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New Drugs: Aptiom, Imbruvica, Luzu, and Sovaldi

Thomas A. Gossel, R.Ph., Ph.D., Professor Emeritus, Ohio Northern University, Ada, Ohio

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Goal. The goal of this lesson is to provide information on eslicarbazepine acetate (Aptiom®), ibrutinib (Imbruvica™), luliconazole (Luzu®) and sofosbuvir (Sovaldi™).

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

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

The four new-molecular entity drugs discussed in this lesson are indicated to treat a variety of pathologies (Table 1). This lesson provides a brief introduction to the drugs, and is not intended to extend beyond an overview of the topic. The reader is, therefore, urged to consult the products' full prescribing information leaflet (package insert), *Medication Guide* when available, and other published sources for detailed descriptions.

Eslicarbazepine Acetate (Aptiom)

Antiepileptic drugs (AED) are the major therapeutic intervention for epilepsy. A sizeable number of people with epilepsy experience pharmacoresistant seizures or encounter significant adverse effects with existing AED treatment. This poor response to seizure control means that combination therapy is recommended, but about 20 to 30 percent of patients continue to have seizures despite treatment with more than one AED. Therefore, there remains a need for new, effective AEDs, particularly those that can be used safely as adjuncts to standard therapy, to further reduce seizure frequency. Although structurally distinct from carbamazepine (e.g., Carbatrol, Tegretol) and oxcarbazepine (e.g., Trileptal, Oxtellar XR), eslicarbazepine acetate is chemically related to these carboxamide derivatives.

Indications and Use. Aptiom (ap-TEE-om) is indicated as adjunctive treatment of partial-onset seizures.

Partial-Onset Seizures. Epilepsy is caused by abnormal or excessive activity in the brain's nerve cells. Epilepsy is one of the most common neurological disorders and, according to the Centers for Disease Control and Prevention, affects nearly 2.2 million people in the United States, and up to 60 million people worldwide. Approximately 200,000 new cases of seizures and epilepsy occur in the United States each year. Partial-onset seizures are the most common type encountered in patients with epilepsy.

The International League Against Epilepsy classifies the disorder into three main types: partial (focal), generalized, and unclassified. Partial-onset epilepsy is restricted to discrete areas of the cerebral cortex while generalized epilepsy occurs in diffuse regions of the brain simultaneously. Because of the focused nature of a partial seizure, only a specific area of the body is usually involved. Treatment of partial-onset seizures is challenging since approximately 60 percent of patients with partial-onset seizures do not achieve seizure control with current AEDs.

Seizures can cause a wide range of symptoms, including repetitive limb movements, unusual behavior and generalized convulsions with loss of consciousness. Seizures can have serious consequences, including physical injury and death.

Mechanism of Action. Eslicarbazepine acetate is extensively converted to eslicarbazepine, which is considered to be responsible for therapeutic effects. The precise mechanism(s) by which eslicarbazepine exerts anticonvulsant activity is unknown, but is believed

Table 1
Selected new drugs

Generic (Proprietary) Name	Distributor	Indication	Dose*	Dosage Form*	Most Common Side Effects	Medication Guide[±]
Eslicarbazepine acetate (Aptiom)	Sunovion Pharmaceuticals Inc.	adjunctive treatment of partial-onset seizures	800 mg once daily	200, 400, 600, 800 mg tablets	(≥4%): dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, tremor	Yes
Ibrutinib (Imbruvica)	Pharmacyclics	mantle cell lymphoma chronic lymphocytic leukemia	560 mg once daily 420 mg once daily	140 mg capsules	(≥20%): thrombocytopenia, diarrhea, anemia, neutropenia, fatigue, vomiting, nausea, musculoskeletal pain, upper respiratory tract infection, bruising, dyspnea, constipation, abdominal pain, decreased appetite, peripheral edema, rash	No
Luliconazole (Luzu)	Medicis (division of Valeant Pharmaceuticals)	interdigital tinea pedis tinea cruris tinea corporis	once daily for 2 weeks once daily for 1 week	1% topical cream	(<1%): application site reactions	No
Sofosbuvir (Sovaldi)	Gilead Sciences	chronic hepatitis C infection	400 mg once daily	400 mg tablets	(>20%): fatigue, headache[§]; fatigue, headache, nausea, insomnia, anemia[#]	No

*Recommended dose for most patients
[§]Sovaldi in combination with ribavirin
[±]Availability at the time of publication of this lesson
[#]Sovaldi in combination with ribavirin and peginterferon alfa

to involve inhibition of voltage-gated sodium channels in rapidly firing neurons. This may make it more effective in persons who have failed other sodium channel blockers due to developing pharmacoresistance to them.

Efficacy and Safety. Three clinical studies in which participants with partial-onset seizures were randomly assigned to receive eslicarbazepine acetate or placebo demonstrated that the drug is effective in reducing the frequency of seizures.

The most common adverse effects reported by patients receiving the drug in these clinical trials included dizziness, drowsiness, nausea, headache, double-vision, vomiting, fatigue and loss of coordination. Like other antiepileptic drugs, Aptiom may cause suicidal thoughts or actions in a very small number of patients.

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

• *Suicidal behavior and ideation*: Monitor for suicidal thoughts or behavior.

• *Serious dermatologic reactions:* Monitor for dermatologic reactions and discontinue in case of serious dermatologic reactions.

• *Drug reaction with eosinophilia and systemic symptoms*: Monitor for hypersensitivity. Discontinue if another cause cannot be established.

• *Anaphylactic reactions and angioedema*: Monitor for breathing difficulties or swelling. Discontinue the drug if another cause cannot be established.

• *Hyponatremia (sodium <125 mEq/L)*: Monitor sodium levels in patients at risk or patients experiencing hyponatremia symptoms. Concurrent hypochloremia may also be present in patients with hyponatremia.

• *Neurological adverse reactions*: Monitor for dizziness, disturbance in gait and coordination, somnolence, fatigue, cognitive dysfunction, and visual changes. Use caution when driving or operating machinery.

• *Withdrawal of Aptiom*: As with all antiepileptic drugs, withdraw Aptiom gradually and avoid abrupt discontinuation to minimize the risk of increased seizure frequency and status epilepticus.

• *Drug-induced liver injury*: Discontinue Aptiom in patients with jaundice or evidence of significant liver injury.

• *Abnormal thyroid function tests*: Dose-dependent decreases in T3 and T4 have been observed. Evaluate for clinical signs and symptoms of hypothyroidism.

Hypersensitivity to eslicarbazepine acetate or oxcarbazepine is a **contraindication** to Aptiom.

Drug Interactions. Several considerations are listed:

- *Carbamazepine*: May need dose adjustment for Aptiom or carbamazepine.
- *Phenytoin*: Higher dosage of Aptiom may be necessary and dose adjustment may be needed for phenytoin based on clinical response and serum levels of phenytoin.
- *Phenobarbital or primidone*: Higher dosage of Aptiom may be necessary.
- *Hormonal contraceptives*: Aptiom may decrease the effectiveness of hormonal contraceptives. Females of reproductive potential should use additional or alternative non-hormonal birth control.

Administration, Dosing, and Availability. Start treatment at 400 mg once daily. After one week, increase dosage to 800 mg once daily, which is the recommended maintenance dose. Some patients may benefit from the maximum recommended maintenance dosage of 1200 mg once daily, although this dosage is associated with an increase in adverse reactions. A maximum dose of 1200 mg daily should only be initiated after the patient has tolerated 800 mg daily for at least a week. For some patients, treatment may be initiated at 800 mg once daily, if the need for additional seizure reduction outweighs an increased risk of adverse reactions during initiation. A dose reduction is recommended in patients with moderate and severe renal impairment (i.e., creatinine clearance <50 mL/min). Aptiom is marketed as tablets containing 200 mg, 400 mg, 600 mg, and 800 mg of eslicarbazepine acetate.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 2.

Ibrutinib (Imbruvica)

Ibrutinib is the third drug approved to treat mantle cell lymphoma (MCL), following bortezomib (Velcade, 2006) and lenalidomide (Revlimid, 2013). FDA approved the drug under the agency's accelerated approval program. This permits FDA to approve a drug to treat a serious disease based on clinical trials showing that the drug has an effect on a surrogate endpoint, that is reasonably likely to predict a clinical benefit to patients. FDA granted orphan-product designation because it is intended to treat a rare disease.

Indications and Use. Imbruvica (im-BRU-vih-kuh) is indicated for treatment of patients with MCL who have received at least one prior therapy. This indication is based on overall response rate.

Imbruvica's indication was expanded in February of 2014 to include chronic lymphocytic leukemia (CLL). The dose for CLL is included in Table 1, but this indication will not be discussed further in this lesson.

Mantle Cell Lymphoma. MCL is a rare, aggressive form of non-Hodgkin lymphoma and represents about 6 percent of all non-Hodgkin lymphoma cases in the United States. Many secondary genetic events contribute to tumor growth in MCL, including the loss of DNA damage-response capacity, activation of cell-survival pathways, and inhibition of apoptosis (natural or programmed cell death). Prognosis in MCL is the worst among all B cell lymphomas. Historically, MCL has been treated like most other forms of B cell non-Hodgkin lymphoma, with regimens such as a combination of cyclophosphamide (e.g., Cytoxan), vincristine (e.g., Oncovin), doxorubicin (e.g., Adriamycin), and prednisone. However, early retrospective studies in the United States and Europe showed that MCL patients treated with such regimens had an overall survival of less than three years.

In the United States, 2,900 new cases of MCL are diagnosed each year with a median age at diagnosis of 65. By the time the cancer is diagnosed, it usually has already spread to the lymph nodes, bone marrow, gastrointestinal tract, spleen, and other organs.

Mechanism of Action. Ibrutinib is a small-molecule inhibitor of a cytoplasmic specific protein called Bruton's tyrosine kinase (BTK) expressed in B cells and myeloid cells. The drug forms a covalent bond with a cysteine residue in the BTK active site, leading to inhibition of BTK enzymatic activity. BTK is a signaling molecule of the B-cell antigen receptor and cytokine receptor pathways. BTK's role in signaling through the B-cell sur-

Table 2
Patient counseling information for Aptiom*

Inform patients:
- to read the FDA-approved *Medication Guide* prior to taking Aptiom and to re-read it each time the prescription is refilled, and to take the drug exactly as prescribed;
- that Aptiom may cause serious side effects including suicidal thoughts or behavior; potentially serious skin reactions including a rash, swelling of the face, eyes, lips, tongue, or difficulty in swallowing; liver disease; and neurological reactions including dizziness or vision problems, and to report any change from normal to their doctor at once;
- that the drug may lower their blood level of sodium and to report symptoms such as nausea, tiredness or lack of energy, irritability, confusion, muscle weakness/spasms, or more frequent or severe seizures to their doctor;
- that the drug may slow thinking or motor skills, so they should not drive or operate heavy machinery until they know how it affects them;
- to not stop taking their medicine without consulting their doctor;
- that female patients of childbearing age should use additional or alternative non-hormonal forms of contraception during treatment with Aptiom and for at least one month after treatment with Aptiom has been discontinued;
- to tell their doctor about all medicines they are taking. They should ask their pharmacist if they are not sure;
- to avoid giving Aptiom to other people even if they have similar symptoms. It may harm them.

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

Table 3
Patient counseling information for Imbruvica*

Inform patients:
- to read the FDA-approved Patient Information leaflet;
- of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Tell them that Imbruvica may need to be interrupted for medical or dental procedures;
- of the possibility of serious infection, and to report any signs or symptoms (fever, chills) suggestive of infection;
- of the possibility of renal toxicity and advise them to maintain adequate hydration;
- that other malignancies have occurred in patients with MCL who have been treated with Imbruvica, including skin cancers and other carcinomas;
- of the potential hazard to a fetus and to avoid becoming pregnant;
- to take Imbruvica orally once daily according to their doctor's instructions and that the capsules should be swallowed whole, without being opened, broken, or chewed, with a glass of water at approximately the same time each day;
- that in the event of a missed daily dose of Imbruvica, it should be taken as soon as possible on the same day with a return to the normal schedule the following day, and that they should not take extra capsules to make up the missed dose;
- of the common side effects associated with Imbruvica;
- to inform their doctor of all medicines including prescription drugs and OTC products, vitamins, minerals, and herbal products they are taking;
- that they may experience loose stools or diarrhea, and to contact their doctor if diarrhea persists.

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

face receptors results in activation of pathways necessary for B-cell trafficking, chemotaxis, and adhesion. Ibrutinib inhibits malignant B-cell proliferation and survival.

Efficacy and Safety. Imbruvica's approval for MCL was based on a study with 111 participants who had received at least one therapy, and were given Imbruvica daily until their disease progressed or adverse effects became intolerable. Results revealed that nearly 66 percent of participants experienced tumor shrinkage or disappearance after treatment. An improvement in survival or disease-related symptoms has not been established.

The most common adverse effects reported for MCL were thrombocytopenia (low levels of platelets in the blood), diarrhea, neutropenia (decrease in infection-fighting white blood cells), anemia, fatigue, musculoskeletal pain, edema, upper respiratory infection, nausea, bruising, shortness of breath, constipation, rash, abdominal pain, vomiting, and decreased appetite. Other clinically significant adverse effects include bleeding, infections, kidney problems, and development of other types of cancers. The adverse reaction most frequently leading to treatment discontinuation with Imbruvica was subdural hematoma.

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

- *Hemorrhage*: Monitor for bleeding. The mechanism for bleeding events is not well understood.
- *Infections*: Monitor patients for fever and infections and evaluate promptly.
- *Myelosuppression*: Check complete blood counts monthly.
- *Serious and fatal renal toxicity*: Monitor renal function and maintain hydration.
- *Second primary malignancies*: Other malignancies have occurred in patients, including skin cancers, and other carcinomas.
- *Embryo-fetal toxicity*: Ibrutinib can cause fetal harm. Advise women of the potential risk to a fetus and to avoid pregnancy while taking the drug.

There are no **contraindications** listed.

Drug Interactions. Imbrutinib is primarily metabolized by cytochrome P450 enzyme 3A. Avoid co-administration with strong or moderate CYP3A inhibitors and consider alternative agents with less CYP3A inhibition. Concomitant use of strong CYP3A inhibitors taken chronically (e.g., ritonavir, indinavir, nelfinavir, saquinavir, boceprevir, telaprevir, nefazodone) is not recommended. For short-term use (seven days or less) of strong CYP3A inhibitors (e.g., antifungals and antibiotics), consider interrupting Imbruvica therapy until the CYP3A inhibitor is no longer needed.

Reduce Imbruvica dose to 140 mg if a moderate CYP3A inhibitor (e.g., fluconazole, darunavir, erythromycin, diltiazem, atazanavir, aprepitant, amprenavir, fosamprevir, crizotinib, imatinib, verapamil, grapefruit products, and ciprofloxacin) must be used.

Administration, Dosing, and Availability. Administer Imbruvica orally once daily, at approximately the same time each day. Swallow the capsules whole with water; do not open, break, or chew the capsules. The recommended dose for MCL is 560 mg orally once daily. If a dose of Imbruvica is not taken at the scheduled time, it can be taken as soon as possible on the same day, with a return to the normal schedule the following day. Extra capsules of the dose should not be taken to make up for the missed dose. The product is available as capsules containing 140 mg of ibrutinib.

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

Luliconazole (Luzu)

Luzu (LOO-zoo) cream is the first topical azole antifungal approved to treat tinea cruris (jock itch) and tinea corporis (ringworm) with a one-week, once-daily treatment regimen. All other currently approved treatments require two weeks of treatment. For interdigital tinea pedis (athlete's foot between the toes), the treatment is once daily for two weeks. Luliconazole provides good efficacy and tolerability with a short duration of

treatment. The drug has been approved in Japan since 2005.

Indications and Use. Luzu cream is an azole antifungal indicated for the topical treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by the organisms *Trichophyton rubrum* and *Epidermophyton floccosum*, in patients 18 years of age and older.

Tinea Infections. Superficial mycoses (fungal) infections are not fatal, but they can seriously interfere with a patient's quality of life in view of the considerable discomfort such as itching and interference with sleep, and/or cosmetic deformity. These diseases are found worldwide and affect 20 to 25 percent of the world's population. Dermatophytosis (tinea infection) is the most common infection among the superficial mycoses. According to an epidemiological survey of ambulatory visits in the United States, the incidences of dermatophytosis were as high as 23.2 percent, 20.4 percent, and 18.8 percent respectively, during 1995 to 2004. *T. rubrum*, an anthropophilic (preferring humans to other animals) fungus, is the most prevalent causative agent of dermatophytosis in developed countries. Its incidence has not changed in recent decades, although many antifungal drugs with potent action against this species have become available during this period.

Mechanism of Action. Although the exact mechanism of action against dermatophytosis is unknown, luliconazole appears to inhibit fungal ergosterol synthesis by inhibiting the enzyme lanosterol demethylase. Inhibition of this enzyme's activity by azole antifungals results in decreased amounts of ergosterol, a constituent of fungal cell membranes, and a corresponding accumulation of lanosterol.

Efficacy and Safety. Approval was based on three pivotal U.S. trials that included 679 adults with either tinea pedis (two trials) or tinea cruris (one trial). For the two studies in tinea pedis with a treatment duration of two weeks, the primary endpoint was defined as complete clearance four weeks post-treatment. In study #1, 26 percent of participants treated with luliconazole were completely cleared, compared with 2 percent of those treated with vehicle alone. In study #2, 14 percent of participants treated with luliconazole were completely cleared, compared with 2 percent of those treated with vehicle alone. In the tinea cruris trial, complete clearance was assessed three weeks post-treatment. After one week of treatment, 21 percent of patients treated with luliconazole were completely cleared, compared with only 4 percent of those treated with vehicle alone.

The most common adverse events were mild application site reactions reported in less than 1 percent of subjects for both luliconazole and vehicle.

Warnings, Precautions and Contraindications. There are no **warnings**, **precautions** or **contraindications** listed.

Drug Interactions. The potential of luliconazole to inhibit cytochrome P450 enzymes (1A2, 2C9, 2C19, 2D6, and 3A4) was evaluated. When applied in therapeutic doses to patients with moderate to severe tinea cruris, luliconazole may inhibit the activity of CYP2C19 and CYP3A4. However, no *in vivo* trials have been conducted to assess the effect of luliconazole on other drugs that are substrates of CYP2C19 and CYP3A4. The drug is not expected to inhibit cytochromes 1A2, 2C9, or 2D6. The induction potential of luliconazole has not been evaluated.

Administration, Dosing, and Availability. When treating interdigital tinea pedis, a thin layer of Luzu cream should be applied to the affected skin areas and to about one inch of the surrounding healthy skin, once daily for two weeks. When treating tinea cruris or tinea corporis, Luzu cream should be applied in the same manner as tinea pedis above, once daily for one week. Luzu cream contains 1 percent luliconazole.

Patient Counseling Information. Specific points for patient counseling are summarized in Table 4.

Table 4
Patient counseling information for Luzu*

Inform patients:
- to read the FDA-approved Patient Information leaflet;
- that this medicine is for use on the skin only, and it should not be used on or near the eyes, mouth, or vagina;
- to tell the doctor if they are pregnant or plan to become pregnant, and about all medicines including prescription drugs and OTC products, vitamins, minerals, and herbal supplements they are taking;
- about possible side effects including skin irritation;
- to use the medicine exactly as the doctor instructs, and to wash their hands after applying Luzu cream.

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

Sofosbuvir (Sovaldi)

Sovaldi (soh-VAHL-dee) is the second drug approved by FDA during the last part of 2013 to treat chronic hepatitis C virus (HCV) infection. The other drug was simeprevir (Olysio).

Indications and Use. The drug is to be used as a component of a combination antiviral treatment regimen for chronic HCV infection. There are several different types of HCV infection. Depending on the type of HCV infection a person has, the treatment regimen could include Sovaldi and ribavirin (Copegus, Rebetol, & others) or Sovaldi, ribavirin, and peginterferon alfa (PEG-intron, Pegasys). Both ribavirin and peginterferon alfa are also used to treat HCV infection. If these other agents used in combination with Sovaldi are permanently discontinued, Sovaldi should also be discontinued. Sovaldi efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma who are awaiting liver transplantation and those with HCV/HIV-1 co-infection.

Table 5
Patient counseling information for Sovaldi*

Inform patients:
- to read the FDA-approved Patient Information leaflet;
- that Sovaldi is used in combination with other antiviral medicines, and they should read the *Medication Guides* supplied with those other drugs. The drug should not be used alone;
- that Sovaldi may cause birth defects or death in an unborn baby, so the drug should not be used during pregnancy or if a female plans to become pregnant. Females and males must use two effective forms of birth control during treatment, and for six months after treatment with Sovaldi;
- to tell their doctor if they have liver problems or a liver transplant, kidney problems or if on dialysis, have HIV or any other medical conditions, or are breastfeeding or plan to breastfeed;
- to tell the doctor about all medicines including prescription drugs and OTC products, vitamins, minerals, and herbal supplements they are taking;
- to take Sovaldi exactly as the doctor prescribes, and to not stop taking it or change doses without telling their doctor;
- to tell the doctor about any side effect that is bothersome or does not go away;
- to keep Sovaldi in its original container and to not use if the seal over the bottle opening is broken or missing.

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

Before initiating treatment with Sovaldi, the following points should be considered: (1) monotherapy of Sovaldi is not recommended for treatment of chronic HCV; (2) treatment regimen and duration are dependent on both the viral genotype and patient population; and, (3) treatment response varies based on baseline host and viral factors.

Hepatitis C. As many as 170 million persons are chronically infected with HCV worldwide, with more than 350,000 dying annually from liver disease caused by HCV. Estimates of the number of persons in the United States who are chronically infected range from 2.7 million to 5.2 million. For previously untreated cases of HCV genotype 1 infection, representing more than 70 percent of all cases of chronic HCV infection in the United States, the current standard of care is 12 to 32 weeks of an oral protease inhibitor, combined with 24 to 48 weeks of peginterferon alfa plus ribavirin, with the duration of therapy guided by the on-treatment response and the stage of hepatic fibrosis. For patients infected with HCV genotype 2 or 3, until Sovaldi was approved, no direct-acting antiviral drugs had been available.

The virus causes inflammation of the liver that can lead to diminished liver function or failure. Most people infected with HCV are without symptoms of the disease until hepatic damage becomes apparent, which may take several years. Some people with chronic HCV infection develop scarring and poor liver function (cirrhosis) over many years, which can lead to complications such as bleeding, jaundice (yellowish eyes or skin), fluid accumulation in the abdomen, infections, or liver cancer.

Mechanism of Action. Sovaldi is a direct-acting antiviral agent against HCV. It is an inhibitor of HCV NS5B RNA-dependent RNA polymerase, which is essential for viral replication. Sofosbuvir is a nucleotide prodrug that undergoes intracellular metabolism to form the pharmacologically active uridine analog triphosphate, which can be incorporated into HCV RNA by the NS5B polymerase and acts as a chain terminator.

Efficacy and Safety. Effectiveness was evaluated in six clinical trials that consisted of 1,947 participants who had not previously received treatment for their disease (treatment-naïve) or had not responded to previous treatment (treatment-experienced), including participants co-infected with HCV and HIV. The trials were designed to measure whether HCV was no longer detected in the blood at least 12 weeks after finishing treatment (sustained treatment virologic response), suggesting a participant's HCV infection had been cured. Results from all clinical trials showed that a treatment regimen containing Sovaldi was effective in treating multiple types of HCV. Additionally, Sovaldi demonstrated efficacy in participants who could not tolerate or take an interferon-based treatment regimen, and in participants with liver cancer awaiting liver transplantation, addressing unmet medical needs in these populations.

The most common adverse effects reported in clinical study participants treated with Sovaldi and ribavirin were fatigue and headache. In participants treated with Sovaldi, ribavirin, and peginterferon alfa, the most common adverse affects reported were fatigue, headache, nausea, insomnia, and anemia.

Warnings, Precautions and Contraindications. The following **warning/precaution** is listed:

- *Pregnancy*: Ribavirin may cause birth defects and fetal death, and animal studies have shown interferons have abortifacient effects; avoid pregnancy in female patients and female partners of male patients. Patients must have a negative pregnancy test prior to initiating therapy, use at least two effective non-hormonal methods of contraception, and have monthly pregnancy tests.

The following **contraindications** are listed:

- When used in combination with peginterferon alfa/ribavirin or ribavirin alone, all contraindications to peginterferon alfa and/or ribavirin also apply to Sovaldi combination therapy.
- Because ribavirin may cause birth defects and fetal death, Sovaldi in combination with peginterferon alfa/ribavirin or ribavirin is contraindicated in pregnant women, and in men whose female partners are pregnant.

Drug Interactions. Drugs that are potent intestinal P-

glycoprotein (P-gp) inducers (e.g., rifampin, St. John's Wort) may significantly reduce plasma concentrations of sofosbuvir and, thus, lead to a reduced therapeutic effect. Rifampin and St. John's Wort should not be used with Sovaldi. An extensive list of other drugs that may lead to potentially significant drug interactions with Sovaldi is included in the product's prescribing information. Consult the full prescribing information prior to use for potential drug-drug interactions.

Administration, Dosing, and Availability. The recommended dose of Sovaldi is one 400 mg tablet, taken orally, once daily with or without food for 12 to 24 weeks. Dose reduction with Sovaldi is not recommended. Sovaldi should be used in combination with ribavirin or with a combination of ribavirin and pegylated interferon. Used in combination with ribavirin, Sovaldi is recommended for up to 48 weeks or until the time of liver transplantation, whichever comes first, to prevent post-transplant HCV reinfection. The product is available as tablets containing 400 mg sofosbuvir. It should be dispensed in its original container.

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

Overview and Summary

The four new drugs are indicated to treat a wide variety of pathologies. In each case, the drugs have been shown to be effective and safe when used as directed. Each offers advantages over earlier treatments used to manage the respective disease states.

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The author, the Ohio Pharmacists Foundation and the Ohio Pharmacists Association disclaim any liability to you or your patients resulting from reliance solely upon the information contained herein. Bibliography for additional reading and inquiry is available upon request.

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

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continuing education quiz

New Drugs: Aptiom, Imbruvica, Luzu and Sovaldi

1. What percentage of people with epilepsy continues to have seizures despite treatment with more than one antiepileptic drug?
   a. 5-10 c. 20-30
   b. 10-20 d. 30-40

2. All of the following statements about Aptiom are true EXCEPT:
   a. its precise mechanism of action is unknown.
   b. it may cause suicidal thoughts and behavior.
   c. sodium levels should be monitored.
   d. taken with phenobarbital, a lower dose of Aptiom may be necessary.

3. The maximum daily recommended maintenance dose of Aptiom is:
   a. 200 mg. c. 1200 mg.
   b. 600 mg. d. 1500 mg.

4. All of the following are true statements about mantle cell lymphoma EXCEPT:
   a. it is a rare, aggressive form of non-Hodgkin lymphoma.
   b. it represents about 2 percent of all non-Hodgkin lymphoma.
   c. about 2,900 new cases are diagnosed in the U.S. each year.
   d. by the time it is diagnosed, it has usually spread to the lymph nodes.

5. Imbruvica is indicated for treatment of patients with mantle cell lymphoma who:
   a. are resistant to ribavirin and peginterferon alfa.
   b. have received at least one prior therapy.
   c. are free of serious systemic fungal infections.
   d. are six years of age and older.

6. The adverse reaction most frequently leading to treatment discontinuation with Imbruvica was:
   a. diarrhea. c. anemia.
   b. subdural hematoma. d. bruising.

7. All of the following are true statements about tinea infections EXCEPT:
   a. they are found worldwide.
   b. they may interfere with sleep.
   c. their incidence has increased since 2005.
   d. they are anthropophilic infections.

Completely fill in the lettered box corresponding to your answer.

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

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1. Rate this lesson: (Excellent) 5 4 3 2 1 (Poor)
2. Did it meet each of its objectives? ❑ yes ❑ no
   If no, list any unmet_____
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6. Comments/future topics welcome.

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8. Which of the following is appropriate patient advice for Luzu cream?
   a. Apply a thin layer to affected skin areas and to about one inch of the surrounding healthy skin.
   b. Squeeze one inch of cream onto the affected area only.
   c. Avoid exposure to sunlight, incandescent lights and excessive heat.
   d. Avoid concomitant use of cosmetic skin lightener ointments and creams.

9. All of the following statements are appropriate in counseling patients on Sovaldi EXCEPT:
   a. do not drive or operate heavy machinery while taking Sovaldi.
   b. take with or without food.
   c. store Sovaldi in its original container.
   d. it should not be used during pregnancy.

10. Which of the following drugs inhibits Bruton's tyrosine kinase?
   a. Aptiom c. Luzu
   b. Imbruvica d. Sovaldi

11. Which of the following drugs was approved to be used in combination with ribavirin or ribavirin and peginterferon alfa?
   a. Aptiom c. Luzu
   b. Imbruvica d. Sovaldi

12. Which of the following drugs was approved with orphan-product designation?
   a. Aptiom c. Luzu
   b. Imbruvica d. Sovaldi

13. Seventy percent of chronic hepatitis C virus infections in the U.S. are caused by which of the following HCV genotypes?
   a. 1 c. 3
   b. 2 d. 4

14. All of the following drugs are taken orally EXCEPT:
   a. Aptiom. c. Luzu.
   b. Imbruvica. d. Sovaldi.

15. The label of which of the following drugs lists no warnings, precautions or contraindications?
   a. Aptiom c. Luzu
   b. Imbruvica d. Sovaldi

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