



PHARMACY CONTINUING EDUCATION FROM WF PROFESSIONAL ASSOCIATES

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“New Drugs Approved in 2016”

July 2017



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The FDA approved only 22 new molecular entities (NME) in 2016. In the next two lessons, we focus on some of the newer agents that are of interest to pharmacy practitioners. Information is provided that includes dosing guidelines, common adverse effects, contraindications and key counseling points.

This lesson provides 1.25 (0.125 CEUs) contact hours of credit, and is intended for pharmacists & technicians in all practice settings. **The program ID # for this lesson is 707-000-17-007-H01-P for pharmacists & 707-000-17-007-H01-T for technicians.**

Participants completing this lesson by June 30, 2020 may receive full credit. Release date for this lesson is July 1, 2017.

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:

For Pharmacists:

1. Describe the new drugs approved by FDA in 2016.
2. Discuss the role of these agents in therapy.
3. Summarize adverse effects associated with these agents.
4. Recommend counseling points associated with these drugs.

For Technicians:

1. List new drugs approved in 2016.
2. Discuss the uses of these new drugs.

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INTRODUCTION

In the next two lessons, we focus on some of the newer agents that are of interest to pharmacy practitioners. Information is provided that includes dosing guidelines, common adverse effects, contraindications and key counseling points.

The FDA approved only 22 new molecular entities (NME) in 2016 (Table 1)¹. This number is lower than the 45 products approved in 2015 or the 29 drug approvals per year which have been seen over the last decade. One reason cited is that the FDA's Center for Drug Evaluation and Research approved 5 products in 2015 ahead of their scheduled approval date in 2016.²

Table 1—New drugs of 2016¹.

Generic Name	Brand Name	Approval Date	Indication
Elbasvir and grazoprevir	Zepatier	1-28-2016	Chronic hepatitis C (HCV) genotypes 1 and 4 infection
Brivaracetam	Briviact	2-18-2016	Partial onset seizures
Obiltoximab	Anthim	3-18-2016	Inhalational anthrax
Ixekizumab	Taltz	3-22-2016	Moderate to severe plaque psoriasis
Reslizumab	Cinqair	3-23-2016	Severe asthma
Defibrotide sodium	Defitelio	3-30-2016	Hepatic veno-occlusive disease following stem cell transplant
Venetoclax	Venclexta	4-11-2016	Chronic lymphocytic leukemia in patients with a specific chromosomal abnormality
Pimavanserin	Nuplazid	4-29-2016	Treatment of hallucinations and delusions from psychosis in Parkinson's disease
Atezolizumab	Tecentriq	5-18-2016	Urothelial type bladder cancer
Daclizumab	Zinbryta	5-27-2016	Multiple sclerosis
Obeticholic acid	Ocaliva	5-27-2016	Rare chronic liver disease
Fluciclovine F 18	Axumin	5-27-2016	Diagnostic imaging agent for recurrent prostate cancer detection
Gallium Ga 68 dotatate	NETSPOT	6-1-2016	Diagnostic imaging agent for rare neuroendocrine tumors
Sofosbuvir and velpatasvir	Epclusa	6-28-2016	Treatment of all 6 major forms of hepatitis C virus
Lifitegrast	Xiidra	7-11-2016	Treat signs and symptoms of dry eye
Lixisenatide	Adlyxin	7-27-2016	Diabetes type 2
Eteplirsen	Exondys 51	9-19-2016	Duchenne muscular dystrophy
Olaratumab	Lartruvo	10-19-2016	Soft tissue sarcoma
Bezlotoxumab	Zinplava	10-21-2016	Reduce the recurrence of <i>Clostridium difficile</i> infection in adults
Crisaborole	Eucrisa	12-14-2016	Atopic dermatitis in patients two years of age or older

Generic Name	Brand Name	Approval Date	Indication
Rucaparib	Rubraca	12-19-2016	Ovarian cancer
Nusinersen	Spinraza	12-23-2016	Spinal muscular atrophy

Of the 22 NMEs, we will discuss 8 of the more significant ones. These include:

- Lixisenatide
- Elbasvir + grazoprevir
- Sofosbuvir 400 mg + velpatasvir 100 mg

The above 3 are covered in this lesson, "Part 1: New Drugs of 2016."

Five additional NMEs are presented in next month's lesson, "Part 2: New Drugs of 2016." These are:

- Eteplirsen
- Ixekizumab
- Lifitegrast
- Daclizumab
- Pimavanserin

Almost 75% of the NMEs approved in 2016 qualified for at least one of the FDA's designations to expedite the approval process (See Table 2)².

Table 2—FDA Programs to shorten the drug approval process²

Program Title	Description	Percent of drugs	Drugs approved under program
First in Class	Mechanism of action different from existing therapies	36% (8/22)	Defitelio, Exondys 51, Ocaliva, Spinraza, Venclexta, Xiidra, Zinbryta, Zinplava
Orphan Drugs	Drug for disease affecting less than 200,000 Americans	41% (9/22)	Anthim, Defitelio, Exondys 51, Lartruvo, Netspot, Ocaliva, Rubraca, Spinraza, Venclexta
Fast Track	Potential to address unmet medical need	36% (8/22)	Anthim, Defitelio, Epclusa, Exondys 51, Lartruvo, Ocaliva, Spinraza, Zinplava
Breakthrough	Drug may result in substantial improvement in at least one clinically significant endpoint over available drugs	32% (7/22)	Epclusa, Lartruvo, Nuplazid, Rubraca, Tecentriq, Venclexta, Zepatier
Priority	Potentially provide a significant advance in medical care. Drug is reviewed in 6 months versus standard 10 months.	68% (15/22)	Axumin, Defitelio, Epclusa, Exondys 51, Lartruvo, Netspot, Nuplazid, Ocaliva, Rubraca, Spinraza, Tecentriq, Venclexta, Xiidra, Zepatier, Zinplava
Accelerated	Early approval of drug for serious or life-threatening illness that offers benefit over current treatment	27% (6/22)	Exondys 51, Lartruvo, Ocaliva, Rubraca, Tecentriq, Venclexta

LIXISENATIDE (ADLYXIN)

Lixisenatide (Adlyxin) was approved on July 28, 2016. It is the fifth glucagon-like peptide-1 (GLP-1) receptor agonist approved. Other approved GLP-1 receptor agonists include exenatide (Byetta), liraglutide (Victoza), albiglutide (Tanzeum) and dulaglutide (Trulicity). Lixisenatide is available as 50 mcg/mL prefilled pens that contains 14 doses. It is also available in a 100 mcg/mL prefilled pen containing 14 doses.^{3,4}

Pharmacology/Pharmacokinetics

Lixisenatide is a GLP-1 receptor agonist. GLP-1 receptor agonists increase glucose-dependent insulin secretion from pancreatic beta cells, suppress glucagon secretion in a glucose-dependent manner, and slow gastric emptying. Lixisenatide is administered subcutaneously in the abdomen, arm or thigh. There is no difference in the rate of absorption between the various recommended administration sites. The volume of distribution after subcutaneous administration is approximately 100 L. Lixisenatide is thought to be eliminated through glomerular filtration, and proteolytic degradation. The elimination half-life is approximately 3 hours.^{4,5}

Indications

Lixisenatide is approved in combination with diet and exercise to treat type 2 diabetes mellitus. It is not approved for use in individuals under 18 years. It has not been studied with short-acting insulin and is not recommended for combination use.^{4,5}

Dosing

The starting dose of lixisenatide is 10 mcg subcutaneously once daily for 14 days. The dose can then be increased to 20 mcg daily if warranted. The dose should be given within one hour prior to the first meal of the day.⁴

Efficacy

Lixisenatide was compared to exenatide in a head to head study. The study determined that once daily lixisenatide was non-inferior to twice daily exenatide in HbA1c reduction. Approximately one-half of patients in each arm of the study achieved an HbA1c less than 7%. Both drugs were associated with some weight loss. Lixisenatide patients did report less hypoglycemic episodes and fewer gastrointestinal side effects than the exenatide group.⁶

Sanofi originally submitted a new drug application for lixisenatide in 2013, but the company pulled that application because the FDA was concerned about the cardiovascular safety of similar diabetes drugs. Sanofi completed a trial to address the FDA's concerns regarding the risk of cardiovascular side effects. The Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial was a multicenter, randomized, double-blind, placebo-controlled trial involving patients with type 2 diabetes who had recent acute coronary syndrome. The trial was designed to assess the effects of lixisenatide on cardiovascular morbidity and mortality.⁷

The ELIXA trial included diabetic patients who had either a myocardial infarction or were hospitalized for unstable angina in the previous 6 months. The study was designed to determine if lixisenatide was non-inferior (and superior) to placebo for cardiovascular death, myocardial infarction or stroke or hospitalization. A total of 6,068 patients completed the trial and the median follow-up was 25 months for both the treatment and placebo groups. Lixisenatide in combination with conventional therapy was not associated with a significant difference in cardiovascular outcomes when compared to conventional therapy mixed with placebo.⁷

Contraindications/Warnings

Lixisenatide is contraindicated in patients with a hypersensitivity to the drug or any component. GLP-1 receptor agonists, including lixisenatide, have been associated with pancreatitis. If pancreatitis occurs, lixisenatide should be discontinued and not restarted.^{4,5}

There is an increased risk of hypoglycemia in patients who take sulfonylureas or basal insulin in combination with lixisenatide. Patients should be closely monitored and a dose reduction of the sulfonylurea or basal insulin may be necessary.⁴

There is a risk of renal damage with the use of GLP-1 receptor agonists. When beginning treatment or increasing the dose of lixisenatide in patients with pre-existing renal impairment, renal function should be closely monitored. This drug should not be used in patients with end stage renal failure.⁴

Some patients may develop antibodies to lixisenatide during treatment. There is a higher risk of allergy and injection site reaction in patients who have developed antibodies to lixisenatide. Alternative therapy should be considered if the patient becomes antibody positive and has a poor response to lixisenatide.⁴

Drug Interactions

Lixisenatide delays gastric emptying and can reduce the absorption of some oral medications. Drugs such as antibiotics and acetaminophen should be closely monitored when combined with lixisenatide. Consider administering these drugs 1 hour before a lixisenatide dose. Oral contraceptives should be given 1 hour before or 11 hours after a dose of lixisenatide.⁴

When lixisenatide is combined with a sulfonylurea or basal insulin, there is a risk of hypoglycemia. As described earlier, a dose reduction of the sulfonylurea or basal insulin may be necessary.⁴

Adverse Effects

Hypoglycemia is a common side effect. Gastrointestinal effects were reported in 5% of patients taking lixisenatide and include nausea (25%), vomiting (10%), headache (9%), diarrhea (8%) and dizziness (7%). Injections site reactions (e.g., pain, pruritus and erythema) were reported in 4% of patients who received lixisenatide.^{4,5}

Pregnancy and Lactation

There is limited information available with lixisenatide in pregnant women; however, based on animal reproduction studies, there may be risks to the fetus from exposure to lixisenatide. There are also risks to both the mother and unborn child if diabetes is not well controlled during pregnancy. Lixisenatide should be used during pregnancy only if the potential benefit justifies the potential risk.⁴

It is not known if lixisenatide is excreted in human breast milk, but it has been reported in rats. The health benefits of breastfeeding should be considered along with the mother's clinical need for lixisenatide and any potential adverse effects on the breastfed infant from lixisenatide.⁴

Counseling the patient

Patients should be shown how to activate and use the pen before its first use. They should be reminded to use a new needle with each dose administered. Lixisenatide should be administered in the abdomen, thigh or arm once a day. Injections should be rotated with each dose. The patient will start with the 10 mcg/mL syringe (green) which is part of the starter pack. After 14 days, if the patient needs a higher dose, the dose can be increased to 20 mcg/mL which is the

burgundy syringe found in the starter kit. The dose of lixisenatide should be given within one hour before the first meal of the day. If a dose is missed, it should be given within one hour before the next meal.⁴ The pharmacist should demonstrate how the patient can monitor their blood sugar levels. Patients should be educated on how to respond to low blood sugar levels.

Role in therapy

Lixisenatide enters a very crowded market of GLP-1 agonists. One concern for this agent is that the ELIXA trial showed no significant effect on cardiovascular outcomes with lixisenatide. More recent trials including LEADER, have shown cardiovascular benefits with type 2 diabetes drugs, including another GLP-1 agonist, liraglutide (Victoza). Liraglutide has been established on the US market for some years and with the recent positive reports from the LEADER trial, providers may not see a strong role for lixisenatide. Lixisenatide may be an alternative for patients who experience hypoglycemic episodes or gastrointestinal side effects with other GLP-1 agonists.

HEPATITIS C DRUGS

There has been a paradigm shift in the treatment of chronic hepatitis C (HCV) since 2011.⁸ The introduction of direct-acting-antiviral agents (DAA) has changed the approach to treatment. These agents have dramatically increased the efficacy in treating HCV infection. As more DAAs were approved, there was even greater efficacy with less frequent dosing and fewer adverse effects. In 2014, combination products provided options for an all-oral therapy approach with exceptional efficacy rates (>90%). Additional research on combination products and shorter durations of treatment continue.

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have updated guidelines available at www.hcvguidelines.org for the management and treatment of HCV infection.⁹ Response to treatment is measured by sustained virologic response (SVR), which is the absence of detectable HCV RNA ≥ 12 weeks after the end of treatment. The newer DAA combinations have shown SVR rates near 100%, making virologic cure now a reality when treating chronic HCV. Pharmacists should consult this website regularly to stay up-to-date on changes in the guidelines.

The FDA approved two additional combination products for HCV treatment in 2016.¹ These agents are elbasvir/grazoprevir (Zepatier) and sofosbuvir/velpatasvir (Epclusa). The AASLD/IDSA guidelines have been updated to include these agents as first line therapy options where appropriate.⁹

ELBASVIR + GRAZOPREVR (ZEPATIER)

The FDA approved elbasvir and grazoprevir on January 28, 2016.¹⁰ This drug is approved for genotype 1 and 4. Genotype 1 accounts for over 70% of HCV cases in the United States. Although genotype 4 is not common in the U.S., it is the most prevalent strain in Africa and the Middle East.

Pharmacology/Pharmacokinetics

This medication combines two DAA agents with different mechanisms of action.¹¹ These agents work at different steps in the virus lifecycle to reduce resistance. Elbasvir is an inhibitor of HCV NS5A, while grazoprevir is an inhibitor of the HCV NS3/4A protease.

Following once daily dosing, this medication reaches steady state in approximately 6 days. Elbasvir and grazoprevir are extensively bound to plasma proteins (> 99.9% and 98.8%,

respectively). The volume of distribution of elbasvir and grazoprevir are approximately 680 L and 1250 L. The elimination half-life of elbasvir is 24 hours and 31 hours for grazoprevir. Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, primarily by CYP3A. The primary route of elimination of elbasvir and grazoprevir is through the feces (90%), with less than 1% excreted in urine.¹¹

Indications

Elbasvir + grazoprevir is indicated for the treatment of chronic HCV genotype 1 or 4 infection in adults. This drug can be used in combination with ribavirin in appropriate populations.^{5,11}

Dosing

Before initiating therapy with elbasvir and grazoprevir, patients should be tested for hepatitis B infection (HBV) and NS5A resistance of genotype 1a.¹¹ Cases of hepatitis B virus reactivation have been reported in some patients who receive direct acting antiviral agents for HCV. If patients test positive, they should be closely monitored for hepatitis flare or reactivation of HBV. The recommended dose of elbasvir and grazoprevir is one tablet once a day for 12 weeks. There is no dosage adjustment needed for elbasvir and grazoprevir for any degree of renal impairment.

Table 3–Dosing of elbasvir and grazoprevir¹¹

Patient Type	Recommended treatment duration
Genotype 1a or 1b: Treatment naïve or previous treatment with Peginterferon and ribavirin	12 weeks
Genotype 4: Treatment naïve	12 weeks
Genotype 1a and high level NS5A polymorphism	16 weeks in combination with ribavirin
Genotype 1a or 1b previously treated with peginterferon, ribavirin and protease inhibitor	12 weeks in combination with ribavirin
Genotype 4 previously treated with peginterferon and ribavirin	16 weeks in combination with ribavirin

Efficacy

Elbasvir + grazoprevir was approved by the FDA based on 5 clinical trials that included both treatment-naïve as well as treatment-experienced patients. In the C-EDGE study, 306 patients with genotype 1 or 4 were treated with elbasvir and grazoprevir for 12 weeks.¹² The SVR12 rates were 95% for the genotype 1 patients and 100% for the genotype 4 patients. No difference was seen in cirrhotic patients. In an open-label trial (C-SALVAGE) of 79 patients previously treated for HCV, the combination of elbasvir, grazoprevir and ribavirin resulted in a 96% SVR12.¹³

Elbasvir + grazoprevir was studied in patients with stage 4 and 5 kidney disease (C-SURFER), and of those 122 patients in the study, the SVR12 rate was 94%.¹⁴ Other clinical trials with elbasvir and grazoprevir showed similar SVR12 rates in the populations studied.

Contraindications

Elbasvir + grazoprevir is contraindicated in patients with moderate to severe hepatic impairment.¹¹

Warning

HBV reactivation

Elbasvir + grazoprevir has a black box warning for the risk of HBV reactivation in patients who have been treated with direct-acting antivirals for HCV. HBV reactivation results in a rapid increase in serum HBV DNA level. Patients may experience hepatitis symptoms (increased liver enzymes, liver failure or possibly death). All patients should be screened for HBsAg and anti-HBc before starting treatment with elbasvir and grazoprevir.¹¹

Elevated ALT levels

Approximately 1% of patients treated with this combination product developed elevations in ALT levels. The elevations were up to 5 times the upper limit of normal. Elevation of ALT levels occurred more commonly in women, the elderly and Asian patients. The medication should be stopped if patients develop symptoms such as fatigue, jaundice, lack of appetite, nausea or vomiting.¹¹

Drug Interactions

There are a number of potential drug interactions with elbasvir + grazoprevir.^{5,11} Table 4 below provides some common examples.

Table 4—Drug interactions with elbasvir and grazoprevir^{5,11}

CONTRAINDICATIONS		
Drug	Effect	Recommendation
Anticonvulsants (carbamazepine and phenytoin)	Reduced clinical effect of elbasvir and grazoprevir	Contraindicated
Rifampin	Reduced clinical effect of elbasvir and grazoprevir	Contraindicated
St John's Wort	Reduced clinical effect of elbasvir and grazoprevir	Contraindicated
Efavirenz	Reduced clinical effect of elbasvir and grazoprevir	Contraindicated
Atazanavir, darunavir, lopinavir, saquinavir, tipranavir	May increase risk for liver damage	Contraindicated
Cyclosporine	May increase risk for liver damage	Contraindicated
WARNINGS		
Nafcillin, ketoconazole	Reduced clinical effect of elbasvir and grazoprevir	Avoid combination
Rosuvastatin	Increased levels of rosuvastatin	Do not exceed 10 mg/day of rosuvastatin
Atorvastatin	Increased levels of atorvastatin	Do not exceed 20 mg/day of atorvastatin
Etravirine or elvitegravir, cobicistat, emtricitabine, tenofovir	Reduced clinical effect of elbasvir and grazoprevir	Avoid combination
Tacrolimus	Increased levels of tacrolimus	Monitor closely

Adverse Effects

The most common side effects reported with elbasvir + grazoprevir are nausea, fatigue and headache. Increases in ALT levels were reported in up to 1% of treated patients. This drug is

contraindicated in patients with severe liver damage.¹¹

Pregnancy and Lactation

Elbasvir + grazoprevir has not been studied in pregnant or lactating women. Animal studies do not indicate any potential dangers to fetal development. If elbasvir and grazoprevir are combined with ribavirin, the warnings and precautions for ribavirin, including the risks associated with pregnancy, apply. Ribavirin is contraindicated in pregnancy and in men whose partners may become pregnant due to its teratogenic and embryocidal effects.¹¹

Counseling the patient

The pharmacist should have a detailed counseling session with the patient when they begin therapy for HCV with elbasvir + grazoprevir. The pharmacist should discuss the importance of adherence to treatment and the risks of developing resistance. The pharmacist should probe for any potential barriers to adherence and address them. Since HBV reactivation has been reported, the pharmacist should ask the patient if they have a history of HBV infection. Since there are significant drug interactions with elbasvir + grazoprevir, the pharmacist should encourage the patient to contact the pharmacy before beginning any new prescription or non-prescription medications to screen for interactions.

Role in therapy

Elbasvir + grazoprevir is an extremely effective option for the treatment of HCV in patients with genotypes 1 or 4 disease. One advantage is that it can be used safely in patients with severe renal impairment. It may be a less costly option for many insurance providers. It is an appropriate agent for first line treatment in patients with HCV genotype 1 or 4.

SOFOSBUVIR 400 MG + VELPATASVIR 100 MG (EPCLUSA)

Sofosbuvir + velpatasvir is the first fixed-dose combination product that can be used in all HCV genotypes. It is a single daily tablet regimen. It is also the first single tablet regimen for Genotype 2 and 3 that does not require ribavirin. The recommended duration of treatment with sofosbuvir and velpatasvir is 12 weeks, regardless of genotype. This drug has the potential to eliminate the need for genotype testing, which can be a barrier to treatment in some areas with limited resources.¹⁵

Pharmacology/Pharmacokinetics

Sofosbuvir and velpatasvir are direct-acting antiviral agents. Sofosbuvir inhibits the HCV NS5B RNA-dependent RNA polymerase. It is a prodrug that is incorporated into HCV RNA and acts as a chain terminator. Velpatasvir inhibits HCV NS5A protein which is necessary for viral replication.¹⁶

The table below summarizes the pharmacokinetic profiles of both sofosbuvir and velpatasvir.

Table 5—Pharmacokinetic profiles of sofosbuvir and velpatasvir.¹⁶

	Sofosbuvir	Velpatasvir
Tmax (h)	0.5-1	3
T ½ (h)	25 (active metabolite)	15
% Plasma protein binding	61-65	>99.5
% of dose excreted in urine	80	0.4
% of dose excreted in feces	14	94

Indications

Sofosbuvir + velpatasvir is approved for the treatment of chronic hepatitis C virus genotypes 1,2,3,4,5, and 6 infections. In patients with decompensated cirrhosis, sofosbuvir and velpatasvir should be combined with ribavirin. All patients should be tested for current or prior hepatitis B (HBV) infection before starting treatment with sofosbuvir and velpatasvir.^{5,16}

Dosing

The recommended dose of sofosbuvir + velpatasvir is one tablet taken by mouth once a day for 12 weeks. The medication can be taken with or without food. Patients with decompensated cirrhosis should receive sofosbuvir and velpatasvir in combination with ribavirin for 12 weeks. Since the safety and efficacy of sofosbuvir and velpatasvir has not been established in patients with severe renal impairment, there are no dose recommendations for use in this group. There is no dose adjustment necessary for patients with hepatic impairment. If a provider needs to combine ribavirin, the starting dose of ribavirin is 1000 mg per day for patients less than 75 kg and 1200 mg for those weighing at least 75 kg, divided and administered twice daily.^{5,16}

Efficacy

Sofosbuvir + velpatasvir fixed dose combination was approved based on the results of 4 clinical trials.¹⁷⁻¹⁹ Table 6 below summarizes the clinical trials and their results. Sofosbuvir + velpatasvir fixed combination was effective in treating HCV in all six genotypes of the disease.

Table 6—Clinical trials with sofosbuvir and velpatasvir ¹⁷⁻¹⁹

Clinical trial	Description	Genotypes	Duration	SVR 12
Treatment naïve or experienced with or without compensated cirrhosis				
ASTRAL-1	Sofosbuvir and velpatasvir vs. placebo	1,2,4,5,6	12 weeks	99% vs. 0%
ASTRAL-2	Sofosbuvir and velpatasvir vs. sofosbuvir and ribavirin	2	12 weeks	99% vs 94%
ASTRAL-3	Sofosbuvir and velpatasvir vs. sofosbuvir and ribavirin	3	12 weeks 24 weeks	95% vs 80%
Treatment naïve or experienced with decompensated cirrhosis				
ASTRAL-4	Sofosbuvir and velpatasvir (12weeks) vs. Sofosbuvir and velpatasvir and ribavirin (12 weeks) vs. sofosbuvir and velpatasvir (24 weeks)	1,2,3,4,5,6	12 or 24 weeks	83% vs.94% vs. 86%

Contraindications

There are no specific contraindications for sofosbuvir and velpatasvir. However, when combined with ribavirin, it should not be used in patients with a contraindication to ribavirin.¹⁶

Warnings

HBV reactivation

Sofosbuvir + velpatasvir has a black box warning for the risk of HBV reactivation in patients that have been treated with direct-acting antivirals for HCV. HBV reactivation results in a rapid increase in serum HBV DNA level. Patients may experience hepatitis symptoms (increased liver enzymes, liver failure or possibly death). All patients should be screened for HBsAg and anti-HBc before starting treatment with sofosbuvir + velpatasvir.¹⁶

Serious bradycardia

Sofosbuvir and velpatasvir should not be used with amiodarone due to the risk for serious symptomatic bradycardia. Symptoms include fainting or near-fainting, lightheadedness, malaise, weakness, shortness of breath, chest pain and confusion. Bradycardia is usually observed within a few hours or days when amiodarone is used with HCV treatment but may occur up to two weeks after starting treatment. In patients taking amiodarone with no alternative therapy option, they should have in-patient cardiac monitoring for the first 48 hours of treatment. They should continue to monitor their heart rate for at least an additional 14 days.¹⁶

Drug Interactions

As with other DAAs, sofosbuvir and velpatasvir have been associated with drug-drug interactions. Pharmacists should review the patient's medications and provide counseling to the patient when dispensing HCV therapy.¹⁶ Table 7 lists the drug-drug interactions reported with sofosbuvir and velpatasvir.

Table 7—Drug interactions with sofosbuvir and velpatasvir¹⁶

Combination drug	Concentration change	Effect and recommendation
Antacid (Aluminum and magnesium hydroxide)	Reduced velpatasvir level	
H2 receptor antagonist	Reduced velpatasvir level	
Proton-pump inhibitors	Reduced velpatasvir level	
Amiodarone	Unknown	Serious symptomatic bradycardia. Combination with amiodarone is NOT recommended.
Digoxin	Increased digoxin levels	Monitor digoxin level and reduce dose if appropriate.
Topotecan	Increased topotecan levels	Do not combine
Anticonvulsants (carbamazepine, phenytoin, phenobarbital)	Decreased sofosbuvir levels Decreased velpatasvir levels	Do not combine
Rifampin	Decreased sofosbuvir levels Decreased velpatasvir levels	Do not combine
Efavirenz	Decreased velpatasvir levels	Do not combine
Tenofovir	Increased tenofovir levels	Monitor for tenofovir side effects, monitor renal function
Tipranavir/ritonavir	Decreased sofosbuvir levels Decreased velpatasvir levels	Do not combine
St John's Wort	Decreased sofosbuvir levels Decreased velpatasvir levels	Do not combine
HMG-CoA Reductase Inhibitors (rosuvastatin, atorvastatin)	Increased level of HMG-CoA Reductase Inhibitor	Do not give more than 10 mg rosuvastatin daily. Increased levels of rosuvastatin can increase risk of myopathy, including rhabdomyolysis. When combined with atorvastatin, monitor for myopathy and rhabdomyolysis

Adverse Effects

The most common adverse effects reported with sofosbuvir and velpatasvir are headache, fatigue, nausea, asthenia and insomnia. In most cases these were reported to be mild in

severity (Grade 1). Less common adverse effects included rash (2-5%) and depression (1%). In addition to these side effects, serious symptomatic bradycardia has been reported in patients taking amiodarone in combination with sofosbuvir and other DAAs. Although the mechanism for this interaction is not known, coadministration of amiodarone and sofosbuvir + velpatasvir is not recommended.^{5,16}

Pregnancy and Lactation

The combination of ribavirin with sofosbuvir and velpatasvir is contraindicated in pregnancy since ribavirin is associated with significant risk to the fetus. There is no data on the use of sofosbuvir + velpatasvir monotherapy in pregnant women. Animal studies of sofosbuvir + velpatasvir did not show any negative effects on the fetus at the doses that were tested.¹⁶

There is no specific data on the effects of sofosbuvir + velpatasvir during breastfeeding in humans. Data in lactating rats did not indicate any specific risks to offspring. However, the risks and benefits of breastfeeding must be considered by the patient and her physician.¹⁶

Counseling the patient

The pharmacist should have a detailed counseling session with the patient when they begin therapy for HCV with sofosbuvir + velpatasvir. The importance of adherence to treatment, and the risks of developing resistance, must be discussed. As adherence is discussed, the pharmacist should probe for any potential barriers to adherence and address them. Since HBV reactivation has been reported, the pharmacist should ask the patient if they have a history of HBV infection. Risks of HBV reactivation should be discussed. Since there are significant drug interactions with sofosbuvir and velpatasvir, the pharmacist should encourage the patient to contact the pharmacy before starting new prescription or non-prescription medications to screen for interactions. Patients or their partners who are taking combination sofosbuvir, velpatasvir and ribavirin should avoid pregnancy during treatment and for 6 months after completing therapy.¹⁶

Role in therapy

Sofosbuvir + velpatasvir is a first line combination therapy for all genotypes of HCV. This drug has the potential to eliminate the need for genotype testing, which can be a barrier to treatment in some areas with limited resources.

CONCLUSION

This concludes our discussion of lixisenatide, elbasvir + grazoprevin, and sofosbuvir + velpatasvir. In the next lesson, we will discuss 5 additional NMEs: eteplersen, ixekizumab, lifitegrast, daclizumab, and pimavanserin. 2016 was a much slower year for drug approvals than the previous ten years. There were 22 new drug approvals, the fewest since 2001. Sixteen of the 22 drugs were approved through one of the expedited categories of FDA approval. It is important for pharmacy practitioners to understand these new drugs and how these medications fit into the current standards 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 the new drugs approved by the FDA in 2016 YES NO

Discuss the role of these agents in therapy YES NO

Summarize the adverse effects & potential drug interactions with these agents YES NO

Recommend counseling points when dispensing these drugs YES NO

2. 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)

1. How many new drugs were approved in 2016?

- A. 22
- B. 29
- C. 33
- D. 43

2. Hepatitis C Genotype 1 accounts for _____% of HCV cases in the U.S.

- A. 40
- B. 50
- C. 70
- D. 90

3. The maximum daily dose of lixisenatide is:

- A. 2.5 mcg
- B. 10 mg
- C. 20 mcg
- D. 30 mcg

4. Studies show that once daily lixisenatide is:

- A. More effective than twice daily exenatide in reducing HbA1C.
- B. Equal to 'bid' exenatide in reducing HbA1C.
- C. Less effective than once daily exenatide in reducing HbA1C.
- D. Equal to once a day exenatide in reducing HbA1C.

5. A patient forgets to take their dose of lixisenatide. What do you suggest?

- A. Wait & take the dose next morning.
- B. Take next dose within 1 hour before the next mail.
- C. Take the next dose immediately.
- D. Skip the dose & resume normal scheduling tomorrow.

6. What percent of NMEs approved in 2016 qualified for at least one of the FDA's designations to expedite the approval process?

- A. 45%
- B. 50%
- C. 70%
- D. 75%

7. SVR is the absence of detected HCV RNA:

- A. ≥ 8 weeks after the end of treatment.
- B. ≥ 12 weeks after the end of treatment.
- C. ≥ 16 weeks after the end of treatment.
- D. ≥ 12 months after the end of treatment.

8. A patient has been diagnosed with HCV and has not received any previous therapy. The patient is going to take elbasvir and grazoprevir. What dose regimen would you suggest?

- A. One tablet daily for 16 weeks.
- B. One table daily for 12 weeks.
- C. One tablet daily for 8 weeks.
- D. One tablet daily for 6 weeks.

9. Which of these does NOT decrease velpatasvir level?

- A. H2 Blockers.
- B. Efavirenz
- C. Anticoagulants
- D. Digoxin.

10. Sofosbuvir + velpatasvir are approved for use in the following HCV genotypes;

- A. A, 1, 4
- B. 1, 4, 6
- C. 1, 2, 3, 4, 5, 6
- D. 1, 6