CE 2.0 CONTACT HOURS

Rx 2.0 CONTACT HOURS

Abstract: This article highlights important prescribing information for some drugs that received FDA approval within the past year. These include: atazanavir and cobicistat (Evotaz®), ceftazidime and avibactam (Avycaz®), edoxaban (Savaysa®), ivabradine (Corlanor®), liraglutide (rDNA origin) injection (Saxenda®), perindopril arginine and amlodipine besylate (Prestalia®), and secukinumab (Cosentyx®) subcutaneous injection.

By Olga M. Klibanov, PharmD, BCPS; Diep Phan; and Kelli Ferguson

▼ HIV-1 infection

Atazanavir and cobicistat (Evotaz)

Atazanavir is a protease inhibitor (PI) that has been coformulated with cobicistat under the brand name Evotaz. Evotaz was approved by the FDA on January 29, 2015 for treating adults with HIV-1 infection.[1] Evotaz is currently listed as an alternative option for treatment-naive HIV-infected patients in the Department of Health and Human Services (DHHS) treatment guidelines.[2] Evotaz is manufactured by Bristol-Myers Squibb, Inc.

Indications

Evotaz fixed-dose tablet contains 300 mg of atazanavir and 150 mg of cobicistat. It is indicated for use in combination with other antiretroviral agents for the treatment of HIV-1 infection. Evotaz can be used in treatment-naive or -experienced patients; however, the use of this drug in the treatment-experienced population should be guided by

Keywords: atazanavir and cobicistat (Evotaz®), ceftazidime and avibactam (Avycaz®), edoxaban (Savaysa®), ivabradine (Corlanor®), liraglutide (rDNA origin) injection (Saxenda®), perindopril arginine and amlodipine besylate (Prestalia®), secukinumab (Cosentyx®) subcutaneous injection

antiretroviral resistance testing and the type of mutations the patient's virus contains.

Mechanism of action

Evotaz is a fixed-dose combination of atazanavir and cobicistat. Atazanavir is an azapeptide inhibitor of the HIV-1 protease, which subsequently prevents formation of mature virions in HIV-infected cells. Similar to other HIV protease inhibitors, atazanavir is metabolized rapidly primarily by P450 CYP 3A enzymes in the liver and intestine. Cobicistat is a potent and selective inhibitor of P450 CYP3A enzymes that prevents atazanavir metabolism. Therefore, the combination of cobicistat and atazanavir results in higher atazanavir plasma concentrations.[3]

Dosing and administration

Evotaz is a fixed-dose combination tablet containing 300 mg of atazanavir and 150 mg of cobicistat. The recommend dose of Evotaz for treatment-naive and -experienced patients is one tablet once daily given with food. Evotaz should be used in combination with other antiretroviral agents.[3]

Contraindications

The use of Evotaz is contraindicated in patients with previously known severe hypersensitivity (such as Stevens Johnson syndrome, erythema multiforme, or toxic skin eruptions) to atazanavir, cobicistat, or any of the excipients. It is contraindicated to use Evotaz with drugs that are highly dependent on CYP3A or UGT1A1 for clearance or with drugs that strongly induce CYP3A. The product label should be consulted for a detailed list of the drugs that are contraindicated with Evotaz.[3]

Warnings and precautions

Severe skin hypersensitivity reactions, such as Stevens-Johnson syndrome, toxic skin eruptions, and erythema multiforme, have been reported in atazanavir clinical trials. Evotaz should be discontinued if severe rash occurs. Nephrolithiasis and/or cholelithiasis, hyperbilirubinemia, new-onset diabetes mellitus, hyperglycemia, hemophilia, and immune reconstitution syndrome have also been reported in Evotaz-treated patients.[3]

Conduction abnormalities have been reported with atazanavir, including prolongation of the PR interval and atrioventricular (AV) block. ECG monitoring should be considered for patients with pre-existing cardiac conduction conditions. If patients have a creatinine clearance (CrCl) less than 70 mL/min, Evotaz, when used in combination with tenofovir, should not be initiated. If Evotaz is given together with tenofovir, careful monitoring of renal function is recommended.

Adverse reactions

The combination of atazanavir and cobicistat has been studied in phase II and III trials.[4,5] In a pooled analysis of 771 patients who received either atazanavir with cobicistat and emtricitabine/tenofovir (n = 394) or atazanavir boosted with ritonavir and emtricitabine/tenofovir (n = 377), the most common adverse reactions (reported in greater than 10% of patients during clinical trials) included jaundice, ocular icterus, nausea, and diarrhea. The incidence of these adverse events was similar whether the patients received cobicistat- or ritonavir-boosted atazanavir. Approximately 7% discontinued the study drug due to adverse events in both groups.[3-5]

The use of Evotaz is contraindicated in patients with previously known severe hypersensitivity.

Pharmacokinetics

Both components of Evotaz, atazanavir and cobicistat, are rapidly absorbed, with a Tmax of approximately 3 hours. Atazanavir is 86% bound to human serum proteins, whereas cobicistat is 97% to 98% bound to human plasma proteins. Atazanavir and cobicistat are both predominantly metabolized by CYP3A enzyme system. Both compounds are mainly excreted in the feces, with the half-lives of approximately 7.5 hours for atazanavir and 3 to 4 hours for cobicistat.[3]

Clinical pearls

- Concomitant use of Evotaz and tenofovir in patients with CrCl less than 70 mL/min is not recommended.
- Evotaz is pregnancy category B and should only be used if the benefits outweigh the risks.
- Mothers who are HIV positive should not breastfeed, regardless of what antiretroviral therapy (ART) they are taking, to avoid the risk of postnatal HIV transmission.

REFERENCES

1. Bristol-Myers Squibb. 2015. http://news.bms.com/press-release/financial-news/us-food-and-drug-administration-approves-bristol-myers-squibbs-evotaz-a.
2. Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2015. http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultandadolescentgl.pdf.
3. EVOTAZ [package insert]. Princeton, NJ: Bristol-Myers Squibb; 2015.
4. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. *J Infect Dis.* 2013;208(1):32-39.
5. Elion R, Cohen C, Gathe J, et al. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir df in the initial treatment of HIV infection. *AIDS.* 2011;25(15):1881-1886.

▼ Infectious disease

Ceftazidime and avibactam (Avycaz)

Ceftazidime is a third-generation cephalosporin that exhibits its activity against Gram-positive cocci and Gram-negative bacilli, including *Pseudomonas aeruginosa*.[1] The use of cephalosporins antibacterial drugs against Gram-negative bacilli has been compromised by the production of bacterial beta-lactamases.[2,3] Based on a recent report from Europe and the United States, in many North America hospitals, more than 10% of *Escherichia coli* isolates from intra-abdominal infections and urinary tract infections currently are resistant to ceftazidime.[4]

Avycaz, a combination of ceftazidime and avibactam, was developed with the intention of inhibiting beta-lactamases activity against ceftazidime and enhancing ceftazidime's antibacterial activity. It was approved by the FDA on February 25, 2015.[5] This drug is manufactured by GlaxoSmithKline Manufacturing and is distributed by Forest Pharmaceuticals, Inc.[6]

Indications

Avycaz is indicated for patients older than 18, for the treatment of complicated intra-abdominal infections (cIAIs) and used in combination with metronidazole for complicated urinary tract infections (cUTIs), including pyelonephritis. Avycaz should not be used as first-line treatment and should be reserved for patients with limited alternative treatment options.[6]

Mechanism of action

Avycaz is a combination of ceftazidime (a third-generation cephalosporin antibacterial drug) and avibactam (a beta-lactamase inhibitor). Ceftazidime exhibits its antibacterial activity by inhibiting bacterial membrane synthesis by binding to penicillin-binding protein. Ceftazidime is degraded by certain beta-lactamases. As a beta-lactamase inhibitor, avibactam protects ceftazidime from being degraded without decreasing ceftazidime's antibacterial activity.[6]

Dosing and administration

Avycaz for injection, packaged as a white to yellow sterile powder in a single-use vial, contains 2 g of ceftazidime and 0.5 g of avibactam. The recommended dosage of Avycaz is 2.5 g (2 g ceftazidime and 0.5 g avibactam) administered via I.V. every 8 hours, infused over 2 hours. The recommended duration of treatment for cIAIs is 5 to 14 days and 7 to 14 days for cUTIs. Avycaz's dosage should be adjusted in patients with kidney dysfunction.[6]

Contraindications

Avycaz is contraindicated in patients with previous severe hypersensitivity to Avycaz, avibactam, ceftazidime, or other agents in the cephalosporin class.

Warnings and precautions

A clinical trial found that patients with baseline creatinine clearance of 30 to 50 mL/min have a decreased clinical response to Avycaz; therefore, CrCl should be monitored at least daily in patients with changing renal function, and the dose of Avycaz should be adjusted appropriately.

Similar to other systemic antibacterial drugs, *Clostridium difficile*-associated diarrhea has been reported in Avycaz-treated patients. Patients receiving ceftazidime have also reported central nervous system adverse reactions, such as seizures, encephalopathy, coma, myoclonia, or asterixis. Patients with kidney dysfunction are more susceptible to these adverse reactions; therefore, the dose of Avycaz should be adjusted appropriately based on CrCl.[6] As with any other antimicrobial agent, resistance to Avycaz can develop if the drug is not used appropriately; therefore, it should only be prescribed for confirmed or suspected bacterial infections.[6]

Adverse reactions

Two phase II trials (where Avycaz was administered to 169 patients) found that nausea and vomiting were the most common adverse reactions (occurring in 10% or greater of patients) in patients treated for cIAIs and constipation and anxiety in patients being treated for cUTIs. Severe adverse reactions reported included skin and subcutaneous tissue disorders.[6-8]

Pharmacokinetics

Since Avycaz is only available as an intravenous formulation, its absorption is immediate. The components of this agent do not accumulate with repeated dosing. Both components of Avycaz, ceftazidime and avibactam, are minimally bound (less than 10%) to proteins in the plasma. Both components are minimally metabolized, and both are eliminated as mostly unchanged drugs by the kidneys, resulting in excellent therapeutic drug concentrations in the urine.[6]

Clinical pearls

- To reduce the development of drug-resistant bacteria, Avycaz should be de-escalated when culture and susceptibility information are available.
- Both ceftazidime and avibactam are dialyzable; hence, Avycaz should be administered after hemodialysis on hemodialysis days.
- Renal function should be monitored carefully when using Avycaz, and the dose of Avycaz should be adjusted accordingly based on CrCl.

- Avycaz is pregnancy category B and should only be used if the potential benefit to the woman outweighs the potential risks to the fetus.

REFERENCES

1. Lagacé-Wiens P, Walkty A, Karlowsky JA. Ceftazidime-avibactam: an evidence-based review of its pharmacology and potential use in the treatment of Gram-negative bacterial infections. *Core Evid.* 2014;9:13-25.
2. Pitout JD. Infections with extended-spectrum beta-lactamase-producing enterobacteriaceae: changing epidemiology and drug treatment choices. *Drugs.* 2010;70(3):313–333.
3. Bush K. Alarming beta-lactamase-mediated resistance in multidrug-resistant Enterobacteriaceae. *Curr Opin Microbiol.* 2010;13(5):558-564.
4. Hawser SP, Badal RE, Bouchillon SK, Hoban DJ. Trending eight years of in vitro activity of ertapenem and comparators against *Escherichia coli* from intra-abdominal infections in North America—SMART 2002-2009. *J Chemother.* 2011;23(5):266-272.
5. U.S. Food and Drug Administration (FDA). 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435629.htm.
6. AVYCAZ [package insert]. Verona, Italy: GlaxoSmithKline; 2015.
7. Lucasti C, Popescu I, Ramesh MK, Lipka J, Sable C. Comparative study of the efficacy and safety of ceftazidime/avibactam plus metronidazole versus meropenem in the treatment of complicated intra-abdominal infections in hospitalized adults: results of a randomized, double-blind, Phase II trial. *J Antimicrob Chemother.* 2013;68(5):1183-1192.
8. Vazquez JA, González Patzán LD, Stricklin D, et al. Efficacy and safety of ceftazidime-avibactam versus imipenem-cilastatin in the treatment of complicated urinary tract infections, including acute pyelonephritis, in hospitalized adults: results of a prospective, investigator-blinded, randomized study. *Curr Med Res Opin.* 2012;28(12):1921-1931.

▼ Anticoagulation

Edoxaban (Savaysa)

Venous thromboembolism (VTE) is a serious condition in which imbalance of clotting factors and endogenous anticoagulants results in thrombosis. VTE leads to many long-term complications, and untreated VTE is often fatal. Current prevention and treatment options for VTE include parenteral and oral anticoagulants.

Atrial fibrillation (AF) is the most common cardiac dysrhythmia, with an increased prevalence in older adults.[1] Patients with AF are at a higher risk for stroke and the risk increases significantly with advancing age.[2] Long-term anticoagulation therapy is the primary method for reducing the risk of stroke in patients with AF.

Savaysa was approved by the U.S. FDA on January 8, 2015 to reduce the risk of stroke and systemic embolism in patients with AF that is not caused by heart valve problems.[3] It is manufactured by Daiichi Sankyo Co., Ltd.

Indications

Savaysa is used to treat deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant. Savaysa is also indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF).[4]

Mechanism of action

Savaysa is a highly selective, direct inhibitor of factor Xa. Factor Xa is a key element in the coagulation pathway. Under normal physiology, successfully activated coagulation factors in both intrinsic and extrinsic pathways activate factor Xa to generate thrombin and fibrin, and subsequently, produce a fibrin clot. Savaysa leads to a halt in fibrin clots by inhibiting factor Xa.[4]

Dosing and administration

Savaysa tablets are available in three dosage strengths: 60 mg, 30 mg, and 15 mg. The dosing of Savaysa varies depending on the indication, kidney function, and concomitant use of P-gp inhibitors as described in the product label. The use of Savaysa in patient with CrCl greater than 95 mL/min should be avoided due to increased risk of ischemic stroke at the higher dose of 60 mg/day compared with warfarin.[4]

To transition patients to and from Savaysa, an algorithm (outlined in the product label) describing the timing and dosing of the anticoagulants should be used.[4]

Contraindications

Savaysa is contraindicated in patients with active pathologic bleeding.

Warnings and precautions

The efficacy of Savaysa is reduced in patients who have NVAF with CrCl greater than 95 mL/min, while the rate of ischemic stroke is increased (compared with patients treated with warfarin); therefore, the use of Savaysa for the treatment of NVAF should be avoided in patients with CrCl greater than 95 mL/min.

Premature discontinuation of Savaysa without adequate alternative anticoagulation results in increased risk of ischemic events. If Savaysa is discontinued due to contraindications, clinicians should consider another anticoagulant using the transition guidance discussed in the product label.

There is a risk of development of epidural or spinal hematoma if patients who are treated with antithrombotic drugs are given spinal or epidural anesthesia. This can result in long-term or permanent paralysis. Therefore, the last dose of Savaysa should be at least 12 hours prior to the removal of indwelling epidural or intrathecal catheters, and at least 2 hours must pass after their removal before Savaysa can be given again.

This drug has not been adequately studied in patients with mechanical heart valves or moderate to severe mitral stenosis and should not be used in these patients.

Savaysa is associated with increased risk of bleeding and can lead to serious and fatal bleeding. Signs or symptoms of blood loss should be monitored closely.[4]

Adverse reactions

Savaysa has been studied in large phase III landmark studies in over 18,000 patients.[4-6] The most common adverse reactions associated with the use of Savaysa for the treatment of NVAF include bleeding and anemia.[4,5] For the treatment of DVT and PE, the most common adverse reactions associated with the use of Savaysa include bleeding, rash, abnormal liver function tests, and anemia.[4,6]

Pharmacokinetics

Approximately 62% of Savaysa is systemically absorbed, with peak plasma levels achieved within 1 to 2 hours and steady-state achieved within 3 days. The drug is widely distributed into tissues, with minimal accumulation when given once daily. It is minimally metabolized, with the main pathways being hydrolysis, conjugation, and oxidation by CYP3A4. Savaysa is predominantly excreted as unchanged drug in the urine, with the half-life of 10 to 14 hours.[4]

Clinical pearls

- Savaysa is a pregnancy category C drug and should only be used if the potential benefits outweigh the risks.
- Savaysa can be taken with or without food.
- Patients should be advised to report unexplained bruises and to call or seek medical help immediately if they experience severe bleeding that cannot be controlled.

REFERENCES

1. Fuster V, Rydén LE, Cannom DS, et al. ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation.* 2011;123(10):e269-e367.
2. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22(8):983-988.
3. U.S. Food and Drug Administration (FDA). 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm429523.htm.
4. SAVAYSA [package insert]. Parsippany, NJ: Daiichi Sankyo; 2015.
5. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013;369(22):2093-2104.
6. Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.

▼ Heart failure

Ivabradine (Corlanor)

More than 650,000 new cases of heart failure are diagnosed annually, and the incidence continues to increase with age. Heart failure is diagnosed in more than one million hospitalizations each year and correlates with a 25% readmission rate within 1 month.[1]

Corlanor is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalizations for patients with worsening heart failure who already have chronic heart failure.[2] It was approved by the FDA on April 15, 2015 and is manufactured by Amgen Inc.[3]

Indications

Corlanor is indicated in patients with heart failure to reduce the risk of hospitalization due to worsening heart failure. Patients must meet several criteria in order to qualify for therapeutic intervention with Corlanor. Patients must have stable, symptomatic chronic heart failure with left ventricular ejection fraction 35% or less. Patients must also be in normal sinus rhythm with a measured resting heart rate 70 beats/minute or greater. In addition, patients must be taking maximally tolerated doses of a beta-blocker or have a contraindication to the use of beta-blockers.[2]

Mechanism of action

Corlanor works to reduce the spontaneous pacemaker activity of the cardiac sinus node by blocking the hyperpolarization-activated cyclic nucleotide-gated channel, which controls the cardiac pacemaker I_f current. The I_f current regulates heart rate. As a result, Corlanor selectively inhibits the I_f current. Thus, heart rate is reduced without any effect on ventricular repolarization or myocardial contractility.[2]

Corlanor has the potential to also inhibit the retinal current (I_h). I_h limits retinal responses to any stimulus of bright light. The inhibition of I_h by Corlanor may likely cause the luminous phenomena, otherwise known as phosphenes, experienced by patients. This phenomena is described as an enhanced brightness in a limited area of a patient's field of vision.[2]

Dosing and administration

The starting dose of Corlanor is 5 mg twice daily with meals. Patients with a history of conduction defects or bradycardia with the potential for hemodynamic instability should be initiated at 2.5 mg twice daily (50% of the normal starting dose). Patients should be assessed after 2 weeks, and if needed, dose adjustments should be made to achieve a resting heart rate between 50 and 60 beats/minute. Appropriate dosing changes based upon measured heart rates are outlined in the product label. The maximum dose of Corlanor is 7.5 mg twice daily.[2]

Contraindications

Corlanor is contraindicated in patients with the following characteristics:

- Acute decompensated heart failure
- BP less than 90/50 mm Hg
- Sick sinus syndrome, sinoatrial block, or third-degree

AV block unless the patient has a functioning demand pacemaker
- Resting heart rate less than 60 beats/minute prior to treatment
- Severe hepatic impairment
- Pacemaker dependence, such that the heart rate is maintained exclusively by the pacemaker
- Concomitant use of strong CYP3A4 (cytochrome P450 3A4) inhibitors

Warnings and precautions

Corlanor has been shown to cause fetal toxicity in animals; therefore, females taking Corlanor should be advised to use an effective form of contraception while on this medication.[2]

Corlanor can increase the risk of atrial fibrillation. In the landmark trial with Corlanor (the SHIFT trial), the rate of atrial fibrillation in patients treated with Corlanor was 5% per patient-year in comparison to 3.9% per patient-year in patients treated with placebo. Cardiac rhythm should be regularly monitored in patients taking Corlanor, and it should be discontinued if atrial fibrillation develops.[2,4]

Corlanor has been associated with bradycardia, sinus arrest, and heart block in the landmark SHIFT trial.[4] The use of verapamil or diltiazem with Corlanor can increase the exposure of Corlanor and can also lead to a lower heart rate; therefore, this combination should be avoided. Corlanor should also be avoided in patients with a second-degree AV block unless the patient has a functioning demand pacemaker.[2]

Adverse reactions

Significant adverse reactions of Corlanor include fetal toxicity, atrial fibrillation, and bradycardia with conduction disturbances. Another common adverse reaction of Corlanor is a type of visual disturbance known as phosphenes. Phosphenes are a luminous phenomena often described as enhanced brightness in a limited area of the visual field, halos, kaleidoscopic effects, colored bright lights, or multiple images of sight. This effect is typically triggered by sudden changes in light intensity, causing brightness in a patient's field of vision. Corlanor has an effect on retinal photoreceptors and may cause phosphenes, which generally appear within the first 2 months of treatment and may resolve during or after treatment.[2]

Adverse reactions noted in postmarketing experience with Corlanor include syncope, hypotension, angioedema, erythema, rash, pruritus, urticarial, vertigo, diplopia, and visual impairment.[2]

Pharmacokinetics

Corlanor undergoes extensive first-pass metabolism in the liver and gut, which is why only 40% of the drug is systemically absorbed after oral administration, with peak plasma levels being achieved within 1 hour when the drug is taken on an empty stomach. It is recommended that Corlanor be taken with meals, which increases its systemic exposure by 20% to 40% and also delays its absorption by approximately 1 hour. It is well distributed into bodily tissues and is approximately 70% bound to plasma proteins. Oxidation via the liver and intestinal CYP3A4 enzyme system is the main metabolic pathway for Corlanor, which results in production of the active metabolite (S 18982) of Corlanor. This metabolite is also further metabolized by the CYP3A4 system. Since Corlanor is extensively metabolized, only 4% of the oral dose is excreted unchanged in the urine. The metabolites are eliminated via feces and urine. The half-life of the drug is approximately 6 to 8 hours.[2]

Clinical pearls

- Corlanor may cause fetal harm when administered to a pregnant woman and the patient should be advised on the potential risk. Females of reproductive age should use contraception.
- Corlanor has only been studied in a limited number of patients 75 years old and older; however, no differences in safety and efficacy have been observed in the older adults (65 years and older) in comparison to the general population.
- No dose adjustment is needed for patients with mild or moderate hepatic impairment. Corlanor is contraindicated in patients with severe hepatic impairment due to an expected increased systemic exposure.
- No dose adjustment is needed for patients with a creatinine clearance between 15 and 60 mL/min. There are no data available for patients with a creatinine clearance less than 15 mL/min.

REFERENCES

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation*. 2013;128(16):e240-e327. http://circ.ahajournals.org/content/128/16/e240.full.pdf+html.
2. CORLANOR [package insert]. Thousand Oaks, CA: Amgen, Inc.; 2015.
3. U.S. Food and Drug Administration (FDA). 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm442978.htm.
4. Swedberg K, Komajda M, Böhm M, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. *Lancet*. 2010;376(9744):875-885.

▼ Obesity

Liraglutide (rDNA origin) injection (Saxenda)

More than one-third of adults in the United States are obese.[1] Saxenda was approved by the U.S. FDA on December 23, 2014 to be used in combination with a healthy lifestyle to manage

chronic obesity. Liraglutide is also the active ingredient in Victoza, but the drugs are supplied in different dosages. Unlike Victoza, Saxenda is not approved for the management of type 2 diabetes mellitus, as there are not yet enough data for this indication.[2]

Indications

Saxenda is indicated as an adjunct to nonpharmacologic measurements for chronic weight management in adult patients who have initial body mass index of 30 or greater or 27 or greater with at least one weight-related comorbid condition, such as hypertension, type 2 diabetes mellitus, or dyslipidemia. Saxenda is not indicated for type 2 diabetes mellitus treatment.[3]

Mechanism of action

Saxenda is a glucagon-like peptide-1 (GLP-1) receptor agonist. GLP-1 is a gut-derived hormone that regulates appetite and calorie intake by the activation of GLP-1 receptors in the brain.[4] Similar to endogenous GLP-1, Saxenda induces weight loss by activating the GLP-1 receptors to increase satiety and decrease calorie intake.[3]

Dosing and administration

The target dose of Saxenda is 3 mg daily. Due to gastrointestinal adverse reactions, a titration schedule of Saxenda should be followed as outlined in the product label.[3] Saxenda should be administered once daily regardless of time of day or timing of meals. Saxenda can be administered subcutaneously in the abdomen, upper arm, or thigh.[3] If a dose is missed, the prescribed regimen should be resumed with the next scheduled dose. If more than three doses are missed, patients should reinitiate Saxenda and follow the dose escalation schedule described in the product label.[3]

Contraindications

Saxenda is contraindicated in patients with a personal or family history of medullary thyroid carcinoma, patients with multiple endocrine neoplasia syndrome type 2 (MEN 2), patients with a history of a serious hypersensitivity reaction to liraglutide or to any of the drug components, and women who are pregnant. Saxenda is pregnancy category X drug.[3]

Warnings and precautions

Postmarketing reports have noted cases of acute pancreatitis in patients who initiated liraglutide. Careful monitoring for signs and symptoms of pancreatitis is recommended. Saxenda should be promptly discontinued if pancreatitis is suspected and should not be restarted if it is confirmed.

A higher incidence of gallbladder disease (cholelithiasis and cholecystitis) was also seen in patients who received Saxenda in clinical trials compared to placebo. If suspected, appropriate clinical work-up and monitoring is recommended.

Using Saxenda together with antidiabetic agents can increase the risk of serious hypoglycemia. Close glucose monitoring and adjustments of antidiabetic medications should be implemented in these cases.

In clinical trials with Saxenda, an increase in resting heart rate was seen with this drug. The clinical significance of this effect is not well understood, but heart rate should be monitored on a regular basis, as part of typical medical care.

Serious hypersensitivity reactions, including angioedema, have been reported in patients treated with GLP-1 receptor agonists. Saxenda should be used cautiously if the patient has previously experienced angioedema with this class of drugs, as the risk of cross-sensitivity with Saxenda is not known.

Suicidal ideation and attempt was reported in 0.2% of patients treated with Saxenda in clinical studies and in none of the patients treated with placebo. New or worsening signs/symptoms of mental illness (depression, unusual changes in mood or behavior, or suicidal thoughts) should be monitored in patients on this drug, and it should be avoided in those who have a history of suicidal ideation and/or attempts.

Reports of acute kidney failure as well as worsening chronic kidney disease with Saxenda have occurred. Saxenda should be used with caution in patients with renal and hepatic impairment.[3]

Adverse reactions

Saxenda was studied in eight large clinical trials, with various add-on insulin medications. The most common adverse reactions reported in these studies were: nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decreased appetite, dyspepsia, fatigue, dizziness, abdominal pain, and increased lipase. Serious adverse reactions include risk of thyroid C-cell tumors, acute pancreatitis, acute gallbladder disease, and suicidal behaviors.[3,4]

Pharmacokinetics

Approximately 55% of Saxenda is systemically absorbed after subcutaneous administration, with a Tmax of 11 hours post dose. The drug has a low volume of distribution and is greater than 98% bound to plasma proteins. After administration, the drug is metabolized endogenously, similar to large proteins, without any involvement from hepatic or renal metabolism systems. The elimination half-life of Saxenda is approximately 13 hours, which is the reason it is given once daily. Less than 6% of the drug is excreted in the urine and feces as related metabolites; unchanged drug is not detected in the urine or feces.[3]

Clinical pearls

- Saxenda should be administered once daily regardless of time of day or timing of meals.
- Saxenda is not indicated for the treatment of type 2 diabetes mellitus.
- The change in body weight should be evaluated 16 weeks after initiating Saxenda. If the patient has not lost at least 4% of baseline body weight, discontinuation of Saxenda is warranted.
- Saxenda is pregnancy category X.

REFERENCES

1. Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation.* 2014;129(25 suppl 2):S102-S138. http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437739.71477.ee
2. U.S. Food and Drug Administration (FDA). 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm427913.htm.
3. SAXENDA [package insert]. Plainsboro, NJ: Novo Nordisk A/S; 2014.
4. Scott LJ. Liraglutide: a review of its use in adult patients with Type 2 diabetes mellitus. *Drugs.* 2014;74(18):2161-2174.

▼ Hypertension

Perindopril arginine and amlodipine besylate (Prestalia)

According to the JNC-8 guidelines on hypertension, individuals age 60 years and older should be treated to a BP goal of less than 150/90 mm Hg. Individuals less than 60 years old, those with diabetes mellitus, or chronic kidney disease should be treated to a BP goal of less than 140/90.[1,2]

Prestalia is a single-pill combination containing an angiotensin-converting enzyme (ACE) inhibitor perindopril and a dihydropyridine calcium channel blocker amlodipine. It was approved by the FDA on January 26, 2015 for treating hypertension.[3]

Indications

Prestalia is indicated for the treatment of hypertension to lower BP. It may be used in patients whose BP is not controlled using monotherapy as the treatment intervention as well as initial drug therapy in patients who may need multiple drugs to achieve desired BP goals.[4]

Mechanism of action

Perindopril is an ACE inhibitor that acts through the renin-angiotensin-aldosterone system to reduce BP. Amlodipine is a dihydropyridine calcium channel blocker that inhibits the influx of calcium ions into vascular smooth muscle and cardiac muscle.[4]

Dosing and administration

The starting dose of Prestalia is 3.5 mg of perindopril and 2.5 mg of amlodipine (Prestalia 3.5/2.5 mg) once daily with or without food. Dosing should be adjusted according to individual BP goals with a 7- to 14-day treatment period before titrating doses. Dosing of Prestalia should not exceed 14 mg of perindopril and 10 mg of amlodipine (Prestalia 14/10 mg) once daily.[4]

Contraindications

Prestalia is contraindicated in patients with hereditary or idiopathic angioedema, those who are hypersensitive to perindopril or any other ACE inhibitors, and patients who are hypersensitive to amlodipine. Concomitant administration of aliskiren with any ACE inhibitors (including Prestalia) in patients with diabetes mellitus is contraindicated.

Warnings and precautions

Prestalia is a pregnancy category D drug. Fetal kidney function is reduced during the second and third trimester of pregnancy. In addition, the risk of fetal and neonatal morbidity and death increases.

ACE inhibitors (including perindopril) can cause angioedema of the face, extremities, lips, tongue, glottis, and larynx. The drug should be discontinued, and the patient should be observed until the swelling disappears. If needed, appropriate therapy with subcutaneous epinephrine should be administered.

Prestalia increases the risk of worsening angina and acute myocardial infarction, especially in patients with severe obstructive coronary artery disease. The drug may also cause symptomatic hypotension. ACE inhibitors, including Prestalia, are associated with elevations in serum potassium. Serum potassium levels should be monitored in patients taking Prestalia.[4]

ACE inhibitors may cause a nonproductive cough. Discontinuation of therapy should be considered if a cough develops.

Patients taking Prestalia may experience changes in kidney function, including acute kidney failure. Renal function should be monitored in patients on Prestalia. If a decrease in kidney function is noted, Prestalia should be withheld or discontinued.[4]

Adverse reactions

The Perindopril Amlodipine for the treatment of hypertension (PATH) trial studied Prestalia in 837 patients with hypertension. The most common adverse reactions that occurred in at least 2% of patients who were treated with Prestalia included peripheral edema, cough, headache, and dizziness. The most common reason Prestalia was discontinued was

due to peripheral edema. Other adverse reactions associated with Prestalia included rash and diarrhea.[4]

Pharmacokinetics

After oral administration, the components of Prestalia, perindopril, and amlodipine reach peak concentrations at different time frames (1 hour for perindopril, 4 hours for the active metabolite perindoprilat, and 6 to 12 hours for amlodipine). Food does not affect absorption of the components of Prestalia. The perindopril component of Prestalia is extensively metabolized via hydrolysis, glucuronidation, and cyclization via dehydration, resulting in 6 metabolites, including the active metabolite perindoprilat. The amlodipine component is extensively metabolized in the liver to inactive metabolites. Approximately 4% to 12% and 10% of perindopril and amlodipine, respectively, are excreted in the urine as unchanged drugs. The terminal half-life of perindoprilat is approximately 100 hours, whereas it is approximately 30 to 50 hours for amlodipine.[4]

Clinical pearls

- Pregnant women in their second and third trimester should not take Prestalia.
- Prestalia is a pregnancy category D drug.
- Prestalia is not recommended as a treatment option for patients over the age of 65.
- Prestalia is not recommended as a treatment option for patients with a creatinine clearance less than 60 mL/min.

REFERENCES

1. James PA, Oparil S, Carter BL, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520.
2. U.S. Food and Drug Administration. High Blood Pressure (Hypertension). 2015. www.fda.gov/forconsumers/byaudience/forwomen/ucm118529.htm.
3. Drugs.com FDA Alerts. 2015. www.drugs.com/newdrugs/fda-approves-prestalia-amlodipine-perindopril-hypertension-4150.html.
4. PRESTALIA [package insert]. Cincinnati, OH: Symplmed Pharmaceuticals, Inc.; 2015.

▼ Psoriasis

Secukinumab (Cosentyx) subcutaneous injection

Plaque psoriasis is a chronic inflammatory skin disease that affects approximately 3% of the population.[1] Psoriasis leads to significant implications of quality of life and is commonly associated with multiple comorbidities, such as psoriatic arthritis, inflammatory bowel diseases, and metabolic disorders. Cytokine interleukin (IL)-17A plays a key role in the pathogenesis of psoriasis.[2] Cosentyx is an antagonist of IL-17A and was approved by the U.S. FDA on January 21, 2015 as an additional treatment for plaque psoriasis.[3]

Indications

Cosentyx is approved to treat moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.[4]

Mechanism of action

Cosentyx is a human IgG1 monoclonal antibody, a first-in-class agent that selectively binds to and inhibits IL-17A. IL-17A is a naturally occurring cytokine that is involved in inflammatory and immune responses.[2,4] The level of IL-17A is significantly higher in lesional skin compared with nonlesional skin of plaque psoriasis patients. Cosentyx treats plaque psoriasis by inhibiting the release of proinflammatory cytokines and chemokines.[4]

Dosing and administration

The recommended dose of Cosentyx is 300 mg, injected subcutaneously at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks.[4]

Contraindications

Cosentyx is contraindicated in patients with a history of severe hypersensitivity reaction to Cosentyx or to any of the excipients.

Warnings and precautions

Because Cosentyx modulates the body's immune system, it may increase the risk of infections. Therefore, Cosentyx should be used cautiously in patients with a chronic infection or a history of recurrent infections.[4]

Administrating Cosentyx to patients with active tuberculosis (TB) infection is contraindicated. Patients with latent TB should receive treatment of latent TB prior to initiating Cosentyx therapy.

Since exacerbations of Crohn disease were reported during clinical trials, Cosentyx should be used with cautions in patients with active Crohn disease.

Anaphylaxis and cases of urticaria were also reported in the clinical trials; therefore, Cosentyx should be discontinued immediately if severe hypersensitivity reactions occur. In addition, the removable cap of the Cosentyx Sensoready pen and the Cosentyx prefilled syringe contains latex; therefore, the Cosentyx pen or prefilled syringe should not be handled by individuals with latex sensitivity.

Because Cosentyx may weaken the body's immune system, completion of recommended immunizations prior to

initiating Cosentyx therapy should be considered. Live vaccines are contraindicated in patients treated with Cosentyx.[4]

Adverse reactions

Cosentyx was studied in two pivotal phase III trials (FIXTURE and ERASURE) in over 2,000 patients with plaque psoriasis.[5] The most common adverse reactions reported during clinical trials included infections (upper respiratory tract infections were the most common), exacerbations of Crohn disease, and hypersensitivity reactions.[4,5]

Pharmacokinetics

After a subcutaneous dose of Cosentyx, approximately 55% to 77% is absorbed. Maximum concentrations are reached in the serum approximately 6 days after administration, and steady-state is typically achieved by week 24 with every 4 week dosing regimens. Within 1 and 2 weeks of a single 300 mg subcutaneous dose, drug concentrations in the interstitial fluid of lesional and non-lesional skin of plaque psoriasis are 27% to 40% of serum concentrations, indicating good penetration at the site of activity. The exact metabolic pathway of Cosentyx is not known, but is thought to be via catabolic pathways, similar to endogenous IgG. The half-life of Cosentyx is approximately 22 to 31 days.[4]

Clinical pearls

- Cosentyx is pregnancy category B and should only be used if the benefits to the mother outweigh the risks to the fetus.
- Tuberculosis infection should be evaluated prior to initiating Cosentyx therapy. Signs and symptoms of active TB infection should be monitored closely during and after treatment.
- It is important to counsel patients to seek medical help if signs or symptoms of an infection occur. NP

REFERENCES

1. Jacobson CC, Kumar S, Kimball AB. Latitude and psoriasis prevalence. *J Am Acad Dermatol.* 2011;65(4):870-873.
2. Gisondi P, Dalle Vedove C, Girolomoni G. Efficacy and safety of secukinumab in chronic plaque psoriasis and psoriatic arthritis therapy. *Dermatol Ther (Heidelb).* 2014;4(1):1-9.
3. U.S. Food and Drug Administration (FDA). 2015. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm430969.htm.
4. COSENTYX [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2015.
5. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis–results of two phase 3 trials. *N Engl J Med.* 2014;371(4):326-338.

Olga M. Klibanov is a professor of pharmacy, Wingate University, Wingate, N.C.

Diep Phan is a student at Wingate University, Wingate, N.C.

Kelli Ferguson is a student at Wingate University, Wingate, N.C.

The authors and planners have disclosed that they have no financial relationships related to this article.

DOI-10.1097/01.NPR.0000473071.26873.3c