New Drugs 2015 PART 1

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THIS ARTICLE reviews seven drugs recently approved by the FDA, including:

- a new combination product to treat menopause-associated symptoms such as hot flashes.
- a new treatment for erectile dysfunction.
- two antiepileptic drugs indicated to help prevent partial-onset seizures.

Unless otherwise specified, the information in the following summaries applies to adults, not children. Consult a pharmacist or the package insert for information on drug safety during pregnancy and breastfeeding. Consult a pharmacist, the package insert, or a current and comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions* for all these drugs.

SELECTED REFERENCES

Drug Facts and Comparisons. St. Louis, MO: Facts and Comparisons, Inc.; 2015.

Nursing2015 Drug Handbook. Philadelphia, PA: Lippincott Williams & Wilkins; 2015.

Physician's Desk Reference. 69th ed. Montvale, NJ: Medical Economics; 2015.

*Common adverse reactions are italicized throughout this article.

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ANTIDIABETIC DRUG

Dapagliflozin propanediol

Second in a new class of medications

Dapagliflozin propanediol (*Farxiga*, Bristol-Myers Squibb; AstraZeneca) is the second drug in a new class of orally administered antidiabetic drugs designated as sodium-glucose cotransporter 2 (SGLT2) inhibitors, joining canagliflozin (Invokana). Expressed in the proximal renal tubules, SGLT2 is responsible for the reabsorption of most of the glucose filtered by the kidneys. By inhibiting SGLT2, canagliflozin and dapagliflozin reduce the reabsorption of filtered glucose, increase urinary glucose excretion, and reduce blood glucose and glycosylated hemoglobin (A1c) concentrations.

Like canagliflozin, dapagliflozin is specifically indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.[1] Its effectiveness has been demonstrated in studies in which it was used as monotherapy or in combination regimens with metformin, glipizide, glimepiride, pioglitazone, sitagliptin, or insulin.

In clinical trials, dapagliflozin reduced A1c and fasting plasma glucose (FPG) concentrations—and, in many patients, body weight. Patients treated with regimens that included dapagliflozin typically lost an average of 1 to 3 kg of body weight over 24 weeks; in contrast, most of those treated with other antidiabetic agents either lost less weight or experienced weight gain. The use of dapagliflozin in combination with other antidiabetic agents resulted in greater reductions in A1c and FPG concentrations.

Although dapagliflozin doesn't cause hypoglycemia, it can increase the risk of hypoglycemia when used in combination with insulin or an insulin secretagogue such as a sulfonylurea. A lower dosage of the latter agent may be indicated when such a combination regimen is prescribed.

Dapagliflozin increases serum creatinine concentrations and decreases estimated glomerular filtration rate (eGFR). Older adults and patients with impaired renal function are more susceptible to associated risks.

Because of a possible link between dapagliflozin and bladder cancer, dapagliflozin shouldn't be used in patients with active bladder cancer and used with caution in patients with a history of bladder cancer. The FDA has included an assessment of bladder cancer risk among the postmarketing studies required for dapagliflozin.

Precautions: (1) Not recommended in patients with type 1 diabetes mellitus or for the treatment of patients with diabetic ketoacidosis. (2) Contraindicated in patients with a history of a serious hypersensitivity reaction to dapagliflozin. (3) Contraindicated in patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or end-stage renal disease, or in patients on dialysis. Renal function should be evaluated before treatment starts and periodically thereafter. Treatment shouldn't be initiated in patients with an eGFR less than 60 mL/min/1.73 m^2. If the eGFR is persistently less than this value during treatment, the drug should be discontinued. (4) In clinical trials of dapagliflozin, patients with moderate renal impairment didn't experience improvement in glycemic control and had more renal-related adverse reactions, so dapagliflozin shouldn't be used in these patients. No dosage adjustment is needed for patients with mild renal impairment. (5) Because dapagliflozin causes intravascular volume contraction, patients may experience symptomatic hypotension. Volume status should be assessed and corrected if necessary in older adults, patients with impaired renal function or low systolic blood pressure, and patients treated with a diuretic.

Adverse reactions: female genital mycotic infections such as *vulvovaginal candidiasis, nasopharyngitis*, urinary tract infection, increased urination, back pain, nausea, dyslipidemia, male genital mycotic infections such as balanitis

Supplied as: 5 mg and 10 mg film-coated oral tablets

Dosage: 5 mg/day in the morning; may be increased to 10 mg/day if indicated

Nursing considerations: (1) Tell patients the drug may be administered without regard to food. (2) Monitor patients for hypotension, hypo- or hyperglycemia, and fluid volume deficit. (3) Monitor renal function studies.

REFERENCE

1. Prescribing information. Farxiga (dapagliflozin) tablets, for oral use. http://www.farxiga.com.

ANTI-INFLAMMATORY DRUG

Apremilast

Relief from the pain of psoriatic arthritis

Of the approximately 7.5 million Americans who experience psoriasis, up to 30% also develop psoriatic arthritis, which is most often characterized by joint pain, stiffness, and swelling.[1] A nonsteroidal anti-inflammatory drug is often used as the initial treatment for mild forms of psoriatic arthritis. Medications used to treat moderate-to-severe disease include the disease-modifying antirheumatic drugs (DMARDs) such as methotrexate; corticosteroids; tumor necrosis factor (TNF) blockers such as adalimumab, certolizumab, etanercept, golimumab, and infliximab; and the

interleukin-12/interleukin-23 inhibitor ustekinumab.

Apremilast (*Otezla*, Celgene) is a phosphodiesterase-4 (PDE4) inhibitor indicated for adult patients with active psoriatic arthritis and those with moderate-to-severe plaque psoriasis who are candidates for phototherapy or systemic therapy.[2] Because it's effective following oral administration, it has an advantage over parenteral TNF blockers and ustekinumab, which is also administered parenterally.

PDE4 mediates the conversion of cyclic adenosine monophosphate (cAMP) to AMP that can contribute to inflammation. By inhibiting PDE4, apremilast increases intracellular cAMP concentrations, reducing the inflammatory response.

The effectiveness of apremilast was evaluated in three placebo-controlled studies in patients with active psoriatic arthritis despite prior or current DMARD therapy. Some patients had been previously treated with a biologic, including TNF blockers. The primary endpoint was the percentage of patients achieving an American College of Rheumatology (ACR) 20 response (representing at least a 20% improvement from baseline in most measures of disease activity) at week 16. Measures of disease activity included the number of tender joints, number of swollen joints, patient's assessment of pain, and patient's global assessment of disease activity. Patients whose tender and swollen joint counts hadn't improved by at least 20% by week 16 were considered nonresponders.

In the three studies, the percentages of patients treated with apremilast who achieved an ACR 20 response were 38%, 32%, and 41%, compared with 19%, 19%, and 18% in patients receiving placebo. Patients treated with the new drug experienced improvement in each of the seven components of the ACR evaluation. The percentages of patients achieving an ACR 50 response (at least a 50% improvement from baseline) or an ACR 70 response (at least a 70% improvement from baseline) at 16 weeks were 16%, 11%, and 15%, compared with 4%, 1%, and 4% in patients receiving placebo, but these results weren't statistically significant.

Although apremilast hasn't been directly compared with other medications in clinical studies, results of studies of the individual agents suggest that the new drug is less effective than the TNF blockers and ustekinumab in improving the ACR responses.

Apremilast should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus. A pregnancy registry has been established (1-877-311-8972) to monitor outcomes in women exposed to the drug during pregnancy.

Precautions: (1) Use cautiously in patients with a history of depression or suicidal ideation. In trials, 1% of patients reported depression or depressed mood, and suicidal ideation or behavior was observed in 0.2%. (2) Dosages should be reduced in patients with severe renal impairment. (3) The concurrent use of apremilast with strong cytochrome P450 enzyme inducers such as rifampin, carbamazepine, phenobarbital, and phenytoin may reduce apremilast's efficacy and isn't recommended.

Adverse reactions: *nausea, diarrhea*, headache

Supplied as: 10 mg, 20 mg, and 30 mg film-coated oral tablets

Dosage: titrate over the first 5 days of treatment to the recommended maintenance dosage of 30 mg twice a day. Dosage titration is recommended to reduce gastrointestinal symptoms associated with initial therapy. Consult the product labeling for details, including recommended dosage adjustments for patients with severe renal impairment (creatinine clearance less than 30 mL per minute).

Nursing considerations: (1) Apremilast can be taken without regard to food. (2) If the drug is prescribed for a patient at risk for depression or suicidal ideation, teach patients, family members, and/or caregivers to be alert for new or worsening signs and symptoms. (3) Teach patients to monitor their weight. In trials, 10% of patients treated with apremilast lost between 5% and 10% of body weight, compared with 3% of those receiving placebo. If excessive weight loss occurs, consideration should be given to discontinuing treatment. (4) Apremilast is provided in a 2-week starter pack that includes tablets in three potencies for the dosage titration period, plus additional 30 mg tablets. For maintenance use, a package is available that contains two blister cards that each contain 14 of the 30 mg tablets.

REFERENCES

1. National Psoriasis Foundation. http://www.psoriasis.org.

2. Prescribing information. Otezla (apremilast) tablets, for oral use. http://www.otezla.com.

DRUG FOR ERECTILE DYSFUNCTION

Avanafil

Faster onset of action than others in its class

The fourth phosphodiesterase type 5 (PDE5) inhibitor to be approved for erectile dysfunction, avanafil (*Stendra*, Auxilium; Vivus) joins sildenafil, tadalafil, and vardenafil. The physiologic mechanism of erection of the penis involves release of nitric oxide (NO) in the corpus cavernosum during sexual stimulation. NO then activates the enzyme guanylate cyclase that results in increased concentrations of cyclic guanosine monophosphate (cGMP), producing smooth muscle relaxation in the corpus cavernosum and allowing increased blood flow into the penis and erection. Because PDE5 degrades cGMP in the corpus cavernosum, inhibiting PDE5 enhances the effect of NO.

Sexual stimulation is required to initiate the local release of NO, so inhibiting PDE5 has no effect in the absence of sexual stimulation.[1]

Each of the PDE5 inhibitors has been demonstrated to be significantly more effective than placebo in the treatment of erectile dysfunction in clinical trials. Men who benefit from these agents include those with diseases or clinical situations associated with a higher frequency of erectile dysfunction, such as diabetes and radical prostatectomy. The PDE5 inhibitors haven't been directly compared with each other, but they appear to be similar in efficacy. Preferences for one or another of these agents may be based on onset of action or duration of action. For example, tadalafil has a longer duration of action and more dosage/treatment options that may be an advantage in permitting greater spontaneity in facilitating intercourse. However, it has a slower onset of action than the other agents.

Avanafil appears to have a faster onset of action than the other drugs in its class. Most patients can take it about 15 minutes before sexual activity. In contrast, sildenafil and vardenafil are usually taken approximately 60 minutes before sexual activity.

The risks and adverse reactions associated with avanafil are generally similar to those for sildenafil, tadalafil, and vardenafil.

Precautions: (1) Not recommended for use in men for whom sexual activity is inadvisable because of their underlying cardiovascular status. (2) Contraindicated in patients with a known hypersensitivity to any component of the tablet formulation. (3) As with the other PDE5 inhibitors, the use of avanafil with any form of an organic nitrate, such as nitroglycerin, either regularly or intermittently, is contraindicated because it may potentiate the hypotensive effects of nitrates. If a nitrate is necessary in a life-threatening situation, at least 12 hours should elapse after a dose of avanafil before nitrate administration is considered. If a nitrate is used in these circumstances, it should be administered under close medical supervision with appropriate hemodynamic monitoring. (4) The PDE5 inhibitors cause vasodilation and can also increase the BP-lowering effect of alpha-adrenergic blocking agents such as tamsulosin and antihypertensive drugs. In patients who are stabilized on alpha-blocker therapy, the use of a PDE5 inhibitor should be initiated at the lowest dose (50 mg of avanafil). In patients already using a PDE5 inhibitor, treatment with an alpha-blocker should be initiated at the lowest dose. (5) Because alcohol also has a vasodilating action, patients should avoid substantial consumption of alcoholic beverages. Consuming more than 3 units (3 glasses of wine or shots of whiskey) in combination with avanafil increases the risk of orthostatic signs and symptoms, such as a decrease in standing BP and dizziness. (6) The PDE5 inhibitors have been infrequently associated with prolonged erection greater than 4 hours and priapism (painful erections lasting longer than 6 hours). If an erection persists for longer than 4 hours, the patient should seek immediate medical assistance. Avanafil should be used with caution in patients with conditions that may predispose them to priapism (such as sickle cell anemia and multiple myeloma) and in those who have an anatomical deformity of the penis. (7) Rarely, patients using a PDE5 inhibitor have experienced a sudden loss of vision in one or both eyes. This may be a sign of nonarteritic anterior ischemic optic neuropathy, which has been reported in temporal association with the use of these agents. Patients who experience such a reaction should discontinue use of the drug and seek medical attention. (8) The PDE5 inhibitors have also been associated with a sudden decrease in or loss of hearing, which may be accompanied by tinnitus or dizziness. If this occurs, the drug should be discontinued and medical attention sought. (9) Avanafil use should be avoided in patients being treated with a strong CYP3A4 inhibitor such as clarithromycin, itraconazole, or ritonavir, which increase avanafil's action. In patients being treated with a moderate CYP3A4 inhibitor such as diltiazem, fluconazole, or verapamil, the maximum recommended dose of avanafil is 50 mg and it shouldn't be used more than once every 24 hours. (10) The safety of avanafil in patients with bleeding disorders or active peptic ulceration is unknown. (11) Avanafil hasn't been studied in patients with severe hepatic or renal impairment and isn't recommended for these patients.

Adverse reactions: *headache, flushing*, nasal congestion, nasopharyngitis, back pain

Supplied as: 50 mg, 100 mg, and 200 mg tablets

Dosage: Initially, 100 mg as needed approximately 15 minutes before sexual activity. Subsequent doses may be increased to a maximum of 200 mg or reduced to 50 mg, depending on patient response and tolerance. The maximum recommended dosing frequency is once a day.

Nursing considerations: (1) Inform patients that avanafil can be taken without regard to food, but that prior consumption of a high-fat meal may reduce the rate of absorption and delay the onset of action. Taken in a fasting state, avanafil is rapidly absorbed and reaches maximum concentration in 30 to 45 minutes. (2) Tell patients to seek immediate medical assistance if an erection persists for more than 4 hours. (3) Advise patients about the risk of orthostatic hypotension associated with excessive alcohol consumption. (4) Warn patients about the risk of a sudden loss of vision or hearing; hearing loss may be accompanied by tinnitus or dizziness. Patients who experience any

such reaction should stop using the drug and seek medical attention. (5) Teach patients to recognize signs and symptoms of a hypersensitivity reaction, such as pruritus or eyelid edema, and to discontinue the drug and seek medical attention if these occur.

REFERENCE

1. Prescribing information. Stendra (avanafil) tablets. https://www.stendra.com.

BRONCHODILATOR

Umeclidinium bromide/vilanterol trifenatate

Unique formulation helps patients catch their breath.

Chronic obstructive pulmonary disease (COPD) affects an estimated 24 million people and is the third leading cause of death in the United States. Cigarette smoking is the most common cause.[1,2] Maintenance treatment of COPD often involves the use of a long-acting beta$_2$-adrenergic agonist (LABA), such as salmeterol, formoterol, indacaterol, or vilanterol (in combination with fluticasone) and/or a long-acting muscarinic antagonist (LAMA) such as tiotropium or aclidinium via oral inhalation. Both the LABAs and LAMAs provide a bronchodilating action. An inhaled corticosteroid may also be added to the regimen.

Umeclidinium bromide joins tiotropium and aclidinium in the group of LAMAs, also designated as long-acting anticholinergic or antimuscarinic agents. It was initially approved in a formulation with the LABA vilanterol trifenatate (*Anoro Ellipta*, GlaxoSmithKline), becoming the first combination formulation to include both a LAMA and LABA. This formulation may offer an advantage for patients who haven't experienced adequate benefit from one inhaled bronchodilator because they can be treated with two bronchodilators with different mechanisms of action via one dose from the same delivery device. Although a combination formulation of ipratropium and albuterol is also available, these agents have a shorter duration of action and must be administered more frequently.

Administered by oral inhalation, the umeclidinium/vilanterol formulation is indicated for long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD.[3] It's not indicated to treat acute bronchospasm, acutely deteriorating COPD, or asthma. The effectiveness of the combination was demonstrated in studies in which the new formulation provided a larger increase in FEV_1 (forced expiratory volume in the first second of expiration) at 24 weeks than either of the individual components or placebo.

Following approval of the combination formulation, the FDA approved umeclidinium for use as a single agent (*Incruse Ellipta*) via oral inhalation. Vilanterol continues to be available only in combination formulations.

Precautions: (1) Contraindicated in patients with severe hypersensitivity to milk proteins or any other ingredients of the formulation. The powder mix of the two drugs includes lactose monohydrate, which contains milk proteins. (2) Contraindicated for treatment of acute bronchospasm or asthma. Vilanterol, like the other LABAs, is associated with an increased risk of asthma-related death, and this is the subject of a boxed warning in its labeling and multiple observations that the new product isn't indicated for treatment of asthma. Discontinue treatment if the patient experiences paradoxical bronchospasm. (3) Because of its anticholinergic action, umeclidinium may worsen urinary retention or narrow-angle glaucoma. (4) Avoid concurrent use with other medications with anticholinergic activity (such as tolterodine and diphenhydramine), which may increase the activity of umeclidinium. (5) Vilanterol and other beta$_2$-agonists must be used with caution in patients with cardiovascular disorders, convulsive disorders, thyrotoxicosis, ketoacidosis, and diabetes. (6) The new formulation shouldn't be used concurrently with another LABA because of the risk of an excessive response. (7) Avoid concurrent use with a beta-adrenergic blocker, which can inhibit the bronchodilating action of vilanterol and may produce severe bronchospasm. (8) Use caution if the new formulation is used concurrently with a CYP3A4 inhibitor, such as ketoconazole or clarithromycin. These drugs may increase the exposure and activity of vilanterol, which is a substrate for the CYP3A4 pathway. (9) Avoid concurrent use with a monoamine oxidase inhibitor or tricyclic antidepressant, which increase the risk of cardiovascular adverse reactions. If concurrent use with vilanterol or another beta-agonist is considered clinically necessary, extreme caution must be exercised.

Adverse reactions: *pharyngitis, diarrhea, pain in extremity*

Supplied as: a powder mix in a plastic inhaler containing two double-foil blister strips, each with 30 blisters. Each blister on one strip contains 62.5 mcg of umeclidinium; each blister on the other strip contains 25 mcg of vilanterol. When the inhaler is activated, the powder in both blisters is exposed and available for dispersion into the airstream created by the patient inhaling through the mouthpiece. An institutional pack containing 7 blisters per strip is also available.

Dosage: one oral inhalation per day

Nursing considerations: (1) Review the Medication Guide provided with the medication and educate patients about use of the product and proper inhalation technique. Teach patients to take a dose at the same time every day and not to take more than 1 dose every 24 hours. (2) The

umeclidinium/vilanterol inhalation system is supplied in a moisture-protective foil tray and should only be removed from the tray immediately before initial use. The inhaler should be discarded when the dose counter reads "0" after all blisters have been used (presumably after 30 days when used once daily as recommended) or 6 weeks after opening the foil tray, whichever comes first. (3) Warn patients about potential adverse reactions, including anticholinergic responses that increase the risk of worsening urinary retention or narrow-angle glaucoma. Teach patients to recognize signs and symptoms that they should immediately report to their healthcare provider. (4) Make sure patients understand that the inhaler isn't reusable and shouldn't be taken apart.

REFERENCES

1. COPD Foundation. http://www.copdfoundation.org.

2. National Institutes of Health/National Heart, Lung, and Blood Institute. What is COPD? http://www.nhlbi.nih.gov/health/health-topics/topics/copd.

3. Anoro Ellipta. Prescribing information. http://www.gsksource.com/anoro.

DRUG FOR MENOPAUSE-ASSOCIATED CONDITIONS

Conjugated estrogens/ bazedoxifene acetate

Reducing the risk of endometrial hyperplasia associated with estrogens

Menopause is associated with reduced functioning of the ovaries during aging that results in lower concentrations of estrogens and other hormones. Lower estrogen concentrations are often accompanied by moderate-to-severe vasomotor symptoms (hot flashes), followed by bone loss and an increased risk of osteoporosis. In the United States, 4.5 million women over age 50 have osteoporosis of the hip.[1] Evidence suggests that about half of women over age 50 will experience a fracture related to osteoporosis in their lifetime.[2]

Estrogens have been used for more than 60 years as a menopausal hormone therapy to manage menopausal symptoms. Although effective in reducing menopausal symptoms, estrogen used alone increases the risk of endometrial hyperplasia, a possible precursor to endometrial cancer. To reduce this risk, a progestin has been used in combination with an estrogen.

A combination of conjugated estrogens and bazedoxifene acetate (*Duavee*, Pfizer) has recently been approved for the treatment of menopause-associated conditions.[3] Bazedoxifene, an estrogen agonist/antagonist, is a new therapeutic agent that's also designated as a selective estrogen receptor modulator that activates estrogen receptors in some tissues while inhibiting estrogen activity in others, such as the uterus. Bazedoxifene joins several other drugs classified as estrogen agonist/antagonists that are indicated for use in postmenopausal women, such as raloxifene and ospemifene.

The new combination product is the first to be approved that includes an estrogen agonist/antagonist instead of a progestin to reduce the risk of endometrial hyperplasia associated with the use of estrogen alone. It's indicated for women with a uterus for the treatment of moderate-to-severe vasomotor symptoms associated with menopause and for prevention of postmenopausal osteoporosis.

As with other products containing estrogen, conjugated estrogens/bazedoxifene should be used for the shortest duration consistent with treatment goals and risks for each patient. When treatment is considered solely for the prevention of postmenopausal osteoporosis, the new product should be used only in women at significant risk of osteoporosis and nonestrogen medication should be carefully considered as an alternative.

The effectiveness of conjugated estrogens/bazedoxifene to treat vasomotor symptoms was demonstrated in a placebo-controlled study in which the new product significantly reduced the number and severity of hot flashes. In studies in which the new product was evaluated for the prevention of postmenopausal osteoporosis, it significantly increased lumbar spine bone mineral density and total hipbone mineral density.

Precautions: (1) Contraindicated in patients with undiagnosed abnormal uterine bleeding; known, suspected, or history of breast cancer; known or suspected estrogen-dependent neoplasia; active or history of venous or arterial thromboembolism; known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorder; and known hepatic impairment or disease, and in those who are hypersensitive to any component of the product. (2) Contraindicated in pregnant patients, patients who may become pregnant, and nursing mothers. The product is classified in Pregnancy Category X, indicating that the risks to the fetus clearly outweigh potential benefits of the drug. (3) Studies have reported increased risks of stroke and deep vein thrombosis, as well as probable dementia in postmenopausal women age 65 and older; these concerns are included as boxed warnings in the labeling for the conjugated estrogens/bazedoxifene combination. (4) Boxed warnings also state that the combination product shouldn't be used for prevention of cardiovascular disease or dementia, and the risk of endometrial cancer is increased in women with a uterus who use unopposed estrogen. (5) Estrogen therapy has also been associated with an increased risk of cardiovascular disorders, hypertriglyceridemia, gallbladder disease, visual abnormalities, and hypothyroidism. Thyroid function should be monitored as women who are being treated with thyroid replacement therapy who are also receiving estrogens may require increased doses of thyroid replacement therapy. (6) Women

taking the conjugated estrogens/bazedoxifene combination shouldn't take additional estrogens, estrogen agonist/antagonists, or progestins. (7) Not recommended for women with renal impairment or women age 75 or older. (8) The concurrent use of a CYP3A4 inhibitor such as clarithromycin, itraconazole, or grapefruit juice may increase the exposure of conjugated estrogens. CYP3A4 inducers such as carbamazepine, rifampin, or St. John's wort may reduce plasma concentrations and the activity of estrogens. Inducers of uridine diphosphate glucuronosyltransferase such as carbamazepine or rifampin may increase the metabolism of bazedoxifene, reduce its exposure, and increase the risk of endometrial hyperplasia.

Adverse reactions: *muscle spasms, nausea, diarrhea, dyspepsia, abdominal pain, oropharyngeal pain*, neck pain, dizziness

Supplied as: film-coated oral tablets containing 0.45 mg of conjugated estrogens and 20 mg of bazedoxifene

Dosage: one tablet daily

Nursing considerations: (1) Tell patients using the product to prevent postmenopausal osteoporosis to take supplemental calcium and/or vitamin D daily if recommended by the healthcare provider. (2) Tell patients to keep the product in its original blister package, not a pill box or pill organizer, to protect it from moisture. (3) Instruct patients to remove only one tablet from the blister package at the time of use. (4) If more than one blister package is dispensed to a patient, instruct her to open one foil pouch at a time. (5) Instruct patients to record the date they open the blister package in the space provided on the blister package label, and tell them not to use the product if the blister package has been open more than 60 days. (6) The daily dose can be taken without regard to food.

REFERENCES

1. Centers for Disease Control and Prevention. FastStats. Osteoporosis. http://www.cdc.gov/nchs/fastats/Osteoporosis.htm.
2. National Osteoporosis Foundation. http://nof.org/articles/7.
3. Duavee—estrogens, conjugated and bazedoxifene acetate tablet, film coated. Prescribing information. http://labeling.pfizer.com/ShowLabeling.aspx?id=1174.

ANTIEPILEPTIC DRUGS

Perampanel

Adjunctive therapy for partial-onset seizures

The most common type of seizure experienced by people with epilepsy, partial-onset seizures initially affect only a limited or localized area of the brain but can spread to other parts of the brain.[1] Perampanel (*Fycompa*, Eisai) is a newly approved antiepileptic drug (AED) indicated as adjunctive therapy for treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy age 12 and older.

Perampanel is a noncompetitive antagonist of the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptor on postsynaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS) and is implicated in many neurologic disorders caused by neuronal overexcitation. Perampanel is the first AED with this mechanism of action, but the precise manner in which it provides its antiepileptic action hasn't been determined.

Perampanel's effectiveness was demonstrated in three placebo-controlled studies in patients who had a mean duration of epilepsy of approximately 21 years, a median baseline seizure frequency ranging from 9.3 to 14.3 seizures per 28 days, and who typically were also taking 2 to 3 concomitant AEDs. Study results showed improvement in seizure control in patients treated with perampanel compared with those receiving placebo. Approximately 50% of patients were also taking at least one AED known to induce the CYP3A metabolic pathway (carbamazepine, oxcarbazepine, or phenytoin) and cause a significant reduction in the serum concentration of perampanel.[2]

In clinical trials, neurologic effects such as dizziness and somnolence were most often responsible for discontinuation of treatment; 8% and 19% of patients treated with 8 mg/day and 12 mg/day, respectively, experienced an adverse reaction, compared with 5% of those receiving placebo. The concurrent use of alcoholic beverages or other CNS depressants is likely to cause an additive or supra-additive CNS response.

Studies of perampanel's abuse potential have demonstrated an incidence of euphoria that's higher than with alprazolam but lower than with ketamine. Its potential to produce withdrawal symptoms hasn't been adequately studied. The new drug has been classified as a Schedule III controlled substance.

Precautions: (1) The risk of serious psychiatric and behavioral reactions is the subject of a boxed warning in perampanel's labeling. Reactions may include aggression, hostility, irritability, anger, and homicidal ideation and threats. Monitor patients for these reactions and for changes in mood, behavior, or personality that aren't typical for the patient, particularly during the titration period and at higher doses. If such symptoms occur, the dosage should be reduced. Discontinue the drug immediately if symptoms are severe or worsening. (2) Like other AEDs, perampanel is associated with an increased risk of suicidal thoughts or behavior. Patients treated with any AED for any indication should be monitored for depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. (3) Use with caution in older adults due to the increased risk of adverse CNS effects such as dizziness and somnolence, which may lead to falls.

(4) Consult the product labeling for suggested dosage adjustments for patients with moderate renal impairment and/or mild-to-moderate hepatic impairment. Perampanel isn't recommended for patients with severe hepatic or renal impairment or for patients undergoing dialysis. (5) The concomitant use of known CYP enzyme inducers, including other AEDs such as oxcarbazepine, reduces the plasma concentration of perampanel by one-half to two-thirds. Consequently, a higher dosage of perampanel should be prescribed to initiate treatment in patients already being treated with enzyme-inducing AEDs. Avoid the concurrent use of other strong CYP3A inducers, such as rifampin and St. John's wort. (6) Perampanel is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the fetus. If the drug is prescribed during pregnancy, patients should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334).

Adverse reactions: *dizziness, somnolence, fatigue*, irritability, nausea, balance disorder, falls, gait disturbance, weight gain, vertigo, ataxia

Supplied as: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg oral tablets

Dosage: Initially, 2 mg/day at bedtime in patients not also being treated with enzyme-inducing AEDs; 4 mg/day at bedtime in patients who are being treated with enzyme-inducing AEDs. Dosage may be increased by 2 mg/day increments no more frequently than every week to a recommended dosage range of 4 to 8 mg/day or 8 to 12 mg/day, respectively, depending on whether the patient is on concurrent enzyme-inducing AED therapy. When an enzyme-inducing AED is introduced or withdrawn from the regimen, the patient's response and tolerability should be closely monitored and the dosage adjusted as needed. Consult the product labeling for recommended dosage adjustments for older adults and patients with renal or hepatic impairment.

Nursing considerations: (1) Tell the patient to take each daily dose at bedtime. (2) Advise a woman using a hormonal contraceptive containing levonorgestrel that perampanel may reduce the contraceptive's effectiveness. Recommend using an additional nonhormonal form of contraception. (3) For older adults, dosage increases during titration should occur no more frequently than every 2 weeks. (4) Warn patients not to engage in driving or other potentially hazardous activities requiring alertness until they learn how the drug affects them. (5) Tell patients to avoid concurrent use of alcohol or medications with CNS depressant effects because they increase the risk of adverse reactions such as sedation and dizziness. (6) Warn patients not to discontinue the drug abruptly, which would increase the risk of seizures. If necessary, the drug should be discontinued gradually as directed by the healthcare provider.

REFERENCES

1. Epilepsy Foundation. Types of seizures. http://www.epilepsy.com/learn/types-seizures.

2. Fycompa (perampanel) tablets. Prescribing information. https://www.fycompa.com.

Eslicarbazepine acetate

Indicated to help prevent partial-onset seizures

Also indicated as adjunctive treatment for partial-onset seizures in adults age 18 and older, eslicarbazepine acetate (*Aptiom,* Sunovion) has properties that are most similar to those of oxcarbazepine and carbamazepine. The antiepileptic activity of these drugs is thought to involve inhibition of voltage-gated sodium channels, although their precise mechanism of action isn't known.

Eslicarbazepine's effectiveness was demonstrated in three placebo-controlled studies in patients who had a median duration of epilepsy of 19 years, a median baseline seizure frequency of 8 seizures per 28 days, and were also taking one or two concomitant AEDs. The most commonly used AEDs were carbamazepine, lamotrigine, and valproic acid; oxcarbazepine wasn't permitted as a concomitant AED.[1] Eslicarbazepine was effective in reducing the frequency of seizures in each of the three studies. However, in the largest study (approximately 600 participants), the reduction in seizure frequency over 28 days was considered statistically significant only for subjects taking 1,200 mg/day, not for those taking 800 mg/day.

Precautions: (1) Contraindicated in patients with a hypersensitivity to eslicarbazepine or oxcarbazepine. Anaphylaxis, angioedema, serious dermatologic reactions, including Stevens-Johnson syndrome, and drug reaction with eosinophilia and systemic symptoms/multiorgan hypersensitivity have been reported. If a patient experiences any such reaction not attributable to another cause, eslicarbazepine should be discontinued. It shouldn't be used in patients who've had prior reactions of this type with either it or oxcarbazepine. (2) Like other AEDs, eslicarbazepine may increase the risk of suicidal thoughts or behavior in some patients. Patients should be monitored for changes in mood or behavior, or other indicators that might suggest greater risk. (3) Monitor for neurologic adverse reactions such as dizziness, during the dosage titration period; older adults are especially at risk. In clinical trials, the incidence of dizziness was higher in patients who were also treated with carbamazepine as part of their AED regimen, and dosage modifications of both drugs should be considered. (4) Dose-dependent increases in cognitive dysfunction-related events (such as memory impairment and disorientation) have been associated with eslicarbazepine. (5) Monitor serum sodium and chloride concentrations if

indicated, particularly if the patient is taking other medications known to reduce sodium concentrations. Some patients have experienced hyponatremia during treatment with eslicarbazepine. (6) Baseline evaluations of liver function tests are recommended. Treatment with eslicarbazepine should be discontinued in patients with jaundice or evidence of significant liver injury. Eslicarbazepine isn't recommended for patients with severe hepatic impairment. (7) Eslicarbazepine shouldn't be used with oxcarbazepine because of the extent to which their actions overlap and the potential for an excessive response. Enzyme-inducing AEDs such as phenytoin, phenobarbital, and primidone may reduce the plasma concentration of eslicarbazepine and necessitate increasing the eslicarbazepine dosage. Concurrent use with carbamazepine may increase the risk of adverse reactions such as dizziness. Consult the product labeling for other potential drug interactions and recommended dosage adjustments. (8) Eslicarbazepine is classified in Pregnancy Category C and should be used during pregnancy only if the anticipated benefit justifies the risk to the fetus. Pregnant women who are being treated with the new drug should be encouraged to enroll in the North American Antiepileptic Drug Pregnancy Registry (1-888-233-2334).

Adverse reactions: *dizziness, headache, somnolence, nausea, diplopia*, blurred vision, vomiting, fatigue, ataxia, vertigo, tremor

Supplied as: 200 mg, 400 mg, 600 mg, and 800 mg tablets

Dosage: Initially, 400 mg once a day. After one week, the dosage should be increased to 800 mg once a day, the recommended maintenance dosage. Some patients who tolerate the 800 mg daily dosage for at least a week may benefit from a further increase to the maximum recommended maintenance dosage of 1200 mg once a day, although this dosage increases the incidence of adverse reactions. Consult the product labeling for recommended dosage adjustments for patients with moderate or severe renal impairment.

Nursing considerations: (1) Inform women of reproductive potential that eslicarbazepine may reduce the effectiveness of hormonal contraception. Recommend that they use additional or alternative nonhormonal contraception. (2) Warn patients to avoid alcohol and other substances with CNS depressant effects, and to avoid engaging in driving or other potentially hazardous activities requiring alertness until they learn how the drug affects them. (3) Warn patients not to discontinue the drug abruptly, which would increase the risk of seizure activity or status epilepticus. If treatment is to be discontinued, the eslicarbazepine dosage should be tapered as directed by the healthcare provider. (4) Eslicarbazepine can be taken without regard to food. ■

REFERENCE

1. Prescribing information. Aptiom (eslicarbazepine acetate) tablets. http://www.aptiom.com.

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