New Drugs: Breo Ellipta, Invokana, Osphena, and Tecfidera

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Dr. Thomas A. Gossel has no relevant financial relationships to disclose.

Goal. The goal of this lesson is to provide information on canagliflozin (Invokana™), dimethyl fumarate (Tecfidera™), fluticasone furoate & vilanterol (Breo™ Ellipta™) and ospemifene (Osphena™).

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. identify the new drugs by generic name, trade name and chemical name when relevant;
3. select the indication(s), pharmacologic action(s), clinical applications and route of administration for each drug;
4. recognize important therapeutic uses for the drugs and their applications in specified pathologies;
5. demonstrate an understanding of adverse effects and toxicity, warnings, precautions, contraindications, and significant drug-drug interactions for these drugs; and
6. list important patient information to convey to patients and/or their caregivers.

The lesson provides a brief introduction to the new 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 reference sources for detailed descriptions.

Canagliflozin (Invokana) Due to the progressive nature of Type 2 diabetes mellitus (T2DM), therapy with oral agents is associated with a high failure rate over ensuing years. Moreover, current therapies for T2DM are often limited by their significant adverse effects. The traditional focus of therapeutic strategies has been on developing drugs that improve insulin sensitivity, enhance endogenous insulin secretion, or both. Research efforts in recent years have pursued development of therapies with a new, alternative mechanism of action: the enhancement of glucose excretion through the kidneys. These efforts over the past two decades have led to introduction of a novel class of agents, the sodium-glucose co-transporter 2 (SGLT2) inhibitors, which appear to offer an alternative mechanism of action. Canagliflozin is the first in this new class of diabetes drugs that represents a promising new treatment pathway.

Indications and Use. Invokana (in-vo-KAHN-uh) is indicated as adjunct therapy to diet and exercise to improve glycemic control in adults with T2DM. The drug should not be used in patients with Type 1 diabetes mellitus, diabetic ketoacidosis, renal impairment, end stage renal disease, or in patients on dialysis.

Type 2 Diabetes Mellitus. T2DM has become endemic throughout the world, and is projected to be the seventh leading cause of death by 2030. The World Health Organization estimates that diabetes affects more than 347 million people, approximately 80 percent of whom live in low- and middle-income countries. About 24 million people in the United States are affected. T2DM accounts for approximately 90 percent of diabetes cases diagnosed in this country and around the world. T2DM is linked with multisystem complications and comorbidities, including nephropathy and peripheral neuropathy; glaucoma, cataracts, and retinopathy; bacterial infections, fungal infections, and other dermatologic pathologies; cardiovascular disease, myocardial infarction, cerebrovascular disease, and stroke; digestive problems; sexual dysfunction; periodontal disease; and depression.

The kidneys play an important role in glucose homeostasis through glomerular filtration and reabsorption in the proximal convoluted tubule. Approximately 180 g of glucose is filtered daily in a normal healthy adult. The kidneys reabsorb most of this with less than
1 percent of the glucose excreted into the urine. The normal tubular glucose load is approximately 120 
mg/min. Glucosuria occurs when the tubular glucose load exceeds 220 mg/min. This corresponds to 
a plasma glucose concentration of approximately 200 mg/dL. The plasma glucose concentration is an 
important modulator of SGLT2 expression within the kidney and its activity. The fundamental concept 
underlying current research on SGLT2 inhibitors is that by blocking the action of SGLT2, increased 
urinary glucose excretion and reduced plasma glucose levels can be achieved. A potential benefit of this 
action is the caloric loss of approximately 200 to 300 kcal/day, which may contribute to weight loss.

**Mechanism of Action.**
SGLT2, expressed within the proximal renal tubules, is the primary means for reabsorption of filtered 
glucose from the tubular lumen. Canagliflozin inhibits SGLT2.

Thus, it reduces reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby 
increasing urinary glucose excretion, which leads to glucosuria.

**Safety.** Drug safety was assessed based on four 26-week, placebo-controlled trials involving 1,667 patients. The most common adverse reactions associated with canagliflozin (incidence ≥5 percent) included female genital mycotic (fungal) infections (e.g., vulvovaginal candidiasis, vulvovaginal candidiasis), urinary tract infection, and increased urination.

As with all antihyperglycemic agents, the potential for hypoglycemia associated with canagliflozin use is of major concern. The overall frequency of hypoglycemia in clinical trials of the new drug has been low, with the majority of cases defined as non-severe. The highest risk of hypoglycemia appears to be with concurrent use of insulin.

FDA is requiring the following postmarketing studies for Invokana: a cardiovascular outcomes trial; an enhanced pharmacovigilance program to monitor for malignancies, serious cases of pancreatitis, severe hypersensitivity reactions, photosensitivity reactions, liver abnormalities, and adverse pregnancy outcomes; a bone safety study; and two pediatric studies, including a pharmacokinetic and pharmacodynamic study and a safety and efficacy study.

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

- **Hypotension:** assess the volume status and correct hypovolemia in patients with renal impairment or low systolic blood pressure, in the elderly, and in patients on diuretics, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers. Monitor for signs and symptoms during therapy.

- **Impaired renal function:** monitor renal function during therapy.

- **Hyperkalemia:** monitor potassium levels in patients with impaired renal function and those predisposed to hyperkalemia.

- **Hypoglycemia:** consider a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycemia.
**Hypersensitivity reactions:** discontinue Invokana and monitor the patient.

**Increased LDL-Cholesterol:** monitor LDL-C and treat per standard of care.

**Contraindications** include a history of serious hypersensitivity reactions to Invokana, severe renal impairment, end-stage renal disease, or patients on dialysis.

**Drug Interactions.** Co-administration of canagliflozin with rifampin, a non-selective inducer of several UGT (phase 2 transferase) enzymes, including UGT1A9 and UGT2B4, may decrease the area under the curve (AUC) of canagliflozin by 51 percent. This decrease may reduce drug efficacy. Studies show there was an increase in the AUC and peak drug concentration (Cmax) of digoxin (20 percent and 36 percent, respectively) when co-administered with Invokana 300 mg. Patients taking Invokana and digoxin concomitantly should be monitored appropriately.

**Administration and Dosing.** The usual starting dose is 100 mg once daily, taken before the first meal of the day. This dose can be increased to 300 mg once daily in patients who tolerate 100 mg once daily, and who have an estimated glomerular filtration rate (eGFR) of 60 mL/min/1.73 m² or greater and require additional glycemic control. Invokana dosage should be limited to 100 mg once daily in patients whose eGFR is 45 to less than 60 mL/min/1.73 m². The drug should not be taken if the eGFR is below 45 mL/min/1.73 m², and should be discontinued if the eGFR falls below 45 mL/min/1.73 m². Assessment of renal function is recommended before starting Invokana therapy. In patients with volume depletion, correcting the condition before initiating therapy with Invokana is recommended. Invokana is available in 100 and 300 mg tablets.

**Patient Counseling Information.** An FDA-approved Medication Guide must be dispensed with each prescription for Invokana and patients urged to read it carefully. Specific points for counseling are summarized in Table 2.

### Table 2
**Patient counseling information for Invokana**

<table>
<thead>
<tr>
<th>Information</th>
<th>Details</th>
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<tbody>
<tr>
<td><strong>Dimethyl Fumarate (Tecfidera)</strong></td>
<td>Available therapies to treat multiple sclerosis (MS), although effective in modifying disease progression, are not without limitations. First-line treatment requires parenteral administration. Long-term efficacy of interferon beta therapy may be reduced by formation of neutralizing antibodies which decrease the bioavailability of interferon beta. New oral drugs, especially those that benefit clinical outcomes in patients with MS while reducing side effects, are of importance. Dimethyl fumarate is such a therapy. To date, no drug provides a cure, so it is important to have a variety of treatment options available for patients.</td>
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<tr>
<td><strong>Indication.</strong> Tecfidera (tekf-DI-rah) is indicated to treat relapsing forms of MS.</td>
<td><strong>Multiple Sclerosis.</strong> MS is a chronic, potentially disabling, inflammatory, and neurodegenerative disease of the central nervous system that disrupts communication between the brain and other parts of the body. The process is believed to start after autoreactive T cells cross the blood brain barrier. A cascade of events ensues with injury to the myelin membrane resulting in demyelinated axons that are unable to transmit action potentials efficiently. This slowed or blocked nerve conduction results in a variety of MS symptoms. MS affects approximately 400,000 persons in the United States, and each week an additional 200-plus persons in this country are diagnosed with MS. Women are two to three times more likely to be affected than men. The disease most often presents initially in the third to fourth decades of life, and is second only to trauma as the most common cause of neurologic disability in young adults. Life expectancy is reduced by five to 10 years, usually resulting in death at a median of 30 years from disease onset. While the incidence does not seem great when compared to other disease states, patients with MS experience decreased quality of life. MS is an incurable disease with a progressive course that may be controlled by strict adherence to disease modifying drugs. For most persons with MS, episodes of worsening function (relapses) are initially followed by recovery periods (remissions). Over time, recovery periods may be incomplete, leading to progressive decline in function and increased</td>
</tr>
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*Summarized from the Medication Guide*
disability. MS patients often experience muscle weakness, and difficulty with coordination and balance. 

Mechanism of Action. The mechanism by which dimethyl fumarate exerts its action in MS is unknown. It is believed to have anti-inflammatory properties and to improve cellular response to oxidative stress, with both implied in the pathophysiology of MS. Dimethyl fumarate and its primary metabolite, monomethyl fumarate (MMF), have been shown to increase expression of anti-inflammatory cytokines, while inhibiting expression of proinflammatory cytokines. Dimethyl fumarate has also been implicated in modulating cellular response to oxidative stress via the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo. By its activation, antioxidant protein expression is enhanced leading to neuronal cell protection, as well as immune system and blood-brain-barrier homeostasis.

Safety. In two clinical trials extending over a period of two years, the most common adverse reactions (incidence ≥10 percent and ≥2 percent placebo) were flushing, abdominal pain, diarrhea, and nausea. Gastrointestinal complaints should decrease after the first month of therapy.

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

• Lymphopenia: A recent complete blood count (CBC) should be available before initiating treatment with Tecfidera. A CBC is recommended annually, and as clinically indicated. Consider withdrawing treatment in patients with serious infections.

• Flushing (e.g., warmth, redness, itching, burning sensation): Flushing symptoms generally begin soon after initiating the drug and usually improve or resolve over time. In the majority of patients who experienced flushing, it was mild or moderate in severity. There are no contraindications listed.

Drug Interactions. No potential drug interactions with dimethyl fumarate or MMF were identified in in vitro cytochrome P450 (CYP) inhibition and induction studies, or in P-glycoprotein studies. Single doses of interferon β-1a or glatiramer acetate, or as close to 240 mg twice a day. Tecfidera should be swallowed whole. It should not be crushed or chewed, and the capsule contents should not be sprinkled on food. The drug can be taken with or without food. Administration with food may reduce the incidence of flushing.

Tecfidera is available as hard gelatin delayed-release capsules containing 120 mg or 240 mg dimethyl fumarate. The capsules should be stored at 59°F to 86°F in their original container, protected from light. Once a bottle is opened, unused drug should be discarded after 90 days.

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

Fluticasone Furoate and Vilanterol (Breo Ellipta) Chronic obstructive pulmonary disease (COPD) is a significant cause of morbidity and mortality that makes breathing difficult and contributes substantially to health care costs worldwide. It is the third leading cause of death in the United States and its prevalence is increasing. Therefore, there is a need for therapies that can reduce disease-associated morbidity and mortality. Combining the inhaled corticosteroid fluticasone furoate (that has a duration of action up to 24 hours) with vilanterol (a long-acting β₂-adrenergic agonist [LABA] that provides 24-hour bronchodilation in patients with COPD) provides an additional treatment option for the millions of Americans who suffer from COPD.

Indications and Use. Breo Ellipta (BREE-oh-ee-LIP-ta) is indicated for long-term, once-daily, maintenance treatment of airflow obstruction and for reducing exacerbations in patients with COPD, including chronic bronchitis and/or emphysema. The product should not be used for relief of acute bronchospasm or for treatment of asthma, and should not be used as rescue therapy to treat sudden breathing problems (e.g., acute bronchospasm). It is not recommended for persons younger than 18 years of age.

COPD. COPD, which includes emphysema and chronic bronchitis, is a serious lung disease that worsens over time. In fact, COPD is one of a few chronic diseases that has shown an increase in mortality in recent years. Symptoms can
include chest tightness, chronic cough, and excessive phlegm. According to the National Heart, Lung, and Blood Institute, cigarette smoking is the leading cause of COPD. Approximately 12 million adults in the U.S. have a confirmed diagnosis of COPD, and it is estimated that another 12 million are undiagnosed.

Pathological changes in COPD are noted in the large (central) airways, the small (peripheral) bronchioles and the lung parenchyma (functional, versus supporting, tissue). The pathogenic mechanisms are most likely diverse. The large number of activated polymorphonuclear leukocytes and macrophages release elastases, enzymes that destroy lung tissue. The main offender is leukocytic elastase. A possible synergistic role has been proposed for protease 3 and macrophage-derived matrix proteinases, cysteine proteinases and plasminogen activation. Moreover, increased oxidative stress caused by free radicals (e.g., from cigarette smoking), the oxidants released by phagocytes, and polymorphonuclear leukocytes all may lead to apoptosis (natural, or programmed cell death) or necrosis of exposed cells. While COPD affects the lungs primarily, it also produces significant systemic pathology. The disease is also associated with significant inflammation, with the cascade of inflammatory events leading to tissue damage.

**Mechanism of Action.** Fluticasone furoate is a synthetic trifluorinated corticosteroid with anti-inflammatory activity. The precise mechanism by which fluticasone furoate treats COPD symptoms is not known.

Vilanterol is a long-acting $\beta_2$-adrenergic agonist similar in action to salmeterol. $\beta_2$-adrenergic receptors are the predominant adrenergic receptors in bronchial smooth muscle; $\beta_1$-adrenergic receptors are predominant in the heart. However, there are also $\beta_2$-adrenergic receptors in the heart which comprise 10 to 50 percent of the total $\beta$-adrenergic receptors. This raises the possibility that even highly selective $\beta_2$-agonists may have cardiac effects.

Clinical trials with vilanterol show that this LABA has a significantly faster onset of action than salmeterol, and a longer duration of action than either salmeterol or formoterol. Moreover, vilanterol has significantly greater selectivity for the $\beta_2$-adrenergic receptors than either salmeterol or formoterol. Single doses of vilanterol produce a rapid (within five minutes) increase in FEV$_1$, an effect that is maintained over 24 hours.

The pharmacologic effects of $\beta_2$-adrenergic agonist drugs are at least in part due to stimulation of intracellular adeny1 cyclase, the enzyme that catalyzes conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cyclic AMP). Increased cyclic AMP levels relax bronchial smooth muscle and inhibit release of mediators of immediate hypersensitivity response from cells, especially from mast cells.

**Safety.** The most common adverse reactions (incidence $\geq 3$ percent) identified in six-month and 12-month pre-marketing clinical trials were nasopharyngitis, upper respiratory tract infection, headache, and oral candidiasis. Breo Ellipta may cause serious side effects, including increased risk of pneumonia and bone fractures.

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

- **LABA toxicity:** LABAs increase the risk of asthma-related death. Avoid use in combination with additional products containing a LABA because of the risk of overdose. A boxed warning advises that it is not indicated for treatment of asthma.
- **Acutely deteriorating COPD:** do not initiate use in acutely deteriorating COPD or to treat acute symptoms, i.e., as rescue therapy.
- **Candida albicans infection of the mouth and pharynx:** monitor patients periodically.
- **Increased risk of pneumonia:** monitor patient for signs and symptoms of pneumonia.
- **Potential worsening of infections:** use with caution in patients with infections such as existing tuberculosis; fungal, bacterial, viral, or parasitic infection; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles can occur in susceptible patients.
- **Hypercorticism and adrenal suppression:** if such situations occur, slowly discontinue drug use, consistent with accepted procedures for reducing systemic corticosteroids.
- **Paradoxical bronchospasm:** discontinue use and institute alternative therapy, such as an inhaled, short-acting bronchodilator.
- **Cardiovascular disorders:** use with caution because of $\beta$-adrenergic stimulation.
- **Decreased bone mineral density:** assess patient initially and periodically thereafter.
- **Glaucoma and cataracts:** closely monitor patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.
- **Convulsive disorders, thyrotoxicosis, diabetes mellitus, and ketoacidosis:** use the drug with caution in these patients.
- **Hypokalemia and hyperglycemia:** be alert to these conditions.
- The only contraindication to Breo Ellipta is severe hypersensitivity to milk proteins or any product ingredient.

**Drug Interactions.** Strong CYP inhibitors (e.g., ketoconazole, ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole) may cause systemic corticosteroid and cardiovascular effects. Use with caution. Monoamine oxidase inhibitors and tricyclic antidepressants may potentiate the effect of vilanterol on the vascular system. Use with extreme caution.

$\beta$-adrenergic blockers may block bronchodilatory effects of $\beta$-adrenergic agonists and produce
severe bronchospasm. Use with caution.

Diuretics should be used with caution. Electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with concomitant β-agonists.

Administration and Dosing. Breo Ellipta should be inhaled orally, once daily. After inhalation, the patient should rinse his/her mouth with water, without swallowing, to help reduce the risk of oropharyngeal candidiasis. The product should be administered at the same time every day, and not used more often than once every 24 hours.

Breo Ellipta is available as an inhalation powder. The product consists of a disposable plastic inhaler containing two double-foil blister strips, each with 30 blisters containing powder for oral inhalation only. One strip contains fluticasone furoate (100 µg per blister) and the other strip contains vilanterol (25 µg per blister). Under standardized in vitro test conditions, Breo Ellipta delivered 92 µg fluticasone furoate and 22 µg of vilanterol per blister when tested at a flow rate of 60 L/min for four seconds. After the inhaler is activated by opening the lid, the powder within both blisters is exposed and ready for dispersion into the airstream created by the patient inhaling through the mouthpiece. An institutional pack containing 14 blisters per strip is also available.

Breo Ellipta should be stored in a dry place away from direct heat or sunlight, at room temperature between 68°F and 77°F; exceptions are permitted from 59°F to 86°F. Breo Ellipta should be stored inside the unopened moisture-protective foil tray and only removed from the tray immediately before use. Unused product should be discarded six weeks after opening the foil tray or when the counter reads “0” (after all blisters have been used), whichever comes first. The inhaler is not reusable, and should not be taken apart.

Patient Counseling Information. An FDA-approved Medication Guide must be dispensed with Breo Ellipta and patients urged to read it carefully. Specific points for counseling are summarized in Table 4.

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<thead>
<tr>
<th><strong>Table 4</strong></th>
<th>Patient counseling information for Breo Ellipta*</th>
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<tr>
<td>Inform patients:</td>
<td>*to read the Medication Guide before starting Breo Ellipta and to reread it each time the prescription is filled; *this product is not meant to relieve acute symptoms of COPD. Acute symptoms should be treated with a rescue inhaler such as albuterol; *the product should not be used for treatment of asthma; *to avoid use of other inhaled medicines that contain a long-acting β₂-adrenergic agonist; *to contact their doctor if symptoms get worse or if they need more inhalations from their rescue inhaler; *to not stop using Breo Ellipta without their doctor’s guidance; *to rinse their mouth with water without swallowing after inhaler use; *that certain side effects can be serious; they should contact their doctor if they develop symptoms of pneumonia, or worsening of symptoms or other serious infections, or feel chest pain or rapid heart beats; *that regular eye examinations for cataracts and glaucoma are recommended; *that opening and closing the cover without inhaling will cause a dose to be lost. The lost dose will be held securely inside the inhaler, but will no longer be able to be inhaled. It is not possible to accidentally take an extra dose in one inhalation.</td>
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**Osphena (Ospemifene)**

Following menopause, up to half of postmenopausal women experience symptoms of vaginal atrophy. Historically, these symptoms have been treated with lubricants and systemic or intravaginal estrogens. Although topically applied lubricants can provide temporary relief, they do not treat the underlying condition. Given the controversies surrounding estrogen, there is motivation to explore alternative therapies. Selective estrogen receptor modulators (SERMs) represent a class of drugs with an ever-growing number of compounds that act as estrogen receptor agonists/antagonists in a tissue-specific manner. SERMs are chemically diverse compounds that lack the steroid structure of estrogens, but possess a tertiary structure that allows them to bind to the estrogen receptors. Ospemifene, a SERM, may represent the first safe and effective treatment for vulvovaginal atrophy.

**Indications and Use.** Ospemifene (os-FEE-nah) is indicated for treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Dyspareunia is defined as painful intercourse, or persistent genital pain that occurs just before, during, or after intercourse.

**Dyspareunia.** The vagina is a highly estrogen-responsive organ, which changes dramatically during menopause. Following menopause, women may experience vaginal dryness and/or dyspareunia, which are caused primarily by regression of the vaginal epithelium. Loss of estrogen can make vaginal tissues thinner, drier, and more fragile, resulting in pain during intercourse or with tampon insertion.

**Mechanism of Action.** Ospemifene is an estrogen agonist/antagonist with tissue selective effects. Its biological actions are mediated through binding to estrogen receptors, which results in activation of estrogenic pathways in some tissues (agonism) and blockade of estrogenic pathways in others (antagonism). Ospemifene acts like estrogen on vaginal tissues to make them thicker and less fragile, resulting in reduced pain.

**Safety.** Adverse reactions (incidence ≥1 percent) reported in three placebo-controlled clinical trials of 1,889 postmenopausal women with symptoms of vulvar and vaginal atrophy included hot flush, vaginal discharge, muscle spasms, genital discharge, and hyperhidrosis.
Warnings, Precautions and Contraindications. The following warnings and precautions are listed:

- **Venous thromboembolism**: risk of deep vein thrombosis and pulmonary embolism.
- **Known, suspected or history of breast cancer**: the drug has not been studied in women with breast cancer; thus, it should not be used in those with known or suspected breast cancer or with a history of breast cancer.
- **Severe hepatic impairment**: Ospemifene should not be used in women with severe hepatic impairment.
- **A boxed warning advises about the potential for endometrial cancer and cardiovascular events**. The boxed warning provides the incidence rates of thrombotic and hemorrhagic strokes (0.72 and 1.45 per thousand women, respectively), and the incidence rate of deep vein thrombosis (1.45 per thousand women). These rates are considered to represent low risks in contrast to the increased risks of stroke and deep vein thrombosis seen with estrogen-only therapy. Ospemifene should be prescribed for the shortest duration consistent with treatment goals and risks for the specific patient.

The following contraindications are listed: undiagnosed abnormal genital bleeding; known or suspected estrogen-dependent neoplasia; active deep vein thrombosis, pulmonary embolism, or a history of these conditions; active arterial thromboembolic disease (e.g., stroke and myocardial infarction) or a history of these conditions. It is also contraindicated in known or suspected pregnancy.

Drug Interactions. Ospemifene is primarily metabolized by CYP3A4 and CYP2C9. CYP2C19 and other pathways also contribute to the metabolism of ospemifene. Estrogens and estrogen agonist/antagonist drugs should not be used concomitantly with ospemifene. Safety of concomitantly used drugs has not been studied.

Fluconazole is a moderate CYP3A, strong CYP2C9, and moderate CYP2C19 inhibitor and should not be used with ospemifene. Fluconazole increases the systemic exposure of ospemifene by 2.7-fold. Rifampin, a strong CYP3A4, moderate CYP2C9, and moderate CYP2C19 inducer, decreases systemic exposure of ospemifene by 58 percent, and should not be used with ospemifene. Ketoconazole, a strong CYP3A4 inhibitor increases the systemic exposure of ospemifene by 1.4-fold.

Ospemifene is more than 99 percent bound to serum proteins and may interfere with protein binding of other highly protein-bound drugs.

Administration and Dosing. Generally, when a product with estrogen agonistic effects on the endometrium is prescribed for a post-menopausal woman with a uterus, a progestin should be considered to reduce the risk of endometrial cancer. A woman without a uterus does not need a progestin.

Ospemifene should be used for the shortest duration consistent with treatment goals and risks for the individual patient. Postmenopausal women should be re-evaluated periodically as clinically appropriate to determine if treatment is still necessary.

The dose is 60 mg orally once daily with food. Osphena tablets contain 60 mg of ospemifene.

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

Overview and Summary. These newly approved drugs represent different pharmacologic classes and intended uses. As with all new drugs, they offer additional treatment options to improve patient quality of life.

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**Table 5**

**Patient counseling information for Osphena**

*Summarized from the Prescribing Information leaflet

Inform patients:
- to tell their doctor if they are taking prescription or over-the-counter medications, vitamins, or herbal supplements;
- that taking Osphena has been associated with increased risk of uterine cancer. Tell their doctor right away if they have unusual vaginal bleeding while taking Osphena;
- to tell their doctor if they are pregnant, plan to become pregnant, or are breastfeeding;
- to not start taking Osphena if they currently have or have had cancer, blood clots, or stroke;
- to tell their doctor if they have unusual vaginal bleeding, any other medical condition, are going to have surgery, or will be on bed rest;
- to take Osphena exactly as directed by their doctor and pharmacist;
- to have a pelvic exam, breast exam, and mammogram every year, unless directed otherwise by their doctor;
- that if members of their family had breast cancer or if they have ever had breast lumps or an abnormal mammogram, they may need to have breast exams more often;
- if they have high blood pressure, high cholesterol, diabetes, are overweight, or use tobacco, they may have a higher risk of heart disease;
- to not take Osphena for conditions for which it was not prescribed, to not give Osphena to other persons, even if they have the same symptoms.

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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: Breo Ellipta, Invokana, Osphena, and Tecfidera

1. A drug classified as an SGLT2 inhibitor would most likely be used to treat:
   a. type 2 diabetes mellitus.
   b. multiple sclerosis.
   c. chronic obstructive pulmonary disease.
   d. vulvar and vaginal atrophy.

2. The normal tubular plasma glucose load is about:
   a. 60 mg/min.
   b. 120 mg/min.
   c. 180 mg/min.
   d. 220 mg/min.

3. Invokana dosage should be limited to which of the following when the patient’s eGFR is 45 to <60 mL/min/1.73 m²?
   a. 50 mg
   b. 100 mg
   c. 200 mg
   d. 300 mg

4. MS most often presents initially in which of the following decades of life?
   a. First to second
   b. Second to third
   c. Third to fourth
   d. Fourth to fifth

5. All of the following are true about dimethyl fumarate EXCEPT:
   a. it has anti-inflammatory properties.
   b. it inhibits expression of proinflammatory cytokines.
   c. it inhibits antioxidant protein expression.
   d. its mechanism of action in MS is unknown.

6. All of the following is advice to give patients when beginning therapy with Breo Ellipta EXCEPT:
   a. get regular eye examinations.
   b. rinse the mouth with water after use.
   c. do not use the product to treat asthma.
   d. use to treat sudden acute symptoms (e.g., bronchospasms).

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]

☐ I am enclosing $10 (member); $15 (nonmember) for this month’s quiz made payable to: Ohio Pharmacists Association.

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 ________________________________
3. Was the content balanced and without commercial bias?
   ☐ yes ☐ no
4. Did the program meet your educational/practice needs?
   ☐ yes ☐ no
5. How long did it take you to read this lesson and complete the quiz? ________________
6. Comments/future topics welcome.

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