



# CE PRN

PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

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## “New Drugs: 2014”

June 2015

In this lesson we discuss the more significant new drugs that were approved in the last 12 – 18 months. The goal is to focus on these newer agents. Information will be provided that includes dosing guidelines, common adverse effects, contraindications and key counseling points.

### Pharmacists will be able to:

1. Describe new drugs approved by the Food and Drug Administration in 2014.
2. Discuss the role of these agents in therapy.
3. Comment upon the adverse effects and potential drug interactions related to these new agents.
4. Recommend specific counseling points that are essential when dispensing these agents to patients.



### Technicians will be able to:

1. List new drugs that have been approved by the FDA in 2014.
2. Discuss the uses of these new drugs.

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## Introduction

The Food and Drug Administration (FDA) approved a record 41 new molecular entities (NME) in 2014 (Table 1).<sup>1</sup> This is the highest number since 1996, when 53 new drugs were approved. Seventeen of these agents were designated as first in class (Table 2). There were 12 new infectious disease agents. With 2 new drugs for hepatitis C, research in infectious disease is on the upswing and there are more agents expected in 2016. New cancer treatments continue to be approved at a rapid rate with 8 new oncology drugs given the green light from the FDA. There were also a total of 16 biologics (35%) approved this year which is up from 22% last year.

Fifteen of this year's approved NMEs were designated as orphan drugs, the highest number since the Orphan Drug Act passed in 1983.<sup>1</sup> Almost 60% of the drugs that were approved had Priority Review, speeding up the approval process.

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 conditions 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. This year, 8 drugs were awarded that designation.

Table 1 summarizes the new chemical entities approved as well as the new biologics.

**Table 1- New drugs of 2014<sup>1</sup>**

Generic Name	Brand Name	Manufacturer	Indication
1. Nivolumab	Opdivo	Bristol Myers Squibb	Unresectable or metastatic melanoma
2. Peramivir	Rapivab	Biocryst	Influenza in adults
3. Ceftolozane/tazobactam	Zerbaxa	Cubist	Complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI).
4. Ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir	Viekira Pak	AbbieVie	Chronic hepatitis C infection
5. Olaparib	Lynparza	Astra Zeneca	Advanced ovarian cancer associated with defective BRCA genes
6. Finafloxacin	Xtoro	Alcon	Acute otitis externa (swimmers ear)
7. Blinatumomab	Blincyto	Amgen	Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia (B-cell ALL)
8. Pirfenidone	Esbriet	Intermune	Idiopathic pulmonary fibrosis
9. Nintedanib	Ofev	Boehringer Ingelheim	Idiopathic pulmonary fibrosis
10. Netupitant and palonosetron	Akynzeo	Eisai	Chemotherapy associated nausea and vomiting
11. Ledipasvir and sofosbuvir	Harvoni	Gilead	Chronic hepatitis C-genotype 1
12. Dulaglutide	Trulicity	Eli Lilly	Type II diabetes REMS
13. Naloxegol	Movantik	Astra Zeneca	Opioid induced constipation

Generic Name	Brand Name	Manufacturer	Indication
14. Pembrolizumab	Keytruda	Merck	Advanced or unresectable melanoma
15. Eliglusta	Cerdelga	Genzyme	Gaucher disease Type 1
16. Peginterferon beta-1a	Plegridy	Biogen	Multiple sclerosis
17. Suvorexant	Belsomra	Merck	Insomnia
18. Oritavancin	Orbactiv	Medicines	Acute bacterial skin and skin structure infections (ABSSSI)
19. Empagliflozin	Jardiance	Boehringer Ingelheim	Type II diabetes
20. Olodaterol	Striverdi Respimat	Boehringer Ingelheim	Chronic obstructive respiratory disease
21. Idelalisib	Zydelig	Gilead	Chronic lymphocytic leukemia (CLL) has returned (relapsed). Relapsed follicular B-cell non-Hodgkin lymphoma (FL) and relapsed small lymphocytic lymphoma (SLL)
22. Tavaborole	Kerydin	Anacor	Onychomycosis of the toenails
23. Belinostat	Beleodaq	Spectrum	Peripheral T-cell lymphoma
24. Tedizolid	Sivextro	Cubist	Acute bacterial skin and skin structure infections (ABSSSI)
25. Efinaconazole	Jublia	Dow	Onychomycosis of the toenails
26. Ibavancin	Dalvance	Durata	Acute bacterial skin and skin structure infections (ABSSSI)
27. Vedolizumab	Entyvio	Takeda	Moderate to severe ulcerative colitis or Crohn's disease
28. Vorapaxar	Zontivity	Merck	Reduce the risk of heart attack and stroke in high risk patients
29. Ceritinib	Zykadia	Novartis	Metastatic non-small cell lung cancer (NSCLC)
30. Siltuximab	Sylvant	Janssen	Multicentric castlemans disease (MCD)
31. Ramucirumab	Cyramza	Eli Lilly	Metastatic non-small cell lung cancer (NSCLC); gastroesophageal junction (GEJ) adenocarcinoma
32. Albiglutide	Tanzeum	Glaxo Smith Kline	Type II diabetes
33. Apremilast	Otezla	Celgene	Moderate to severe plaque psoriasis
34. Miltefosine	Impavido	Paladin	Leishmaniasis
35. Metreleptin	Myalept	Amylin	Generalized lipodystrophy
36. Droxidopa	Northera	Chelsea Therapeutics	Neurogenic orthostatic hypotension
37. Elosulfase	Vimizim	Biomarin Pharmaceuticals	Mucopolysaccharidosis Type IVA (Morquio A syndrome).
38. Tasimelteon	Hetlioz	Vanda Pharmaceuticals	Non-24- hour sleep-wake disorder
39. Dapagliflozin	Farxiga	Bristol Myers Squibb	Type II diabetes

Generic Name	Brand Name	Manufacturer	Indication
40. Recombinant C1 esterase inhibitor	Ruconest	Salix	Hereditary angioedema
41. Tavaborole	Kerydin	Anacor	Onychomycosis

Table 2 - 2014 New drugs - First in Class<sup>1</sup>

Generic name	Brand name
1. Olaparib	Lynparza
2. Blinatumomab	Blinicyto
3. Pirfenidone	Esbriet
4. Nintedanib	Ofev
5. Neisseria meningitides, Type B	Trumenba
6. Pembrolizumab	Keytruda
7. Suvorexant	Belsomra
8. Idelalisib	Zydelig
9. Vorapaxar	Zontivity
10. Siltuximab	Sylvant
11. Apremilast	Otezla
12. Miltefosine	Impavido
13. Recombinant C1 esterase inhibitor	Ruconest
14. Metreleptin	Myalept
15. Droxidopa	Nothera
16. Elosulfase	Vimizim
17. Ledipasvir and sofosbuvir	Harvoni

## ANTI-INFECTIVE AGENTS

2014 was a banner year for anti-infective agents. There were a total of 12 new agents approved, with 2 new drugs for hepatitis C, and several drugs approved for drug resistant skin infections.

### Hepatitis C

Hepatitis C is a viral infection that causes inflammation of the liver. This inflammation can lead to liver failure and the need for transplant. Complications of hepatitis C include bleeding abnormalities, cirrhosis and liver cancer.<sup>2</sup>

Currently, it is estimated that there are 3.2 million individuals in the United States with hepatitis C and up to 30% of those patients may develop cirrhosis.<sup>2</sup> Baby boomers born between 1945 and 1965, veterans, males, people in low income groups, prisoners, African Americans and Latino populations are at a higher risk of infection. Some people may never know how they acquired the infection; however, the most common risk factors include:

- Blood transfusion before 1992
- Sharing needles/syringes for injecting drugs
- Needle stick injuries in healthcare settings
- Potentially infected body art tools and ink for tattoos or unsterile equipment for body piercing
- Child born of a hepatitis C infected mother

- Unprotected or high risk sex

The Centers for Disease Control and the United States Preventive Services Task Force recommend a onetime Hepatitis C Virus antibody test for those born between 1945 and 1965 regardless of risk factors.<sup>3</sup> Sixty-six percent (66%) of those living with hepatitis C belong to this age group and 75% of hepatitis C related deaths occur in this population.

In 2013 the first oral direct acting antiviral agent, sofosbuvir (Sovaldi), was approved. This class of drugs has revolutionized the treatment of hepatitis C. In 2014, two additional oral products were approved, ledipasvir and sofosbuvir (Harvoni) and ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir (Viekira Pak).

### **Ledipasvir and sofosbuvir (Harvoni)**

Harvoni (ledipasvir and sofosbuvir) was approved on October 10, 2014 and was the seventh new drug with breakthrough therapy designation to receive FDA approval.<sup>1</sup> Ledipasvir and sofosbuvir was approved to treat chronic hepatitis C virus (HCV) genotype 1 infection.<sup>4</sup> This is also the first combination drug to be approved for hepatitis C and the first agent that does not require co-administration with interferon or ribavirin. Harvoni contains 90 mg of ledipasvir and 400 mg of sofosbuvir in one tablet.

#### Pharmacology/Pharmacokinetics

Sofosbuvir is a direct-acting antiviral agent that works against the hepatitis C virus.<sup>4</sup> It inhibits HCV-NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a prodrug which is converted in the body to its active form GS-461203. Dephosphorylation of GS-461203 results in GS-331007, a metabolite that lacks anti-HCV activity. Sofosbuvir is well absorbed after oral ingestion and absorption is not affected by meals. Peak concentration of sofosbuvir is reported to be 1 hour post dose. Sofosbuvir is approximately 65% plasma protein bound; however, protein binding of the metabolite GS-331007 is negligible. The dose is excreted primarily (78%) in the urine. The elimination half-life is 27 hours.

Ledipasvir inhibits a specific protein, HCV NS5A, which is required for hepatitis viral replication.<sup>4</sup> It is well absorbed, and food does not affect absorption. The peak concentration of ledipasvir is seen approximately 4 hours following the dose. It is 99.8% plasma protein bound. Ledipasvir does not undergo metabolism, and 98% of the dose is excreted unchanged in the feces.

#### Indications

Ledipasvir/sofosbuvir is approved to treat chronic hepatitis C virus (HCV) genotype 1 infection in adults.<sup>4</sup>

#### Dosing

Ledipasvir/sofosbuvir is administered as a single tablet once a day without regard to food.<sup>4</sup>

See table 3 for recommended length of therapy based on previous treatment status.

**Table 3. Recommendations for length of therapy with ledipasvir/sofosbuvir.<sup>4</sup>**

<b>Previous treatment status</b>	<b>Duration of therapy</b>
Treatment naïve with or without cirrhosis	12 weeks
Previous treatment without cirrhosis	12 weeks
Previous treatment with cirrhosis	24 weeks

There are currently no dose recommendations for patients with severe renal impairment or end-stage renal disease.<sup>4</sup>

### Efficacy

The drug's efficacy was evaluated in three clinical trials (ION 1,2 and 3) that included 1,518 patients.<sup>5</sup> Both treatment naïve and treatment experienced patients were studied in these trials. All three trials showed a 94-99% response rate defined as sustained virologic response (SVR), indicating that a participant's HCV infection had been cured.

The American Association for the Study of Liver Diseases (AASLD) 2015 guidelines recommend ledipasvir/sofosbuvir as an initial treatment option for patients with genotype 1.<sup>2</sup> This recommendation includes both treatment-naïve and treatment-experienced individuals.

### Contraindications/Warnings

There are no specific contraindications to ledipasvir/sofosbuvir treatment.<sup>4</sup> However, this drug should be used with caution in patients receiving amiodarone. Bradycardia and fatal cardiac arrest have been reported in patients using this combination. When there is no alternative for the patient, this combination should be started in a hospital with cardiac monitoring conducted for 48 hours. Heart rate should continue to be monitored daily for 2 weeks following initiation of the combination. Since amiodarone has an extremely long half-life (58 days), patients starting ledipasvir/sofosbuvir following discontinuation of amiodarone should undergo the same cardiac monitoring.

### Drug Interactions

Ledipasvir and sofosbuvir are substrates of the drug transporter P-gp.<sup>4</sup> Drugs that are potent P-gp inducers may decrease the effectiveness of ledipasvir/sofosbuvir. Drugs that are potent P-gp inhibitors should not be given to patients receiving this therapy.

Table 4 summarizes the drug-drug interactions reported with this product.

**Table 4. Common drug interactions with ledipasvir/sofosbuvir.<sup>4,6</sup>**

Interacts with	Effect
<b>Acid reducing agents, wAntacids, H2 blockers, Proton pump inhibitors</b>	The solubility of ledipasvir decreases as pH increases. These drugs can reduce the concentration of ledipasvir. Antacids should not be given within 4 hours of ledipasvir/sofosbuvir administration and doses of H2 blockers should be separated by 12 hours. Low doses of proton pump inhibitors may be given (20 mg omeprazole) on empty stomach.
<b>Amiodarone</b>	Serious bradycardia. Mechanism is unknown. Coadministration is not recommended.
<b>Digoxin</b>	Increased digoxin levels. Monitor digoxin level when taking this combination.
<b>Anticonvulsants</b> Carbamazepine Phenytoin Phenobarbital Oxcarbazepine	Coadministration of ledipasvir/sofosbuvir with phenytoin, phenobarbital or oxcarbamazepine will reduce the effectiveness of ledipasvir/sofosbuvir. Do not administer these agents in combination with ledipasvir/sofosbuvir.
<b>Antimycobacterials</b> Rifabutin Rifampin Rifapentine	Coadministration with rifampin or rifapentine will decrease the concentration of ledipasvir/sofosbuvir and the active metabolite GS-331007. It may reduce the effectiveness of ledipasvir/sofosbuvir.  Rifampin is a potent intestinal P-gp inducer. Do not administer this combination.

Interacts with	Effect
St John's Wort	St John's Wort is a potent intestinal P-gp inducer. Coadministration will reduce the effectiveness of ledipasvir/sofosbuvir. Do not administer this combination.
Rosuvastatin	Combining ledipasvir/sofosbuvir with rosuvastatin results in elevations of rosuvastatin levels and increasing the risk of myopathy. Do not use this combination.
Tipranavir/ritonavir	Coadministration leads to reduced effectiveness of ledipasvir/sofosbuvir. Do not administer this combination.
HIV combinations containing tenofovir	Tenofovir concentrations are elevated when combined with ledipasvir/sofosbuvir leading to adverse effects. Consider alternative HIV therapies.

### Adverse Effects

The most common adverse effects with ledipasvir/sofosbuvir reported after 12 weeks were fatigue (13%), headache (14%), nausea (7%), diarrhea (3%) and insomnia (5%).<sup>4</sup>

### Pregnancy and Lactation

Ledipasvir/sofosbuvir is pregnancy category B.<sup>4</sup> It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known if ledipasvir/sofosbuvir is excreted in human milk. The risks of any potential adverse effects should be considered and breastfeeding should be discontinued or the drug therapy should be discontinued.

### Counseling the patient

Be sure to review the potential drug interactions with this medication, especially the interactions with acid reducing agents since these products are available without a prescription. Verify the patient is not currently taking amiodarone, rosuvastatin or tenofovir because of the risks associated with these agents. When discussing hepatitis C treatment with your patient, it is important for them to understand the importance of compliance with therapy to avoid the development of resistance. Verify that the patient understands how and when to request refills of the medication. This is a good opportunity to discuss prescription delivery service and automatic refill. You may want to discuss having this medicine delivered at the same time each month.

### Role in therapy

The FDA granted ledipasvir/sofosbuvir its priority review and breakthrough therapy designation, which is granted to drugs that offer major advances in treatment over existing options. Ledipasvir/sofosbuvir is the first completely oral treatment for hepatitis C. Many patients are not able to tolerate the side effects of injectable interferon or ribavirin. This product offers a therapy that is very well tolerated and extremely effective.

### **Ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir (Viekira Pak)**

Viekira Pak was approved by the FDA on December 19, 2014.<sup>1</sup> Viekira Pak was approved as breakthrough therapy to treat chronic HCV genotype 1 infection.<sup>7</sup> It is an all oral combination therapy that can be used with or without ribavirin for hepatitis C. The Viekira Pak contains two 12.5/75/50 mg ombitasvir, paritaprevir, ritonavir tablets and two 250 mg dasabuvir tablets.

### Pharmacology/Pharmacokinetics

Viekira Pak combines three different direct acting antiviral (DAA) agents that all have differing mechanisms of action.<sup>7</sup> Ritonavir has no effect on hepatitis C, but it inhibits CYP3A and allows for higher serum concentrations of the DAA, paritaprevir.



Ombitasvir is an NS5A inhibitor, paritaprevir is an NS3/4A protease inhibitor and dasabuvir is a non-nucleoside NS5B polymerase inhibitor.<sup>7</sup> These three drugs work together to attack the HCV at three separate stages of the disease lifecycle to inhibit it from reproducing.

The drugs in the Viekira Pak are well absorbed, and studies indicate that Viekira Pak should always be taken with meals.<sup>7</sup> All four drugs are highly plasma protein bound (97-99%). The drugs in Viekira Pak are metabolized in varying ways. Table 5 describes the metabolism.

**Table 5: Metabolism of components of Viekira Pak<sup>7</sup>**

Drug	Metabolism
Ombitasvir	Amide hydrolysis
Paritaprevir	CYP3A4 and to a lesser extent by CYP3A5
Ritonavir	CYP3A, and to a lesser extent, by CYP2D6
Dasabuvir	CYP2C8, and to a lesser extent by CYP3A

These drugs are primarily excreted in the feces. Viekira Pak should not be administered to patients with moderate hepatic impairment and is contraindicated in severe hepatic disease (Child Pugh C).<sup>7</sup>

#### Indications

Viekira Pak, with or without ribavirin, is indicated for the treatment of patients with genotype 1 chronic HCV infection.<sup>7</sup>

#### Dosing

The dosing of Viekira Pak is dependent on previous treatment as well as genotype subgroup.<sup>6,7</sup> See Table 6 for recommended dosing regimens.

**Table 6. Dosing of Viekira Pak<sup>6,7</sup>**

Patient	Recommended treatment	Duration of therapy
Genotype 1a, no cirrhosis	Viekira Pak and ribavirin	12 weeks
Genotype 1a, cirrhosis	Viekira Pak and ribavirin	24 weeks
Genotype 1b, no cirrhosis	Viekira Pak	12 weeks
Genotype 1b, cirrhosis	Viekira Pak and ribavirin	12 weeks
If subtype unknown or mixed	Follow recommendations for genotype 1a	12 or 24 weeks
Liver transplant (mild fibrosis)	Viekira Pak and ribavirin	24 weeks

#### Ribavirin (RBV) dosing

The recommended dose of RBV is based on weight: 1000 mg for subjects <75 kg and 1200 mg/day for those ≥75 kg.<sup>7</sup> The dose is divided and administered twice-daily with food. For ribavirin dosage modifications, refer to the ribavirin prescribing information

Do not give Viekira Pak in moderate to severe liver impairment (Child-Pugh B or C)

#### Efficacy

Six clinical trials including 2,308 patients were conducted comparing Viekira Pak (with and without ribavirin) to placebo.<sup>8</sup> These clinical trials included both treatment experienced and treatment naïve patients. The PEARL III, IV trials included treatment naïve patients and demonstrated efficacy of 97 to 100%. The PEARL II and SAPPHERE II trials included treatment experienced patients and showed efficacy of 96-100% after 12 weeks of drug therapy. This

efficacy rate is comparable to that of ledipasvir and sofosbuvir (Harvoni), however; in many cases ribavirin is required.

### Contraindications/Warnings

Do not administer Viekira Pak in severe liver disease (Child Pugh C).<sup>7</sup> Do not use in patients with allergic reaction to ritonavir. Avoid using in combination with drugs that reduce efficacy of Viekira (strong CYP3A, 2C8 inducers) or drugs that increase the chance for QT-prolongation (Strong inhibitors of CYP2C8).

### Drug Interactions

Table 7 summarizes the drug-drug interactions that are encountered with Viekira Pak.

**Table 7. Common drug interactions with Viekira Pak.<sup>6,7</sup>**

<b>Interacts with</b>	<b>Effect</b>
Alfuzosin	Increased risk for hypotension
Carbamazepine, phenytoin and phenobarbital	Reduced efficacy of Viekira Pak
Rifampin	Reduced efficacy of Viekira Pak
Sildenafil (Pulmonary arterial hypertension)	Syncope, priapism, hypotension, visual disturbances
Ergotamine, methylergonovine	Acute ergot toxicity (tissue ischemia, vasospasm)
St John's Wort	Reduced efficacy of Viekira Pak
Simvastatin and lovastatin	Elevations of statin levels and increasing the risk of myopathy
Sedatives (triazolam, midazolam)	Prolonged respiratory depression, large increase in benzodiazepine levels
Gemfibrozil	Increased risk of QT prolongation due to extreme increase in dasabuvir concentration
Pimozide	Increased risk of arrhythmias
Estrogen including oral contraceptives	Significant increase in ALT. Use non-hormonal or progestin only contraception

### Adverse Effects

The most common adverse effects with Viekira Pak reported after 12 weeks were fatigue (34%), nausea (22%), pruritus (18%), skin rash (16%), insomnia (14%) and asthenia (14%).<sup>7</sup> Elevations of ALT were reported in clinical trials and were more common (25%) in women who were taking estrogen containing medication. The elevation occurred during the first 4 weeks of treatment.

### Pregnancy and Lactation

Viekira Pak is pregnancy category B.<sup>7</sup> If this agent is used in combination with ribavirin, it is contraindicated in pregnancy. Ribavirin is also contraindicated in men whose female partners are pregnant. It is not known if the agents included in the Viekira Pak are excreted in human milk. The risks of any potential adverse effects should be discussed if breastfeeding is considered.

### Counseling the patient

Monitor liver enzymes in all patients during the first 4 weeks of therapy. Be sure to review the potential drug interactions with this medication. Discuss the interactions with your patient to ensure they do not start new medication that can reduce the effectiveness of their hepatitis therapy. When discussing hepatitis C treatment with your patient, it is important for them to understand the importance of compliance with therapy to avoid the development of resistance. Verify that the patient understands how and when to request refills of the medication. This is a

good opportunity to discuss prescription delivery service and automatic refill. You may want to discuss having this medicine delivered at the same time each month.

### Role in therapy

Viekira Pak is the fourth therapy for hepatitis C that received a breakthrough therapy designation from the FDA in the past year. Viekira Pak is the second all oral therapy for hepatitis C and has similar efficacy to ledipasvir/sofosbuvir (Harvoni). Although it is similar in efficacy, this therapy requires taking more pills per day, may require additional ribavirin and has the potential for more serious side effects.

## OTHER SELECT AGENTS APPROVED IN 2014

### Suvorexant (Belsomra)

Suvorexant was approved by the FDA on August 13, 2014.<sup>1</sup> It is classified as a Schedule IV controlled substance and requires a medication guide be dispensed to the patient.<sup>9</sup> Like other sedatives, this drug has the potential for dependence and abuse. Suvorexant is the first agent in a new class of sedatives, orexin receptor antagonists. It is available as 5, 10, 15 and 20 mg tablets.

### Pharmacology/Pharmacokinetics

Suvorexant is an orexin receptor antagonist.<sup>9</sup> Orexin receptors promote wakefulness, and blocking these receptors suppresses the wake drive. Patients with narcolepsy suffer from a blockade of these receptors or may not have these neurons at all.

Suvorexant is well absorbed following oral administration.<sup>9</sup> When taken with high fat meals, there is a delay in the onset of sleep. The drug is extensively bound to plasma proteins (99%) and has a volume of distribution of 49 L. Suvorexant is metabolized primarily by the CYP3A enzymes. Sixty five percent of a dose is excreted in the feces and 23% through the urine. The half-life of the drug is 12 hours.

### Indications

Suvorexant is approved for the treatment of insomnia in adults.<sup>9</sup>

### Dosing

The recommended dose of suvorexant is 10 mg.<sup>9</sup> It should be taken 30 minutes prior to sleep at least 7 hours before planned awakening. The dose may be increased to a maximum dose of 20 mg once a day. Suvorexant should be taken on an empty stomach as food can delay the effect of the drug.

The dose of suvorexant should be started at 5 mg in patients who are taking moderate CYP3A inhibitors (diltiazem).<sup>9</sup> The maximum dose in this population is 10 mg once a day. Suvorexant should not be given to individuals who are taking strong CYP3A inhibitors (ketoconazole or itraconazole). Studies have shown that higher serum levels are reported in obese women compared to lean women.<sup>9</sup> Doses should not be increased in obese women due to the risk for adverse effects.

### Efficacy

Suvorexant was studied in three clinical trials comparing it to placebo only.<sup>10</sup> These trials demonstrated that suvorexant was superior to placebo in improving sleep latency. This drug was not compared to active treatment alternatives. The FDA originally rejected the application

of suvorexant 30 and 40 mg tablets in 2013 due to a high incidence of somnolence reported in the clinical trials.

### Contraindications/Warnings

Suvorexant is contraindicated in patients with narcolepsy.<sup>9</sup>

### Drug Interactions

Suvorexant can have an additive effect when given in combination with CNS-active drugs including benzodiazepines and opioid narcotics. The dose of suvorexant should be reduced when administered together with moderate CYP3A inhibitors such as erythromycin, fluconazole, grapefruit juice, ciprofloxacin, diltiazem, verapamil and atazanavir. This drug should not be combined with strong CYP3A inhibitors such as ketoconazole, itraconazole, saquinavir, indinavir and clarithromycin.<sup>6,9</sup>

### Adverse Effects

The most common side effect reported with suvorexant is somnolence. Somnolence is a dose-related side effect.<sup>9</sup> It is reported to be 2% at the 10 mg dose, 5% at the 20 mg dose, 12% at a 40 mg dose and 11% at an 80 mg dose. The manufacturer had originally submitted suvorexant to the FDA at a higher dose of 30 and 40 mg. However these doses were rejected because of the high incidence of next day somnolence. At doses of 20 and 40 mg elderly patients demonstrated balance problems when awakened in the middle of the night following a dose of suvorexant.

Other side effects include diarrhea, dry mouth, dizziness, abnormal dreams and headache.<sup>9</sup>

### Pregnancy and Lactation

Suvorexant is classified as Pregnancy category C.<sup>9</sup> No controlled clinical trials have been done with pregnant women. Some animal studies conducted in rats suggest reduced birth weight in newborn rats. It is unclear if suvorexant is excreted in breast milk. Before breastfeeding, the risks and benefits of potential exposure to suvorexant should be considered.

### Counseling the patient

Patients should be counseled about the potential risk for next day somnolence. As with other sedative agents, patients should have a frank discussion with their healthcare provider about the potential for dependence and abuse of suvorexant. Patients should be counseled about non-drug therapy for insomnia including avoiding caffeine, nicotine and alcohol near bedtime, avoiding naps, and relaxing bedtime routines.

Patients should be counseled about potential drug and food interactions with suvorexant. This medication should not be taken with food as the sleep effects will be delayed. Patients should avoid eating grapefruit or drinking grapefruit juice when taking this medication as it will increase serum levels of this drug.

### Role in therapy

It is unclear how this agent will fit into therapy for insomnia. It has the same warnings of abuse and dependence as other agents on the market. Suvorexant has only been studied against placebo so it is difficult to determine the efficacy of this drug against current therapy. There is concern about the risk of next day somnolence with suvorexant even at the lower doses that were finally approved by FDA. Several agents currently used for insomnia are available generically so cost may also be a concern.

## Vorapaxar (Zontivity)

Vorapaxar was approved by the FDA on May 18, 2014 to reduce thrombotic cardiovascular events in patients with a history of myocardial infarction or peripheral vascular disease.<sup>1</sup> Vorapaxar is the first drug in a new class called **protease activated receptor-1 antagonists (PAR-1)**.<sup>11</sup> This drug is classified as an irreversible antiplatelet agent. The product is available as a 2.08 mg tablet.

### Pharmacology/Pharmacokinetics

Vorapaxar inhibits platelets through a completely different pathway than aspirin or clopidogrel.<sup>11</sup> Aspirin inhibits platelets through the thromboxane pathway while clopidogrel, prasugrel and ticagrelor work by inhibiting the platelet adenosine diphosphate (ADP) receptor. Vorapaxar inhibits PAR-1 which blocks thrombin-induced platelet aggregation.

Vorapaxar is 100% bioavailable following oral administration.<sup>11</sup> The drug may be taken without regard to meals. Vorapaxar is highly plasma protein bound ( $\geq 99\%$ ), primarily to albumin. The drug is metabolized by CYP3A4 and CYP2J2 and eliminated by the feces. The half-life of vorapaxar is 8 days.

### Indications

Vorapaxar is approved for the prevention of thrombotic cardiovascular events in patients with a previous myocardial infarction or patients with peripheral vascular disease.<sup>11</sup>

### Dosing

The dose of vorapaxar is one tablet (2.08 mg) given by mouth once a day.<sup>11</sup> It can be given without regard to meals. No clinical studies have been done with vorapaxar alone. It should be administered with aspirin and or clopidogrel. There is no clinical data at this time with any other antiplatelet drugs.

### Efficacy

Vorapaxar has been studied in patients with stable atherosclerotic disease as well as patients with acute coronary syndrome.<sup>12</sup> These studies have shown that vorapaxar is effective at reducing the risk of ischemic events and death in stable atherosclerotic patients. Vorapaxar lowered this risk from 9.5 percent to 7.9 percent over a 3-year period – about 0.5 percent per year. In patients with acute coronary syndrome (ACS), there was no significant difference in the primary endpoint. Both types of studies resulted in an increased risk of moderate to severe bleeding, including intracranial hemorrhage.

### Contraindications/Warnings

There are two black box warnings for vorapaxar.<sup>11</sup> Vorapaxar is contraindicated in patients with a history of stroke, intracranial hemorrhage, or transient ischemic attack (TIA). It is also contraindicated in patients with active bleeding.

This drug can cause bleeding, including intracranial hemorrhage and fatal bleeding.<sup>11</sup> Prescribers should consider a patient's underlying bleeding risk when prescribing any antiplatelet drug including vorapaxar. Risk factors for bleeding include older age, low body weight, liver or kidney impairment, or co-administration of certain drugs (anticoagulants, NSAIDs, fibrinolytics, SSRIs). There is no reversal agent for vorapaxar. Once the drug is stopped, antiplatelet effects will continue for 4 weeks.

Drug Interactions

Vorapaxar should not be used with strong inhibitors or inducers of CYP3A.<sup>6,11</sup> See Table 8 for examples of these agents. Strong inhibitors increase vorapaxar levels, while strong inducers reduce the levels of the drug.

**Table 8-Inducers and inhibitors of CYP3A<sup>6,11</sup>**

<b>Strong Inhibitors of CYP3A</b>	<b>Strong Inducers of CYP3A</b>
Ketoconazole	Rifampin
Itraconazole	Carbamazepine
Posaconazole	St. John's Wort
Clarithromycin	Phenytoin
Nefazodone	
Ritonavir	
Saquinavir	
Nelfinavir	
Indinavir	
Boceprevir	
Telaprevir	
Telithromycin	
Conivaptin	

Adverse Effects

Vorapaxar was associated with bleeding. In the clinical trials bleeding was categorized as GUSTO severe (fatal, intracranial, or bleeding with hemodynamic compromise).<sup>11</sup>

Other adverse effects reported with vorapaxar include anemia (5%), depression (2.4%), and skin rash (2.2%). Less frequent side effects (< 2%) were diplopia and retinopathy.

Pregnancy and Lactation

Vorapaxar is pregnancy category B.<sup>11</sup> There are no clinical studies in pregnant women. Animal studies indicate that there is a low risk of teratogenic effects with vorapaxar. Although there are no studies that indicate that vorapaxar is excreted in human breast milk, it is excreted in the breast milk of female rats. Because of the potential for side effects, it is recommended that breastfeeding be discontinued or vorapaxar be stopped.

Counseling the patient

When counseling the patient who is starting vorapaxar, there are several key points to discuss. First of all, ensure that the patient is taking either clopidogrel or aspirin as part of their regimen. Vorapaxar should not be administered as single drug therapy. This is a good opportunity to implement a medication synchronization plan to ensure both antiplatelet drugs are refilled together. Explain to the patient that the benefits of vorapaxar have only been seen with combination therapy. The pharmacist may want to make a notation in the patient record to reinforce this information with each refill. Secondly, the patient should be counseled about potential drug interactions with vorapaxar. The pharmacist should verify that the patient is not taking CYP3A inhibitors or inducers. Finally, it is critical that the pharmacist discuss the bleeding risks reported with vorapaxar. Describe that the patient may be at risk for bruising and bleeding. They should report any prolonged or unanticipated bleeding to their doctor immediately.

### Role in therapy

Vorapaxar is the first PAR-1 agent approved by the FDA. It is only approved for use in combination with aspirin or clopidogrel and has been anticipated as an exciting addition to the current treatment of thrombotic risk. Although this drug attacks a different pathway to block platelet aggregation, there is a significant risk of moderate to severe bleeding associated with its use. Some practitioners may use this new agent more prudently because of the risks.

### **Dapagliflozin (Farxiga)**

Dapagliflozin was approved by the FDA on January 8, 2014.<sup>1</sup> It was originally rejected by the FDA in 2012 due to concerns regarding bladder and breast cancer. It is a sodium-glucose cotransporter 2 (SGLT2) inhibitor that increases glucose excretion and blocks reabsorption of glucose in the kidney.<sup>13</sup> It is the second SGLT2 inhibitor available behind canagliflozin. It is available as 5 and 10 mg tablets.

### Pharmacology/Pharmacokinetics

Sodium-glucose cotransporter 2 is located in the proximal renal tubules.<sup>13</sup> It is responsible for reabsorption of glucose from the tubular lumen. Dapagliflozin inhibits this process and prevents glucose reabsorption. This results in an increase in renal excretion of glucose and a reduction in blood glucose.

Dapagliflozin is well absorbed after oral administration.<sup>13</sup> It can be administered without regard to meals. The drug is 91% plasma protein bound. Dapagliflozin is metabolized in the liver and is excreted primarily in the urine. The half-life of dapagliflozin is 13 hours.

### Indications

Dapagliflozin is approved for use in Type II diabetes in combination with diet and exercise.<sup>13</sup>

### Dosing

The starting dose of dapagliflozin is 5 mg once a day.<sup>13</sup> The dose is taken in the morning without regard to meals. The dose can be increased to 10 mg once a day. Patients with moderate renal impairment (estimated GFR below 60 mL/min/1.73 m<sup>2</sup>) should not take dapagliflozin.

### Efficacy

The drug's safety and effectiveness was evaluated in 16 clinical trials involving more than 9,400 patients with type 2 diabetes.<sup>14</sup> The trials showed a statistically significant reduction (0.9%) in HbA<sub>1c</sub>. The drug has been studied in combination with most oral diabetes agents as well as insulin. The FDA remains concerned about the safety of this drug and required six additional clinical trials post-market. These trials look at:

- cardiovascular outcomes to assess the cardiovascular risk of dapagliflozin in patients with high baseline risk of cardiovascular disease.
- studies evaluating the bladder cancer risk.
- studies in pediatrics.
- improved monitoring program for reporting liver abnormalities and pregnancy outcomes.

### Contraindications/Warnings

Dapagliflozin is contraindicated in patients with severe renal dysfunction, and those requiring dialysis.<sup>13</sup> It is also contraindicated in patients allergic to dapagliflozin. There are several warnings for using dapagliflozin. See Table 9 for these warnings.

**Table 9-Warning with dapagliflozin<sup>13</sup>**

<b>Warning</b>	<b>Comments</b>
Bladder cancer	There were 4 cases of bladder cancer reported during clinical trials. There is not enough data to link dapagliflozin with bladder cancer; however, if someone has active bladder cancer, this drug should not be given.
Genital mycotic infections	Dapagliflozin increases the risk of genital mycotic infections and patients with a history of these infections are at a higher risk.
Hypotension	Dapagliflozin causes intravascular volume contraction as a result of increased excretion of glucose in the urine. Patients taking dapagliflozin can experience symptoms of hypotension. Patients at higher risk include those with moderate renal impairment, patients taking loop diuretics or the elderly. Assessment of volume status should be done before starting this medication.
Hypoglycemia	When dapagliflozin is given in combination with insulin or an insulin secretagogue, patients are at a higher risk for hypoglycemia. Patients may require a lower dose of insulin or the secretagogue.
Impaired renal function	Dapagliflozin can increase serum creatinine. Elderly patients and those with pre-existing renal impairment are at risk for decreased glomerular filtration rate.
Increased low density lipoproteins (LDL)	Dapagliflozin can increase LDL. Patients should be carefully monitored and if they have an increase in LDL, they should be treated using standard therapy with statin agents.

### Drug Interactions

There are no specific drug interactions with dapagliflozin.<sup>6,13</sup> There is a warning to avoid monitoring glycemic control with urine glucose tests. Since dapagliflozin increases urinary glucose, the urine glucose test will be positive.

### Adverse Effects

The most common adverse effects of dapagliflozin include female genital mycotic infection (8.4%), nasopharyngitis (6.2%), urinary tract infections (5.7%), increased urination (2.9%), male genital mycotic infections (2.8%), nausea (2.8%), and influenza (2.7%). Less common but serious side effects include hypotension, renal failure, hypoglycemia, and bladder cancer<sup>13</sup>

### Pregnancy and Lactation

Dapagliflozin is pregnancy category C.<sup>13</sup> There have been no clinical trials in pregnant women. Animal studies suggest there may be a risk of impaired renal development. Dapagliflozin should only be used in pregnancy if the risk outweighs the benefit. It is not known if dapagliflozin is excreted into breastmilk. Since many drugs are excreted into breastmilk, a decision should be made to discontinue breastfeeding or dapagliflozin.

### Counseling the patient

When a patient starts therapy with dapagliflozin, the pharmacist must dispense the Medication Guide. As with other therapies for diabetes, the pharmacist should discuss the importance of diet, weight management and exercise with the patient. 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.

In addition, patients should be warned against dehydration since it can result in symptoms of hypotension (dizziness, lightheadedness, weakness). The pharmacist should explain the risk of genital mycotic (fungal) infections reported with this drug. Symptoms in women include vaginal odor, and discharge that is yellow or white. Symptoms in men include foul smelling discharge from penis, and redness or itching of the penis.

Since bladder cancer occurred in a few patients receiving dapagliflozin during clinical trials, patients should notify their doctor if they notice pain during urination or blood in their urine.



### Place in therapy

Dapagliflozin is a SGLT2 inhibitor available for the treatment of Type II diabetes. As it currently stands, there are concerns of associated cancer risk with the use of dapagliflozin, which is still subject to postmarketing trials. Another SGLT2 inhibitor, canagliflozin was approved in 2013 without the bladder cancer warnings. If prescribers want to use an SGLT2 inhibitor, canagliflozin might be an option. If prescribers choose to use dapagliflozin, it is important to counsel the patient about hypotension, dehydration risk and other possible side effects reported.

### **Empagliflozin (Jardiance)**

Empagliflozin was approved by the FDA on August 4, 2014.<sup>1</sup> It is the third SGLT2 inhibitor approved by the FDA. Its pharmacology, warnings and adverse effects are very similar to dapagliflozin.<sup>15</sup> Its efficacy is also similar. Like dapagliflozin, it is a sodium-glucose cotransporter (SGLT2) inhibitor that increases glucose excretion and blocks reabsorption of glucose in the kidney. It is available as 10 and 25 mg tablets.

### Pharmacology/Pharmacokinetics

Sodium-glucose cotransporter 2 is located in the proximal renal tubules.<sup>15</sup> It is responsible for reabsorption of glucose from the tubular lumen. Empagliflozin inhibits this process and prevents glucose reabsorption. This results in an increase in renal excretion of glucose and a reduction in blood glucose.

Empagliflozin is well absorbed after oral administration and can be given with or without food.<sup>15</sup> The drug is 86% plasma protein bound. Empagliflozin is metabolized by glucuronidation in the liver and is excreted in the liver (41.2%) and in the urine (54.4%). The half-life of empagliflozin is 12 hours.

### Indications

Empagliflozin is approved for use in Type II diabetes in combination with diet and exercise.<sup>15</sup>

### Dosing

The starting dose of empagliflozin is 10 mg once a day.<sup>6,15</sup> The dose is taken in the morning with or without food. The dose can be increased to 25 mg once a day in patients who need additional glycemic control. Patients with moderate renal impairment (estimated GFR below 60 mL/min/1.73 m<sup>2</sup>) should not take this drug.

### Efficacy

Like dapagliflozin, this drug was studied with oral anti-diabetic drugs and insulin.<sup>16</sup> Seven clinical trials including 4,480 patients were submitted to the FDA to demonstrate the safety and efficacy of the drug. The trials showed an overall 0.5 to 0.6% reduction in HbA<sub>1c</sub>.

As with dapagliflozin, the FDA remains concerned about the safety of empagliflozin and required four additional clinical trials post-market.<sup>15</sup> These trials look at

- Completing the cardiovascular outcomes trials.
- Evaluating pharmacokinetic data in children.
- Evaluating safety and efficacy in children.
- Investigating teratogenicity (renal development, bone effects) using animal models.

### Contraindications/Warnings

Empagliflozin is contraindicated in patients with severe renal dysfunction, and those requiring dialysis.<sup>15</sup> It is also contraindicated in patients allergic to the drug. There are several warnings for using empagliflozin. It carries many of the same warnings as dapagliflozin, with the exception of bladder cancer warnings:

- Genital mycotic infections
- Hypotension
- Hypoglycemia
- Impaired renal function
- Increased low density lipoproteins (LDL)

### Drug Interactions

Using empagliflozin in combination with diuretics increases the risk for volume depletion.<sup>15</sup> This combination should be avoided. Insulin and insulin secretagogues can increase the risk for hypoglycemia.

### Adverse Effects

The most common adverse effects reported with empagliflozin 10 mg are urinary tract infections (9.3%), female genital mycotic infection (5.4%), dyslipidemia (3.9%), upper respiratory tract infection (3.1%), increased urination (3.4%), male genital mycotic infections (3.1%), nausea (2.3%), and arthralgia (2.2%).<sup>15</sup>

### Pregnancy and Lactation

Empagliflozin is Pregnancy category C.<sup>15</sup> There have been no clinical trials in pregnant women. Animal studies suggest there may be a risk of impaired renal development. Empagliflozin should only be used in pregnancy if the risk outweighs the benefit. It is not known if empagliflozin is excreted into breastmilk. Since many drugs are excreted into breastmilk, a decision should be made to discontinue breastfeeding or empagliflozin.

### Counseling the patient

When a patient starts therapy with empagliflozin, the pharmacist should discuss the importance of diet, weight management and exercise. 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.

In addition, patients should be warned against dehydration since it can result in symptoms of hypotension (dizziness, lightheadedness, weakness). The pharmacist should explain the risk of genital mycotic (fungal) infections reported with this drug. Symptoms in women include vaginal odor, and discharge that is yellow or white. Symptoms in men include foul smelling discharge from penis, and redness or itching of the penis.

### Place in therapy

Empagliflozin is the newest SGLT2 inhibitor available for the treatment of Type II diabetes.

As it currently stands, there are concerns associated with the overall safety of empagliflozin, which, like dapagliflozin, is still subject to postmarketing trials. Another SGLT2 inhibitor, canagliflozin, was approved in 2013 without the bladder cancer warnings or post-marketing safety concerns. If prescribers want to use an SGLT2 inhibitor, canagliflozin might be an

option. If prescribers choose to use empagliflozin, it is important to counsel the patient about hypotension, dehydration risk and other possible side effects reported with this agent.

### **Edoxaban (Savaysa)**

Edoxaban was approved by the FDA on January 8, 2014.<sup>1</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.<sup>17</sup>

#### Pharmacology/Pharmacokinetics

Edoxaban is a factor Xa inhibitor.<sup>17</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>17</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 the 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>17</sup> It is also approved to treat deep vein thrombosis (DVT) or pulmonary embolism (PE) in patients who have had initial therapy with parenteral anticoagulants.

#### Dosing

The recommended dose for edoxaban is 60 mg once a day.<sup>17</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 venous thromboembolism (VTE).<sup>18</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>18</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>17</sup> There are three black box warnings regarding the use of this drug.

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>17</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>6,17</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>17</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>17</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 her physician will need to determine if breastfeeding should be discontinued or the medication discontinued.

### Counseling the patient

When therapy begins, the pharmacist should verify that patients are not taking other anticoagulants or drugs that may affect bleeding. 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 edoxiban with a CrCl > 95 mL/min.

## CONCLUSION

The past year was busy for the FDA. There were 41 new drug approvals. It is the first year that 17 drugs were approved as first in class. It is important for the pharmacist to understand these new drug classes and how these new medications fit into the current standard of care.

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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).

1. Does the program meet the learning objectives?  
 Describe new FDA approved drugs in 2014 YES NO  
 Discuss the role of these drugs in therapy YES NO  
 Comment upon adverse effects & drug interactions of these drugs YES NO  
 Recommend counseling points associated with these drugs YES NO

2. Was the program independent & non-commercial YES NO  
Low Relevance Very Relevant

3. Relevance of topic 1 2 3 4 5 6 7

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

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

- |   |   |
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| <p><b>1. How many new drugs were FDA approved in 2014?</b><br/>                 A. 33 <span style="margin-left: 100px;">B. 41</span><br/>                 C. 45 <span style="margin-left: 100px;">D. 53</span></p> <p><b>2. In the treatment of hepatitis C, ledipasvir &amp; sofosbuvir can be used in:</b><br/>                 A. Genotype I <span style="margin-left: 50px;">B. Genotype II</span><br/>                 C. Genotype III <span style="margin-left: 50px;">D. Genotype IV</span></p> <p><b>3. In Genotype 1a patients without cirrhosis, the duration of treatment with Viekira Pak is:</b><br/>                 A. 12 weeks with ribavirin<br/>                 B. 12 weeks without ribavirin<br/>                 C. 24 weeks with ribavirin<br/>                 D. 24 weeks without ribavirin</p> <p><b>4. The most common adverse effect reported with dapagliflozin is:</b><br/>                 A. Nausea<br/>                 B. Nasopharyngitis<br/>                 C. Female genital mycotic infections<br/>                 D. Urinary tract infections</p> <p><b>5. Vorapaxar has a black box warning for:</b><br/>                 A. Narcolepsy<br/>                 B. Use in pregnant females<br/>                 C. Dialysis<br/>                 D. Patients with history of stroke, TIA or intracranial hemorrhage</p> | <p><b>6. Suvorexant is a:</b><br/>                 A. Direct acting antiviral agent<br/>                 B. Protease activated receptor 1 antagonist<br/>                 C. Orexin receptor antagonist<br/>                 D. Sodium-glucose cotransporter 2</p> <p><b>7. SGLT-2 agents should not be used in conjunction with diuretics because of the risk for volume depletion.</b><br/>                 A. True <span style="margin-left: 100px;">B. False</span></p> <p><b>8. Edoxaban is approved for use in atrial fibrillation. The dose of edoxaban in patients with normal renal function is:</b><br/>                 A. 25 mg twice daily <span style="margin-left: 50px;">B. 30 mg once daily</span><br/>                 C. 60 mg once daily <span style="margin-left: 50px;">D. 60 mg twice daily</span></p> <p><b>9. Currently, it is estimated that there are 3.2 million individuals in the U.S. with hepatitis C. It is estimated that 30% of those patients may develop cirrhosis.</b><br/>                 A. True <span style="margin-left: 100px;">B. False</span></p> <p><b>10. When counseling a patient who is starting vorapaxar, ensure that patient is taking aspirin or clopidogrel; discuss the bleeding; review potential drug interactions; &amp; verify that the patient is not taking CYP3A inducers or inhibitors.</b><br/>                 A. True <span style="margin-left: 100px;">B. False</span></p> |
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