1.5 ANCC CONTACT HOURS CE 1.5 PHARMACOLOGY CREDITS

New Drugs 2019 PART 3

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Abstract: This article reviews seven drugs recently approved by the FDA, including indications, precautions, adverse reactions, and nursing considerations.

Keywords: baloxavir, cannabidiol, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, revefenacin, tafenoquine succinate

THIS ARTICLE reviews seven recently marketed drugs, including:

- an antiepileptic drug that is the first natural product derived from marijuana to receive FDA approval.
- three new drugs indicated for preventive treatment of migraine.
- an antimalarial drug indicated to prevent relapse in certain patients infected with *Plasmodium vivax* malaria.

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

SELECTED REFERENCES

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EPIC CREATIONS / SHUTTERSTOCK

ANTIVIRAL DRUG

Baloxavir marboxil

Unique mechanism of action inhibits viral replication

Immunization continues to be the most effective strategy for reducing the risk and severity of influenza, but vaccine effectiveness varies depending on the type and virulence of the strains of the flu viruses that are most prevalent. The influenza neuraminidase inhibitors oseltamivir and zanamivir may shorten the duration and severity of flu symptoms if treatment starts within 48 hours of symptom onset. Administered orally (oseltamivir) or by oral inhalation (zanamivir), these drugs may also be used for influenza prophylaxis in situations such as community outbreaks of the flu in which the delay in onset of the full protection of immunization would place individuals and communities at risk. A third influenza neuraminidase inhibitor, peramivir, is also approved for treatment of influenza but is administered I.V.

Baloxavir marboxil (*Xofluza*, Genentech; Shionogi) is a polymerase acidic endonuclease inhibitor that is almost completely converted by hydrolysis to its active metabolite, baloxavir.[1] This metabolite exerts activity against both influenza A and influenza B viruses. Its unique mechanism of action inhibits the endonuclease activity of the polymerase acidic protein, which in turn inhibits influenza virus replication. Administered orally as a single-dose treatment, baloxavir is indicated to treat acute uncomplicated influenza in patients age 12 and older who have been symptomatic for no more than 48 hours.

The effectiveness of baloxavir was evaluated in two clinical studies in which the primary endpoint was the time to alleviation of symptoms, defined as the time when all seven symptoms (cough, sore throat, nasal congestion, headache, feverishness, myalgia, and fatigue) had been assessed by the patient as none or mild for at least 21.5 hours. The first study was conducted in 400 patients and was placebo-controlled. The median time to alleviation of symptoms in patients treated with a single dose of 40 mg of baloxavir was 50 hours, compared with a median time of 78 hours in those receiving placebo. The second study was an active- and placebo-controlled trial in 1,436 adult and adolescent patients. The median time to alleviation of symptoms in patients treated with a single dose of 40 mg or 80 mg of baloxavir was 54 hours, compared with a median time of 80 hours in those receiving placebo.

The second study included a group of patients who were treated with oseltamivir (twice a day for 5 days). No difference was found in the median time to alleviation of symptoms between patients who received a single dose of baloxavir and those who received oseltamivir.

Most patients in the clinical studies were infected with influenza A viruses. The subset of patients with influenza B infections in the first study had a shorter median time to alleviation of symptoms than those in the placebo group, but in the subset of patients in the second study with influenza B infections, the median time to alleviation of symptoms was longer in those receiving baloxavir than in those receiving placebo.

In another trial, 2,184 patients were randomized to receive baloxavir, oseltamivir, or placebo. The median times to alleviation of symptoms were about 73 hours, 80 hours, and 102 hours, respectively. In patients with influenza B infections, the median time was significantly shorter with baloxavir than with oseltamivir or placebo.

Baloxavir may be effective for treating influenza caused by strains of the virus that are resistant to the neuraminidase inhibitors. Cross-resistance between these drugs is not expected because they target different viral proteins. Influenza viruses with treatment-emergent amino acid substitutions associated with reduced susceptibility to baloxavir have been identified in fewer than 10% of patients. Oseltamivir is often active against these viruses.

Oseltamivir is approved for the treatment of influenza in patients as young as 2 weeks as well as for influenza prophylaxis. However, baloxavir has not yet been evaluated in patients younger than age 12 or for prophylaxis.

Precautions: (1) Contraindicated for patients with a history of hypersensitivity to baloxavir marboxil or any of its ingredients. (2) Assess patients for coexisting bacterial infections, which may begin with influenza-like symptoms, coexist with influenza, or occur as a complication of influenza. (3) Baloxavir may reduce the effectiveness of live attenuated influenza vaccine; avoid concurrent use. (4) Baloxavir may be less effective if taken concurrently with polyvalent cation-containing products such as antacids, laxatives, dairy products, calcium-fortified beverages, and supplements with agents such as calcium, iron, magnesium, selenium, or zinc.

Adverse reactions: diarrhea, bronchitis, nasopharyngitis, headache, nausea

Supplied as: 20 mg and 40 mg film-coated tablets in blister card packaging

Dosage: *In patients weighting 40 kg to less than 80 kg:* 40 mg in a single dose. *For patients weighing at least 80 kg:* 80 mg in a single dose.

Nursing considerations: (1) Patients should be treated with a single dose of

baloxavir within 48 hours of symptom onset. (2) Baloxavir may be administered with or without food, but advise patients to avoid coadministration with antacids, laxatives, dairy products, calcium-fortified beverages, and supplements containing calcium, iron, magnesium, selenium, or zinc.

REFERENCE

1. Xofluza (baloxavir marboxil) tablets, for oral use. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/210854s000lbl.pdf.

MIGRAINE DRUGS

An estimated 39 million Americans experience migraine headaches. Occurring in approximately three times as many women as men, the headaches are usually characterized by intense, throbbing pain in one area of the head. Many patients also experience nausea and/or vomiting and sensitivity to light and sound. Migraine episodes may be severe and frequent enough to become disabling.[1]

Over 4 million adults have chronic daily migraine, with at least 15 monthly migraine days (MMD).[2] The International Headache Society defines chronic migraine as 15 or more MMD for more than 3 months with at least 8 migraine days per month. Those who experience 4 to 14 MMD are classified as having episodic migraines. Nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans such as sumatriptan are used most often to treat acute migraine attacks.[2,3]

When migraine triggers cannot be identified or avoided, patients who experience migraine attacks may be candidates for preventive management to reduce the frequency and severity of attacks. Certain beta-blockers such as propranolol and timolol, and certain antiepileptic drugs such as divalproex sodium and topiramate, are approved for migraine prevention; in addition, chronic migraine is a labeled indication for onabotulinumtoxinA (Botox). However, many patients do not respond sufficiently to these treatments, which may be associated with unacceptable adverse reactions and other risks. Drugs used off-label for migraine prevention include metoprolol, atenolol, amitriptyline, venlafaxine, verapamil, and NSAIDs.

Calcitonin gene-related peptide (CGRP) is a neuropeptide that is primarily distributed in the central and peripheral nervous systems and acts as a vasodilator. It is involved in the transmission of pain impulses, and elevated concentrations have been associated with the occurrence of migraine attacks.

Three CGRP antagonists discussed in the following section were approved and marketed in 2018. All three are human monoclonal antibodies that are administered subcutaneously for the prevention of migraine in adults. The new drugs' effectiveness has been demonstrated in placebo-controlled trials. They have not been directly compared with drugs such as propranolol that have been used to prevent migraine. However, they have been used effectively in some patients who have experienced an inadequate response to or have not tolerated other therapies or who were not candidates for treatment because of the risk of using other medications.

The new drugs are well tolerated, with injection site reactions being the most commonly reported adverse events. The three new CGRP antagonists are considered on an individual basis in the following discussions.

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Erenumab-aooe

Use caution in patients sensitive to latex

Erenumab-aooe (*Aimovig*, Amgen; Novartis), which exhibits high-affinity binding to the CGRP receptor, is indicated for the prevention of migraine in adults.[1] Its effectiveness was demonstrated in three placebo-controlled clinical trials that excluded patients with medication overuse headache, as well as patients with myocardial infarction (MI), stroke, transient ischemic attacks, unstable angina, coronary artery bypass surgery, or other revascularization procedures within 12 months before screening.

Precautions: (1) Contraindicated in patients with serious hypersensitivity to erenumab or to any of its components. (2) Because certain components of the products contain a derivative of latex, patients sensitive to latex may experience allergic reactions.

Adverse reactions: injection site reactions, constipation

Supplied as: single-dose prefilled syringes and prefilled autoinjectors containing 70 mg or 140 mg of the drug per mL

Dosage: 70 mg or 140 mg once a month, as prescribed, administered subcutaneously in the abdomen, thigh, or upper arm

Nursing considerations: (1) Assess patients for latex sensitivity because certain components contain a latex derivative. (2) Because hypersensitivity reactions have occurred, teach patients to recognize signs and symptoms and contact the healthcare provider if any develop. Tell patients that hypersensitivity reactions may occur more than a week after the last dose. (3) Teach patients how to use the prefilled syringe

or autoinjector correctly and review injection technique. Detailed instructions for use are included in the product labeling. (4) If the patient misses a dose, it should be administered as soon as possible. Subsequent doses should be scheduled monthly from the date of the last dose. (5) Store the drug in the refrigerator. Tell patients to let the product sit at room temperature for at least 30 minutes protected from direct sunlight before injecting a dose.

REFERENCE

1. Aimovig (erenumab-aooe) injection, for subcutaneous use. Prescribing information. www.pi.amgen.com/~/media/amgen/repositorysites/pi-amgen-com/aimovig/aimovig_pi_hcp_english.ashx.

Fremanezumab-vfrm

Longer dosage interval is an option

Fremanezumab-vfrm (*Ajovy*, Teva) binds to CGRP ligand and blocks its binding to receptors. It was the second CGRP antagonist to be approved for the prevention of migraine in adults.

The effectiveness of fremanezumab was demonstrated in two placebo-controlled studies. The studies excluded patients with a history of significant cardiovascular disease, vascular ischemia, or thrombotic events, such as strokes, transient ischemic attacks, deep vein thrombosis, or pulmonary embolism.

One study was conducted in patients with episodic migraine. Over a 3-month treatment period, patients treated with the new drug experienced, on average, one to two fewer migraine days per month than those on placebo at dosages of both 225 mg once a month and 675 mg once every 3 months. Approximately 46% of patients experienced at least a 50% reduction from baseline in migraine days per month compared with 28% of those receiving placebo.

The second study was conducted in patients with chronic migraine. Patients treated with fremanezumab (in both dosage regimens) experienced, on average, two fewer migraine days per month than those receiving placebo. Approximately 39% of patients experienced at least a 50% reduction in monthly average number of headache days of at least moderate severity compared with only 18% of those receiving placebo.

Fremanezumab has an estimated half-life of approximately 31 days and is the only one of the three CGRP antagonists that can be administered in a once-quarterly dosage regimen as well as a once-monthly dosage regimen.

Precautions: (1) Contraindicated in patients with serious hypersensitivity to fremanezumab-vfrm or to any of its components. (2) If the patient experiences a hypersensitivity reaction, discontinue the drug and intervene appropriately; the clinician should consider discontinuing fremanezumab therapy.

Adverse reactions: injection site reactions

Supplied as: single-dose prefilled syringes containing 225 mg of the drug per 1.5 mL

Dosage: 225 mg once a month or 675 mg once every 3 months (quarterly). The 675 mg dose is administered as 3 consecutive injections of 225 mg each.

Nursing considerations: (1) Teach patients how to use the prefilled syringes correctly and review injection technique. Detailed instructions for use are included in the product labeling. (2) Teach patients to recognize and report signs and symptoms of hypersensitivity reactions. (3) Tell patients to store the syringes in a refrigerator. Before administering a dose, they should let the syringe sit at room temperature for at least 30 minutes protected from direct sunlight.

REFERENCE

1. Ajovy (fremanezumab-vfrm) injection, for subcutaneous use. Prescribing information. www.ajovy.com/globalassets/ajovy/ajovy-pi.pdf.

Galcanezumab-gnlm

Higher initial loading dose

The third CGRP antagonist to be approved in 2018 for the preventive treatment of migraine in adults, galcanezumab-gnlm (*Emgality*, Lilly) also binds to CGRP ligand and blocks its binding to receptors. Its effectiveness was demonstrated in three placebo-controlled studies that excluded patients with a history of stroke, MI, unstable angina, percutaneous coronary intervention, coronary artery bypass grafting, deep vein thrombosis, or pulmonary embolism within 6 months of screening.[1]

Like erenumab and fremanezumab, galcanezumab is administered subcutaneously but the initial loading dose is higher.

In June, the FDA approved galcanezumab for treatment of episodic cluster headache in adults. For more information about this indication, see *Drug News* on page 9.

Precautions: (1) Contraindicated in patients with serious hypersensitivity to galcanezumab-gnlm or to any of the product's components. (2) Hypersensitivity reactions have been reported. If a serious hypersensitivity reaction occurs, discontinue administration of galcanezumab and initiate appropriate therapy. Hypersensitivity reactions could occur days after administration and may be prolonged.

Adverse reactions: injection site reactions

Supplied as: single-dose prefilled pens and prefilled syringes containing 120 mg of the drug per mL

Dosage: *Initial loading dose*: 240 mg administered as two consecutive injections of 120 mg each. *Maintenance dosage:* 120 mg once a month.

Nursing considerations: (1) Teach patients how to use the prefilled syringes or pens correctly and review injection technique. Detailed instructions for use are included in the product labeling. (2) Teach patients to recognize and report signs and symptoms of hypersensitivity reactions. Warn them that symptoms may be delayed. (3) Tell patients to store the syringes in a refrigerator. Before administering a dose, they should let the syringe sit at room temperature for at least 30 minutes protected from direct sunlight.

REFERENCE

1. Emgality (galcanezumab-gnlm) injection, for subcutaneous use. Prescribing information. https://pi.lilly.com/us/emgality-uspi.pdf.

ANTIEPILEPTIC DRUG

Cannabidiol

First natural product derived from marijuana to gain FDA approval

Cannabidiol (*Epidiolex*, Greenwich) oral solution is approved to treat seizures associated with Dravet syndrome or Lennox-Gastaut syndrome (LGS) in patients age 2 years and older.[1] It is the first drug to be approved for patients with Dravet syndrome and the first natural product derived from marijuana to be approved by the FDA.

Dravet syndrome is a rare genetic epileptic disease that appears during the first year of life and is associated with frequent febrile seizures.[2] Patients subsequently experience other seizure types, including myoclonic seizures, and have an increased risk of status epilepticus, which can be life-threatening. Children with Dravet syndrome typically experience drug-resistant seizures, poor development of language and motor skills, hyperactivity, and difficulty relating to others, and have a high mortality risk. Before 2018, no drug had been approved for Dravet syndrome, although clobazam, levetiracetam, topiramate, and valproate have been used off-label with limited success.

Children with LGS, another rare epileptic disorder, usually begin having frequent seizures between ages 3 and 5 years.[3] Multiple seizure types may occur, including drug-resistant drop seizures (atonic, tonic, or tonic-clonic seizures) in which patients experience uncontrollable muscle contractions, falls, and possible serious injury. Most children with this seizure disorder have intellectual disability, learning problems, and delayed development of motor skills. Like patients with Dravet syndrome, these children may experience status epilepticus and have a higher mortality risk. As in the treatment of most seizure disorders, regimens that include combinations of antiepileptic drugs are typically employed; clobazam, valproate, lamotrigine, rufinamide, topiramate, and felbamate have labeled indications for treating LGS. However, many patients do not benefit significantly from even the combination regimens.

Cannabidiol (CBD) is a natural component of the *Cannabis sativa* plant (marijuana) that exhibits anticonvulsant activity. However, unlike tetrahydrocannabinol (THC), the major psychoactive component of marijuana that is primarily responsible for its classification in Schedule I of the Controlled Substances Act, CBD does not cause euphoria or intoxication.

Dronabinol and nabilone, marijuana-like products the FDA previously approved, are synthetic cannabinoids not extracted from the plant. CBD may also be derived from hemp, a plant in the cannabis family that contains little THC. Although CBD products derived from hemp are available in the marketplace, they have not been evaluated in clinical studies and have variable CBD content.[4] No legitimate medical claims can be made for their use.

The mechanism through which CBD exerts its anticonvulsant action is unknown, but it does not appear to be related to interaction with cannabinoid receptors. Its effectiveness in patients with Dravet syndrome was evaluated in a placebo-controlled trial in 120 patients ages 2 to 18 years who were inadequately controlled with at least one concomitant antiepileptic drug (AED), most often clobazam. Patients had experienced at least four convulsive seizures while on stable AED therapy during the 4-week baseline period. The median percent reduction in the frequency of convulsive seizures in patients treated with CBD (39%) was significantly greater than the percent reduction in those receiving placebo (13%).

The effectiveness of CBD in patients with LGS was evaluated in two placebo-controlled trials in patients ages 2 to 55 who were inadequately controlled with at least one concomitant AED, most often clobazam. Patients had experienced at least eight drop seizures during the 4-week baseline period. The median percent reduction in the frequency of drop seizures in patients treated with CBD (approximately 43%) was significantly greater than the percent reduction in those receiving placebo (approximately 20%). A secondary endpoint involved analyses of changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score on a

7-point scale at the last visit. A greater improvement on the S/CGIC score was reported in patients treated with CBD (mean score corresponding to "slightly improved") than in those receiving placebo (mean score corresponding to "no change").

When CBD was initially approved by the FDA, it was classified in Schedule I of the Controlled Substances Act and could not be legally marketed. However, when it was evaluated in a human physical dependence study in adults, it did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning 3 days after drug discontinuation. Based on this study and animal abuse-related studies, the Drug Enforcement Administration reclassified CBD to Schedule V.

Data are insufficient to assess the safety of CBD use in pregnant women, but animal studies identify a risk of developmental toxicity. Encourage women who are taking CBD during pregnancy to enroll in the North American Antiepileptic Drug Pregnancy Registry by calling 1-888-233-2334 or visiting www.aedpregnancyregistry.org.

Precautions: (1) The risk of somnolence and other adverse reactions is higher in patients also being treated with clobazam, and the dosage of clobazam may need to be reduced. The concurrent use of other central nervous system depressants, including alcohol, could potentiate these effects. (2) All AEDs, including CBD, increase the risk of suicidal thoughts or behavior, and patients treated with these agents for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior. (3) CBD is contraindicated in patients with a prior hypersensitivity reaction to CBD or any of the ingredients of the product, which includes sesame seed oil. Hypersensitivity reactions have been experienced infrequently. (4) CBD causes dose-related elevations of liver transaminases (alanine aminotransferase and/or aspartate aminotransferase). These elevations usually developed in the first 2 months of treatment. The incidence is increased in patients also being treated with valproate and/or clobazam. Serum transaminases and total bilirubin concentrations should be determined before starting treatment with CBD, at 1 month, 3 months, and 6 months after initiation of treatment, and periodically thereafter, or as clinically indicated. These determinations should also be obtained within 1 month following changes in CBD dosage and the addition of or changes in other medications known to affect liver function. CBD should be discontinued in patients with transaminase elevations greater than three times the upper limit of normal (ULN) and bilirubin concentrations greater than two times the ULN, and in patients with sustained transaminase elevations of greater than five times the ULN. (5) The dosage of CBD should be reduced in patients with moderate or severe hepatic impairment. (6) A dosage adjustment may be indicated if the patient is also taking a drug that inhibits or induces certain metabolic pathways, including the CYP3A4 and CYP2C19 pathway. Consult the prescribing information for warnings and precautions about these and other potential drug interactions.

Adverse reactions: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; infections

Supplied as: oral solution containing the drug in a concentration of 100 mg/mL in bottles containing 100 mL of a clear, colorless to yellow solution. Inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. A calibrated measuring device (either 5 mL or 1 mL oral syringe) is provided to measure and administer the dose accurately.

Dosage: Initially, 2.5 mg/kg twice a day. After 1 week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice a day. Patients who are tolerating this dosage and require further reduction of seizures may be prescribed a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice a day, in weekly increments of 2.5 mg/kg twice a day.

For patients in whom a more rapid titration from 5 mg/kg twice a day to 10 mg/kg twice a day is warranted, the dosage may be increased no more frequently than every other day. Consult the prescribing information for recommended dosage reductions for patients with moderate and severe hepatic impairment.

Nursing considerations: (1) Teach patients and/or parents how to correctly measure each dose with the dosing syringe provided. Instructions for use are provided in the patient Medication Guide. (2) Tell patients to take the drug exactly as prescribed and warn them not to discontinue the drug abruptly, which could trigger increased seizure activity and/or status epilepticus. Discontinue treatment with CBD only as directed by the healthcare provider. (3) Warn patients about the risk of suicidal ideation associated with AEDs and instruct them to report any troubling mood changes to the healthcare provider. (4) Teach patients to recognize and report signs and symptoms of hepatic dysfunction and to keep appointments for lab testing as directed by the healthcare provider. (5) Warn patients about the risk of somnolence and advise

them to avoid activities requiring alertness until they know how the drug affects them. (6) Tell patients to take CBD consistently either with or without food. (7) Store CBD at room temperature. Any solution remaining 12 weeks after the bottle is opened should be discarded.

REFERENCES

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3. National Institutes of Health/US National Library of Medicine. Lennox-Gastaut Syndrome. Genetics Home Reference. https://ghr.nlm.nih.gov/condition/lennox-gastaut-syndrome.

4. US Food and Drug Administration. FDA regulation of cannabis and cannabis-derived products: questions and answers. www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-questions-and-answers.

BRONCHODILATOR

Revefenacin

Another option for oral inhalation delivery

Chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema, affects approximately 16 million Americans and is a leading cause of death in the US.[1] Long-acting muscarinic antagonists (LAMAs), also designated as anticholinergic or antimuscarinic agents, have been used via oral inhalation for first-line maintenance treatment for COPD; examples include tiotropium, aclidinium, and glycopyrrolate. Most of these drugs are administered via metered-dose inhaler (MDI). The effective use of these devices requires manual dexterity and coordination of actuation of the device and inhalation that deviates from regular breathing, which present a challenge for some patients.

Revefenacin (*Yupelri*, Theravance; Mylan) is the second LAMA to be approved for oral inhalation using a nebulizer rather than an MDI, and is the first LAMA administered via nebulization once a day. It is indicated for the maintenance treatment of patients with COPD and is used with a standard jet nebulizer with a mouthpiece connected to an air compressor.[2] Because nebulization permits drug administration while the patient is breathing normally, some patients find a nebulizer easier to use than an MDI. However, many patients find the nebulization drug delivery system more complex, time-consuming, and inconvenient.

The effectiveness of revefenacin was evaluated in two 12-week, placebo-controlled studies in patients with moderate-to-severe COPD. In both studies, revefenacin demonstrated significant improvement in lung function compared with placebo.

Revefenacin has not been directly compared with other LAMAs in clinical trials, but its risks and precautions are similar to those of other LAMAs that are administered by oral inhalation. The effectiveness and safety of revefenacin in pediatric patients have not been determined.

Precautions: (1) LAMAs do not have a rapid onset of action and should not be used to treat acute COPD symptoms such as bronchospasm or acutely deteriorating COPD. Acute symptoms should be treated with an inhaled rapid- (short-) acting beta$_2$-adrenergic agonist such as albuterol. (2) Immediate hypersensitivity reactions have occurred. Treatment should be immediately discontinued if such a reaction occurs. (3) Some patients have experienced paradoxical bronchospasm. Treatment should be discontinued if this response occurs. (4) Because of its anticholinergic action, revefenacin may worsen narrow-angle glaucoma or urinary retention (particularly in patients with benign prostatic hyperplasia or bladder-neck obstruction). (5) Revefenacin's activity may be increased by other medications with anticholinergic activity such as tiotropium, ipratropium, tolterodine, and diphenhydramine. Avoid concurrent use. (6) Concurrent use of revefenacin with an organic anion transporting polypeptide (OATP)1B1 or OATP1B3 inhibitor such as rifampicin or cyclosporine may lead to an increase in exposure of the active metabolite and is not recommended. (7) Not recommended for use in patients with hepatic impairment as exposure to revefenacin's active metabolite is significantly increased in patients with moderate hepatic impairment.

Adverse reactions: cough, nasopharyngitis, headache, upper respiratory tract infection, back pain

Supplied as: a sterile, aqueous solution in polyethylene unit-dose vials. Each vial contains 175 mcg of revefenacin in 3 mL of solution. Vials are overwrapped in a foil pouch and supplied in cartons containing either 30 or 7 individually pouched vials.

Dosage: 175 mcg once a day by nebulizer using a mouthpiece. The drug should be administered by oral inhalation via a standard jet nebulizer connected to an air compressor; administration of a dose takes approximately 8 minutes.

Nursing considerations: (1) Warn patients that this medication is not effective for acute COPD symptoms. Encourage them to keep an inhaled, short-acting beta$_2$ agonist such as albuterol available at all times to manage acute symptoms. (2) Review the instructions for use in the Medication Guide and teach patients to use the nebulizer correctly. Tell patients not to remove a vial from its pouch

until they are ready to take a dose. (3) Instruct patients to seek medical attention if they experience decreasing effectiveness of their inhaled, short-acting beta$_2$ agonist; a significant decrease in lung function as outlined by the healthcare provider; paradoxical bronchospasm; difficult or painful urination; or signs and symptoms of narrow-angle glaucoma, such as eye pain, blurred vision, visual halos or colored images, or conjunctival congestion.

REFERENCES

1. Centers for Disease Control and Prevention. What is COPD? www.cdc.gov/copd/index.html.

2. Yupelri (revefenacin) inhalation solution, for oral inhalation. Prescribing information. www.accessdata.fda.gov/drugsatfda_docs/label/2018/210598s000lbl.pdf.

ANTIPARASITIC DRUG

Tafenoquine succinate

Indicated to prevent relapse in certain patients with *P. vivax* malarial infection

Malaria caused by the parasite *Plasmodium vivax* is common in areas such as Southeast Asia, parts of Africa, and parts of South America. It is characterized by fever, chills, vomiting, malaise, headache, and myalgia. In some cases, the infection may be severe and even fatal.

Following a bite of an infected mosquito, *P. vivax* infects the blood and causes an acute malaria episode.[1] It can also lie dormant in the liver from where it periodically reactivates to cause relapses of malaria. Therefore, a single *P. vivax* infection can give rise to multiple episodes of malaria, and these relapses can occur weeks, months, or even years after the initial infection. Most antimalarial drugs are active against the blood-stage of the parasite but are not very effective against the dormant forms in the liver. The 8-aminoquinoline derivative primaquine is the only antiparasitic agent that has been approved to target the dormant liver stage to prevent relapse, but it must be taken for 14 days to be effective.

Tafenoquine succinate (*Krintafel*, GlaxoSmithKline) is also an 8-aminoquinoline antimalarial agent. It is indicated for the radical cure (prevention of relapse) of *P. vivax* malaria in patients age 16 and older who are receiving appropriate antimalarial therapy for acute *P. vivax* infection.[2] It is administered in conjunction with antimalarial therapy (for example, chloroquine or an artemisinin-based combination regimen) in patients with an acute infection, but it is not a treatment for acute infection.

Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *P. vivax*. The activity against the pre-erythrocytic liver stages of the parasite prevents development of the erythrocytic forms responsible for relapses in *P. vivax* malaria.

The effectiveness of tafenoquine was demonstrated in two clinical trials in patients positive for *P. vivax*. In the larger study, recurrence-free efficacy occurred in 60% of the patients treated with chloroquine and tafenoquine, and in 26% of the patients treated with chloroquine and placebo. The second study also showed a significantly higher rate of recurrence-free efficacy with the chloroquine/tafenoquine regimen at 6 months (84% versus 39%).

In a study comparing chloroquine/tafenoquine and chloroquine/primaquine regimens, the recurrence-free efficacy rates at 6 months were similar. However, the use of tafenoquine in a single dose increases compliance, giving it an important advantage when compared with primaquine, which is administered for 14 days.

After approving Krintafel, the product discussed here, the FDA approved another tafenoquine product, Arakoda, which is supplied as oral tablets containing 100 mg of tafenoquine. In contrast to Krintafel, Arakoda is indicated for the prophylaxis of malaria in patients age 18 and older.[3]

Precautions: (1) Contraindicated in patients with known hypersensitivity to any of the 8-aminoquinoline derivatives. Because of tafenoquine's long half-life (approximately 15 days), symptoms of hypersensitivity and other adverse reactions may be delayed in onset and/or duration. (2) Contraindicated in patients with a deficiency of glucose-6-phosphate dehydrogenase (G6PD) or unknown G6PD status. Patients with a G6PD deficiency are at risk for serious complications, including hemolytic anemia, with the use of tafenoquine. All patients should be tested for G6PD deficiency before therapy begins. In the clinical studies, reduced hemoglobin concentrations were also reported in some G6PD-normal patients. (3) Tafenoquine is not recommended for use during pregnancy. Even if a pregnant woman has normal concentrations of G6PD, she could give birth to a G6PD-deficient infant who could be at risk for hemolytic anemia from exposure to tafenoquine through breast milk. If breastfeeding is being considered, the infant's G6PD status should be determined. (4) Contraindicated in breastfeeding women when the infant is found to be G6PD-deficient or the G6PD status is unknown and, in such situations, women should be advised not to breastfeed for 3 months after the dose of tafenoquine. (5) Monitor patients for methemoglobinemia, characterized by abnormal red blood cells and impaired oxygen delivery to the tissues, and initiate appropriate

therapy as indicated. (6) In patients with a history of psychiatric illness, the benefit of using the new agent must be weighed against the risk of psychiatric adverse events. Psychiatric adverse reactions such as anxiety, abnormal dreams, and insomnia have been reported with the use of tafenoquine, and some patients who were treated with higher-than-recommended doses of tafenoquine experienced psychosis or depression. Psychiatric adverse reactions may be delayed in onset or duration.

Adverse reactions: dizziness, nausea, vomiting, headache, decreased hemoglobin

Supplied as: 150 mg oral tablets

Dosage: a single 300 mg dose, administered as two 150 mg tablets taken with food. Tafenoquine (Krintafel) should be coadministered on the first or second day of appropriate antimalarial therapy for acute *P. vivax* malaria.

Nursing considerations: (1) Administer tafenoquine with food. Tell patients to swallow the tablets whole. If vomiting occurs within 1 hour after administration, a repeat dose should be given, but redosing should not be attempted more than once. (2) Teach patients to recognize and report signs and symptoms of hemolytic anemia, such as darkening of the lips or urine, dizziness, confusion, and shortness of breath. (3) Tell women of reproductive potential to avoid pregnancy and to use effective contraception for 3 months after taking the tafenoquine dose. (4) Teach patients to recognize and report possible signs and symptoms of elevations in blood methemoglobin, such as darkening of the urine, nail beds, lips, or the inside of the mouth. (5) Advise patients to report any new or worsening psychiatric symptoms. ■

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