib and letrozole combination therapy as a first line treatment based on the clinical results reported.

## Eluxadoline (Viberzi)

Eluxadoline was approved by the FDA on May 25, 2015.<sup>2</sup> It is classified by the Drug Enforcement Agency as a schedule IV controlled substance.

Irritable Bowel Syndrome (IBS) affects more than 45 million people, according to the National Institutes of Health.<sup>15</sup> IBS is reported in about twice as many women as men, and it is most frequently seen in individuals under age 45. There are several types of IBS. It can occur with diarrhea as the predominant symptom (IBS-D), constipation (IBS-C) as the primary symptom, or a mixed condition where constipation and diarrhea alternate as symptoms. It is reported that IBS-D occurs in about 15 million patients in the United States.

## Pharmacology/Pharmacokinetics

Eluxadoline is a mu and kappa receptor agonist and a delta receptor antagonist.<sup>16</sup> Opioid receptors in the gastrointestinal tract regulate motility and secretion. The mu and kappa receptors are activated and reduce the number of bowel contractions.

The bioavailability of eluxadoline has not been established.<sup>16</sup> It is 81% plasma protein bound and has an elimination half-life of 4 to 6 hours. It is not clear from clinical trials if eluxadoline is metabolized, although some glucuronidation may occur. Eluxadoline is excreted primarily in the feces with less than 1% of a dose recovered in the urine.

## Indications

Eluxadoline is approved for treatment of irritable bowel syndrome with diarrhea in adults.<sup>16</sup>

## Dosing

The recommended dose of eluxadoline is 100 mg taken twice a day with food.<sup>16,17</sup> The dose should be reduced to 75 mg twice a day with food in the following patients:

- Individuals without a gall bladder
- Patients who are unable to tolerate the 100 mg dose
- Patients with mild to moderate liver disease
- Patients taking OATP1B1 inhibitors

## Efficacy

Eluxadoline was compared in 2,425 patients with IBS-D in two placebo-controlled trials.<sup>15</sup> Patients were randomized to receive 75 or 100 mg of eluxadoline or placebo twice a day. The primary composite endpoint of the study was a decrease in abdominal pain and improvement of stool consistency on over half the days in weeks 1-12 and weeks 1-26. Both studies showed eluxadoline to be significantly better than placebo. At 12 weeks, 23.9% of the 75 mg group and 25.1% of the 100 mg group reached the primary endpoint compared to 17% of placebo patients ( $p=0.01$ ,  $p=0.004$  respectively). In the 26 week measurement, both doses of eluxadoline were statistically superior to placebo ( $p=0.001$ ,  $p<0.001$ , respectively).

## Contraindications/Warnings

Eluxadoline should not be used in patients with known or suspected biliary duct obstruction or any disease of the sphincter of Oddi.<sup>2</sup> It is contraindicated in patients with severe liver disease (Child-Pugh Class C), pancreatic disease, severe constipation or gastrointestinal obstruction. Eluxadoline is also contraindicated in patients with a history of alcoholism, drug addiction or those who drink more than 3 alcoholic beverages per day.

Patients who do not have a gall bladder should be monitored for new or more severe abdominal pain, or acute biliary pain with elevated enzymes.<sup>2</sup> If these symptoms occur, eluxadoline should be stopped and the patient should contact their physician.

## Drug Interactions

There are several drug-drug interactions reported with eluxadoline.<sup>16</sup> Patients should avoid other medications that can cause constipation. Drugs such as aldosterone, anticholinergic agents and opioid narcotics should be avoided. Loperamide may be used for acute management of severe diarrhea.

Drugs that are strong inhibitors of cytochrome P450 (ciprofloxacin, gemfibrozil, fluconazole, paroxetine) may prevent the metabolism of eluxadoline.<sup>16</sup> Patients taking these combinations may have more sedation and should avoid operating machinery or driving a car.

Organic Anion Transporting Polypeptide (OATP1B1) agents like cyclosporine, antiretroviral agents, rifampin and gemfibrozil can result in higher serum levels of eluxadoline when combined together.<sup>16</sup> Patients taking these combinations may have increased risk of sedation and should not operate machinery or drive a car.

## Adverse Effects

The most common adverse effects are constipation, nausea and abdominal pain.<sup>16,17</sup> More severe adverse effects include spasm of the sphincter of Oddi and pancreatitis. Eluxadoline should not be given to individuals with bile duct obstruction, pancreatitis, liver disease, or

severe constipation. It should also be avoided in patients who drink more than three alcoholic beverages each day.

### **Pregnancy and Lactation**

The FDA has not assigned a pregnancy class to eluxadoline.<sup>16</sup> There have not been any studies evaluating the safety of the drug in pregnant women. Studies in animals have not demonstrated any adverse fetal effects. In addition, no studies have been conducted to determine if eluxadoline is excreted in human breastmilk. Studies have shown the drug is present in rat milk. Patients who are considering breastfeeding should consider the risks and benefits associated with eluxadoline.

### **Counseling the patient**

Patients should be counseled about spasm of the Sphincter of Oddi reported with eluxadoline.<sup>16</sup> Symptoms include an increase in liver and pancreatic enzymes, stabbing abdominal pain and nausea. If the patient does not have a gallbladder, they are at higher risk for this side effect. Patients should stop eluxadoline and call their doctor if they develop these symptoms. Eluxadoline can also cause pancreatitis. Patients should stop the medication and alert their physician if they develop pancreatitis. This drug should not be used in an individual with chronic constipation.

If the patient misses a dose of eluxadoline, they should take their next dose at the regular time.<sup>16</sup> Do not take 2 doses at the same time to make up for a missed dose. You should discuss alcohol use with patients taking eluxadoline. They should not drink alcohol while taking this drug.

### **Role in therapy**

The initial approach to the treatment of IBS-D is diet, exercise and medication therapy. These medications include antidiarrheals, antispasmodics, probiotics, and antidepressants. Alosetron is an option to use in women with severe chronic IBS-D; however, it is associated with a serious side effect of ischemic colitis.

Until the availability of eluxadoline, there was no specific medication to alleviate all the symptoms of IBS-D (diarrhea, abdominal pain, urgency and bloating).<sup>17</sup> Eluxadoline provides an effective alternative to patients who are not responsive to conventional treatment.

## **Sacubitril/valsartan (Entresto)**

Sacubitril/valsartan was considered by the FDA as an expedited review. That is reserved for drugs that are intended to treat a serious disease or condition and that may provide a significant improvement over available therapy. It was also granted a fast-track designation, which supports FDA efforts to facilitate the development and expedite the review of drugs to treat serious and life-threatening conditions and fill an unmet medical need. The FDA approved sacubitril/valsartan on July 7, 2015, for use in place of an ACE inhibitor or ARB in patients with New York Heart Association class II, III, or IV heart failure with reduced ejection fraction.<sup>2</sup> Sacubitril is the first neprilysin inhibitor approved in the United States.

### **Pharmacology/Pharmacokinetics**

Neprilysin inhibitors decrease vasoconstriction, reduce sodium retention and remodeling.<sup>18</sup> This is done by inhibition of a peptidase, neprilysin. Neprilysin is responsible for breaking down certain vasoactive peptides, including bradykinin and natriuretic peptides.

Sacubitril is a prodrug that is metabolized to an active form, named LBQ657.<sup>18</sup> The bioavailability

of valsartan is significantly higher in this formulation than as a single product. LBQ657 and valsartan are both highly plasma protein bound (95%). Neither LBQ657 nor valsartan undergo significant metabolism. Approximately 60% of a dose of sacubitril (mostly as LBQ657) is eliminated in the urine and the remainder is excreted in feces. About 85% of a valsartan dose is eliminated in the feces.

### Indications

Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction.<sup>18</sup> It is usually administered in conjunction with other heart failure therapies, in place of an ACE inhibitor or other ARB.

### Dosing

The recommended starting dose of sacubitril/valsartan is 49/51 mg twice a day.<sup>18,19</sup> After 2 to 4 weeks, the dose may be doubled to the target dose of 97/103 mg twice a day. ACE inhibitor therapy should be stopped for 36 hours before starting therapy with sacubitril/valsartan.

In patients with renal or liver impairment, or patients not on an ACE inhibitor, start at the lower dose of 24/26 mg twice a day.<sup>19</sup> The dose may be doubled every two weeks until the patient meets the target of 97/103 mg or as tolerated.

### Efficacy

Sacubitril/valsartan was compared to enalapril in a clinical trial called PARADIGM-HF.<sup>20</sup> The trial was conducted in several countries and compared sacubitril/valsartan to enalapril in patients with NYHA class II-IV chronic heart failure. The primary endpoint of the clinical trial was cardiovascular death or hospitalization for heart failure. This trial included 8,442 heart failure patients. The trial was stopped early due to a lower cardiovascular mortality in the sacubitril/valsartan group. The sacubitril/valsartan group reported 914/4,187 events (21.8%) while the enalapril group reported 1,117/4,212 events (26.5%). This was a statistically significant difference ( $p < 0.0001$ ). Sudden death was reported for 45% of the cardiovascular deaths.

### Contraindications/Warnings

Sacubitril/valsartan is contraindicated in the following:<sup>18</sup>

- hypersensitivity to the drug
- history of angioedema from ACE or ARBs
- currently taking an ACE inhibitor. Wait 36 hours after switching.
- combined with aliskiren (Tekturna)

There are warnings associated with the use of sacubitril/valsartan.<sup>2,18</sup> Sacubitril/valsartan has a black box warning for fetal toxicity. Drugs that affect the renin-angiotensin system can reduce the kidney function of the fetus and increase the risk for morbidity and fetal death. Sacubitril/valsartan should not be given to pregnant women and should be stopped as soon as the pregnancy is detected.

Sacubitril/valsartan can cause angioedema.<sup>18</sup> There is a higher incidence of angioedema in black patients. Patients with a history of angioedema have a higher risk for this adverse effect. This medication should not be used if there is a prior history of angioedema from another ACE inhibitor.

There is an increased risk for hyperkalemia with drugs that affect the renin-angiotensin system.<sup>18</sup> The incidence of hyperkalemia in the clinical studies was around 12%. Patients with

increased risk for hyperkalemia include those with renal disease, diabetes, high potassium diet or hypoaldosteronism.

Another serious adverse effect reported with sacubitril/valsartan is renal failure.<sup>18</sup> Five percent of patients in the studies who received sacubitril/valsartan or enalapril developed renal failure. ACE inhibitors should be used with caution in patients with severe heart failure, since their renal function depends on the renin-angiotensin system. These patients should be closely monitored for signs of renal impairment. The dose of sacubitril/valsartan may need to be lowered or stopped altogether.

### Drug Interactions

There are several drug interactions with sacubitril/valsartan.<sup>2,18</sup> **See Table 6 for drug drug interactions.**

**Table 6-Drug interactions with sacubitril/valsartan<sup>18</sup>**

Drug	Recommendation	Effect
ACE inhibitors	Contraindicated	Serious angioedema
Angiotensin II receptor blockers	Contraindicated	Contains Valsartan
Potassium-sparing diuretics, potassium supplements	Use with caution	Hyperkalemia
NSAID	Use with caution	Acute renal failure
Lithium	Use with caution	Lithium toxicity

### Adverse Effects

The most common adverse effects (> 5%) reported with sacubitril/valsartan include hypotension, hyperkalemia, cough, and elevated serum creatinine.<sup>19</sup> The incidence of angioedema was 0.5%; however, in Black patients it was 2.4%.

### Pregnancy and Lactation

Drugs that affect the renin-angiotensin system can cause oligohydramnios in pregnancy.<sup>18</sup> This can reduce the kidney function of the fetus and increase the risk for morbidity and fetal death. Sacubitril/valsartan should not be given to pregnant women and should be stopped as soon as pregnancy is detected.

Sacubitril/valsartan is excreted in rat milk; however, there is no information on its presence in human breastmilk.<sup>18</sup> The pharmacist should discuss this with women who are considering breastfeeding. Breastfeeding is not recommended during treatment with sacubitril/valsartan.

### Counseling the patient

The pharmacist should explain that this medication is often used in combination with other medications for heart failure. Patients should be sure they understand which medicine they should continue to take. Advise the patient to avoid potassium supplements, salt substitutes and potassium-sparing diuretics since they can increase the chance for hyperkalemia.<sup>2</sup> The pharmacist should be sure to review the symptoms of angioedema, including swelling of the face, lips and tongue. Explain that the patient should get emergency help right away if this occurs.

The pharmacist should discuss the risks associated with this drug in women who are pregnant. Sacubitril/valsartan has been reported to increase the risk of fetal death. Advise women who are of child-bearing potential to use appropriate contraception. If pregnancy occurs, tell the patient they should contact their doctor right away.

## Role in therapy

Sacubitril/valsartan is the first neprilysin inhibitor available in the United States. The clinical trial designed to determine if there is a reduction in cardiovascular death or hospitalization due to heart failure was stopped early due to the superiority of sacubitril/valsartan over enalapril.<sup>20</sup> Certainly the results of this clinical trial would indicate that sacubitril-valsartan should be considered in patients with NYHA II-IV disease with poor ejection fraction. Additional studies are underway that evaluate this agent in patients with a higher ejection fraction (> 45%) and new-onset heart failure.

## Lumacaftor 200 mg/ivacaftor 125 mg (Orkambi)

Lumacaftor/ivacaftor was approved by the FDA on July 2, 2015.<sup>2</sup> It was approved for use in patients 12 years and older with F508del mutation type Cystic Fibrosis.<sup>21</sup> This drug was given breakthrough status by the FDA because there is evidence that it has substantial improvement over current therapy for a significant number of CF patients. It also was reviewed under priority review which reduces the turn-around time for FDA-approval from 10 months to 6 months.

Cystic Fibrosis is a genetic disorder that affects 30,000 people in the United States.<sup>22</sup>

It is the most common fatal genetic disease in Caucasians. There are several different genetic mutations associated with CF. The F508del mutation is the most common and accounts for 50% of all CF cases today. CF is the result of a defective gene that blocks an individual's ability to move salt and water in and out of cells. So the body's secretions that are usually thin and watery become thick and sticky. These thick secretions often result in airway blockage, shortness of breath and lung infection. Other organs can be involved, including the pancreas, gallbladder and liver. The pancreatic ducts become blocked and prevent the enzymes from reaching the stomach. Since the enzymes are not present, food is not digested properly and the patient cannot absorb nutrients. This may lead to scarring of the pancreatic cells and diabetes.

## Pharmacology/Pharmacokinetics

This is a combination product that contains lumacaftor and ivacaftor.<sup>21</sup> CFTR stands for Cystic Fibrosis Transmembrane Conductance Regulator. The CFTR protein is a channel for the movement of chloride ions in and out of cells, which is important for the salt and water balance on epithelial surfaces, such as in the lungs or pancreas. Changes in the CFTR gene can affect the structure of the CFTR protein. Lumacaftor improves the stability of the F508del CFTR protein. Ivacaftor is a CFTR potentiator that increases the period of time that the CFTR channels are open. The combination of lumacaftor with ivacaftor has been associated with a greater increase in chloride ion transport resulting in improved regulation of salt and water balance in various tissues including the lung and pancreas.

## Indications

Lumacaftor/ivacaftor is approved to treat cystic fibrosis in patients 12 years and older, who are homozygous for the F508del mutation (both parents have the mutation).<sup>21</sup> If the patient's genotype is unknown, a CF mutation test should be used to detect the presence of the F508del mutation.

## Dosing

The starting dose of lumacaftor/ivacaftor is two (2) tablets twice a day.<sup>2,21</sup> The dose should be reduced in patients with moderate to severe liver disease. The dose should be reduced

to 2 tablets in the morning and 1 tablet in the evening for patients with moderate hepatic impairment (Child-Pugh Class B).

### Efficacy

The safety and efficacy of lumacaftor/ivacaftor was evaluated in two double-blind, placebo-controlled clinical trials of 1,108 CF participants with the F508del mutation.<sup>22</sup> The primary measure of effectiveness was improvement in patients' percent of predicted FEV<sub>1</sub>, which is a measure of how well the lungs work. Results from the first study showed that after 24 weeks of treatment patients who took lumacaftor/ivacaftor had an average improvement in FEV<sub>1</sub> of 2.41 percentage points more than those who took placebo. In the second study the improvement was 2.65. Treatment with lumacaftor/ivacaftor also resulted in a reduction in the number of exacerbations that resulted in a hospital admission or antibiotic therapy. Overall the number of exacerbations was reduced by 39%.

The efficacy and safety of lumacaftor/ivacaftor has not been established in patients with other gene mutations. If a patient's genotype is unknown, a CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene.

### Contraindications/Warnings

There are no specific contraindications to lumacaftor/ivacaftor; however, there are certain warnings.<sup>21</sup> Lumacaftor/ivacaftor should be used with extreme caution in patients with serious liver impairment. Patient's liver disease may get worse and they may develop hepatic encephalopathy. The use of this drug must be weighed against the potential risks in this population. Liver function tests should be performed at baseline, quarterly for the first year and then annually to monitor for liver disease. If a patient reports an AST or ALT greater than 5X the upper limit of normal (with normal bilirubin), dosing should be interrupted. Dosing should be stopped if the ALT/AST is 3X greater than normal and bilirubin is 2X the upper limit of normal.

### Drug Interactions

**There are several drug-drug interactions with lumacaftor and/or ivacaftor (Table 7).<sup>21</sup>**

**Table 7- Drug interactions with lumacaftor/ivacaftor<sup>22</sup>**

Drug Category	Specific agents	Outcome
Sensitive CYP3A substrates	Budesonide, Felodipine, midazolam, simvastatin, lovastatin	Do not administer with lumacaftor/ivacaftor. Decreased concentrations of CYP3A substrates.
CYP3A substrates with a narrow therapeutic index	Alfentanil, cyclosporine, tacrolimus, fentanyl, pimozide, quinidine	Do not administer with lumacaftor/ivacaftor. Decreased concentrations of CYP3A substrates.
Strong CYP3A Inducers	Rifampin, St John's Wort	Reduces ivacaftor exposure. Do not administer together.
Strong CYP3A Inhibitors	Ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin	Reduce the dose of lumacaftor/ivacaftor.
P-gp substrates	Digoxin	Titrate the dose of digoxin
Hormonal contraception	Oral, injectable, transdermal, implants	May not be an effective form of contraception.

## Adverse Effects

The most common side effects of lumacaftor/ivacaftor include shortness of breath, upper respiratory tract infection, nausea, diarrhea, and rash. Women who took the drug reported menstrual abnormalities such as increased bleeding.<sup>21</sup>

## Pregnancy and Lactation

Lumacaftor/ivacaftor is pregnancy category B.<sup>21</sup> There are no clinical trials in pregnant women. Both lumacaftor and ivacaftor are excreted in the breastmilk of rats; however, there is no data in humans. It should be used with caution during breastfeeding.

## Counseling the patient

The pharmacist should educate patients that this medication must be taken with fat-containing foods.<sup>2,21</sup> Give patients examples of the types of foods that should be eaten. High fat foods include eggs, avocados, nuts, butter, peanut butter, cheese pizza, and whole milk dairy products such as yogurt, cheese and whole milk. If a dose is missed and the patient remembers within 6 hours, take the dose with high fat food. If it has been more than 6 hours, skip the dose and resume the normal schedule. Do not take a double dose. The pharmacist should encourage the patient to be sure to have blood tests to monitor the liver and that follow-up eye exams are recommended for younger patients.

## Role in therapy

Lumacaftor/ivacaftor is a breakthrough treatment for individuals with CF and the F508del mutation. This is the first medication directed at treating the cause of CF in patients who are homozygous for the F508del mutation. Although there is much to be positive about, lumacaftor/ivacaftor has not been evaluated in patients with an FEV1 < 40% predicted value. It has not been studied in advanced CF or after lung transplantation. There are several drug-drug interactions with transplant medications that may reduce its benefits following transplant. Use of this medication in CF patients with the F508del mutation resulted in an average improvement in FEV1 of 2.41 percentage points more than those who took placebo.<sup>22</sup>

Treatment with lumacaftor/ivacaftor also resulted in a reduction in the number of exacerbations that resulted in a hospital admission or antibiotic therapy. Overall the number of exacerbations was reduced by 39%.

## CONCLUSION

2015 was a banner year for the FDA. There were 45 new drug approvals, the most since 1996. Twenty-one drugs were approved in the category of orphan drugs. This is the beginning of a new focus by pharmaceutical manufacturers to target rare conditions. It is important for the pharmacist to understand these new drugs and how these medications fit into the current standard of care.

## UPCOMING TOPICS

- Validation of Pain Medication Rx
- Validation of Pain Medication Rx
- Pharmacy Considerations Regarding the Opioid Crisis of Abuse
- Vaccines—Truths, Myths, Hesitancy, Controversies
- Update *C. diff*—do probiotics and/or yogurt help?

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**LESSON EVALUATION**

Please fill out this section as a means of evaluating this lesson. The information will aid us in improving future efforts. Either circle the appropriate evaluation answer, or rate the item from 1 to 7 (1 is the lowest rating; 7 is the highest).

- Does the program meet the learning objectives?
 

Describe the new drugs approved in 2015 by the FDA	YES NO
Discuss the role of these agents in therapy	YES NO
Summarize the adverse effects & potential drug interactions of these new drugs	YES NO
Recommend specific counseling points for the new drugs	YES NO
- Was the program independent & non-commercial? YES NO

3. Relevance of topic

	Low Relevance							Very Relevant
	1	2	3	4	5	6	7	

4. What did you like most about this lesson? \_\_\_\_\_

5. What did you like least about this lesson? \_\_\_\_\_

**Please Mark the Correct Answer(s)**

- How many new drugs were approved by the FDA IN 2015?
 

A. 33	B. 41
C. 45	D. 53
- When treating Cystic Fibrosis, lumacaftor/ivacaftor can be used in which mutation?
 

A. F508del	B. E805de
C. F104del	D. E851de
- An orphan drug is defined as one that is designed for a disease that affects less than 300,000 patients.
 

A. True	B. False
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- Idarucizumab can be used to reverse Factor Xa inhibitors such as apixiban or edoxaban.
 

A. True	B. False
---------	----------
- A patient presents a prescription for palbociclib. She had started rifampin last week. What is your most appropriate action?
 

A. Refuse to fill the prescription
B. No problem; fill the prescription
C. Tell patient there is an interaction that can reduce absorption, but if the drugs are spaced out over time it should be OK
D. Explain that there is an interaction between palbociclib & rifampin. The rifampin decreases the amount of palbociclib that is absorbed by 85%
- A doctor calls your pharmacy & says that he wants to start a patient on Entresto. The doctor wants to know if the patient should continue the Lisinopril he has been taking for the last year. Your response is: "There is a contraindication. Stop the Lisinopril for 36 hours before starting Ernesto."
 

A. True	B. False
---------	----------
- One of the benefits of insulin degludec is:
 

A. Only given once a week
B. There is a lower incidence of nocturnal hypoglycemia
C. Less costly than Lantus
D. Can be diluted with other insulins
- Lumacaftor/ivacaftor has specific dosing instructions. Which of the following is true?
 

A. Take medication on an empty stomach
B. Take medication every other day
C. Take medication with a low fat food
D. Take this medication with high fat food
- Edoxaban is approved for atrial fibrillation. The dose of edoxaban in patients with normal renal function is:
 

A. 25 mg bid	B. 30 mg once daily
C. 60 mg once daily	D. 60 mg bid
- Which drug was approved as a Schedule IV controlled substance?
 

A. Entresto	B. Ibrance
C. Viberz	D. Tresiba

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