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Rx 3.0 CONTACT HOURS

Abstract: This article highlights important prescribing information for new drugs approved by the FDA over the last year. These include albiglutide, apremilast, dapagliflozin, insulin human inhalation powder, riociguat, timothy grass pollen allergen extract, umeclidinium and vilanterol inhalation powder, and vorapaxar.

By Jeff Sigler, PharmD

▼ Diabetes mellitus

Albiglutide (Tanzeum)

Diabetes mellitus is an expensive disease in the United States in terms of economic impact and mortality. In 2012, 29.1 million Americans were diagnosed with diabetes, and 86 million Americans were diagnosed as prediabetic.[1] This accounts for 12.3% of all adults over 20 years of age with diabetes and 37% with prediabetes.[1] Over $176 billion is spent every year on direct costs in the treatment of diabetes, and $245 billion are spent on indirect costs.[1]

There are many available treatments for diabetes mellitus, and many have been shown to be successful. Albiglutide is a new GLP-1 agonist, which was approved by the FDA in April, 2014, for adjunct treatment of diabetes mellitus. It is available in 30 mg and 50 mg single-dose pens for subcutaneous injection. It is marketed by GlaxoSmith-Kline and Bristol-Myers Squibb under the trade name Tanzeum.

Indication

Albiglutide is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus in adults. It is not

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indicated as first-line therapy and is not indicated for treatment of type 1 diabetes or diabetic ketoacidosis.[2]

Mechanism of action

Albiglutide increases glucose-dependent insulin secretion by stimulation of GLP-1 receptors. It also delays gastric emptying, which may add to its effectiveness.[2]

Pharmacokinetics

Albiglutide is fused to human albumin, which is responsible for its long half-life of 5 days. Steady-state levels are reached about 4 to 5 weeks after continuous once-weekly dosing. Peak plasma levels after a single 30 mg dose were reached in 3 to 5 days. Metabolism most likely occurs via catabolization via proteolytic enzymes in the vascular endothelium.[2]

Dosing and administration

Albiglutide is given as a subcutaneous injection in the abdomen, thigh, or upper arm once weekly. Therapy should be started at 30 mg and increased to 50 mg if glycemic control is not satisfactory.[2]

Contraindications

Albiglutide is contraindicated in patients with multiple endocrine neoplasia syndrome type 2, in patients with a personal or family history of medullary thyroid carcinoma, and in patients with serious hypersensitivity to albiglutide or any of its components.[2]

Warnings and precautions

Albiglutide is not indicated in patients with type 1 diabetes mellitus, a history of pancreatitis, or in patients with severe gastrointestinal disease. It has not been studied in combination with prandial insulin. There are some reported cases of acute kidney failure in patients treated with GLP-1 receptor agonists.[2]

Adverse reactions

Acute pancreatitis and medullary thyroid carcinoma are potentially severe (although rare) adverse reactions with treatment. Most reported adverse reactions occurred only slightly more frequently in patients taking albiglutide versus those taking placebo. The exceptions were increased hypoglycemia, injection site reactions, and gastrointestinal distress.[2]

Drug interactions

Albiglutide causes a delay in gastric emptying; therefore, it may alter the absorption of orally administered medications. However, the results of clinical trials did not show an adverse reaction on orally administered medications.[2]

Clinical pearls

- Albiglutide is a pregnancy category C drug
- If a dose is missed within 3 days of the scheduled dosing regimen, administer the dose, and continue on the regular scheduled dosing regimen
  - If outside the 3-day window, skip the missed dose, and remain on the regular scheduled dosing regimen
- Patients should be told that each dose must be reconstituted per the manufacturer's directions and used within 8 hours of reconstitution

Albiglutide is given as a once-weekly subcutaneous injection.

- Patients should be educated on the proper administration of subcutaneous injections
- Patients should be monitored regularly for serum calcitonin levels
  - Elevated levels may be a sign of medullary thyroid carcinoma
- Patients should be educated about the signs and symptoms of acute pancreatitis (severe abdominal pain with or without vomiting) and told to contact their healthcare provider (HCP) if these occur
- Patients should be encouraged to stay well hydrated during treatment due to the risk of acute kidney failure.[2]

REFERENCES

1. National Diabetes Statistics Report, 2014. 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Tanzeum® [package insert]. Wilmington, DE: GlaxoSmithKline; 2014.

▼ Active psoriatic arthritis

Apremilast (Otezla)

Psoriatic arthritis (PsA) is characterized by chronic joint pain, stiffness, and swelling and can be described as being mild to severe. It is an arthritic condition that presents itself in patients who also suffer from psoriasis. Typically, periods of PsA symptom remission can occur around bouts of symptom flares. The overall incidence of PsA in the United States is estimated at 6 to 7 per 100,000 per year.[1] Peak incidence occurs in individuals between the ages of 30 to 55 years, and it affects men and women equally.[1] PsA occurs in approximately 30% of individuals presenting with psoriasis.[2]

Apremilast was approved by the FDA in March, 2014 for the treatment of PsA in adults. It is the first such oral medication indicated for the treatment of PsA. It is currently marketed under the trade name Otezla by Celgene Corporation and is available in 10 mg, 20 mg, and 30 mg tablets.

Indication

Apremilast is indicated for the treatment of adult patients with active PsA.[3] It is also approved for treatment of patients with moderate-to-severe plaque psoriasis who are eligible for phototherapy or systemic treatment.[3]

Apremilast is an inhibitor of PDE4 that increases intracellular cAMP levels.

Mechanism of action

Apremilast is an inhibitor of phosphodiesterase 4 (PDE4) that increases intracellular cAMP levels.[3] Although the exact mechanism of action of apremilast is unknown, clinical studies show significant improvement in arthritic symptoms versus placebo.[3]

Pharmacokinetics

Absolute oral bioavailability of apremilast is about 73%, and protein binding is moderate at 68%. Peak plasma levels are reached in about 2.5 hours. The primary method of metabolism is via the hepatic CYP3A4 system. The terminal elimination half-life is between 6 and 9 hours with excretion occurring through both the urine and feces.[3]

Dosing and administration

Since apremilast may cause unpleasant gastrointestinal distress at recommended doses, oral therapy should be titrated upward over a 5-day duration with maintenance dosing starting on day 6. Patients start with 10 mg in the morning on the first day and on day 2 to 5 take a morning and evening dose that is titrated until the recommended dose of 30 mg twice daily is reached.[3] The recommended dose in severe kidney impairment is 30 mg once daily.[3]

Contraindications

Apremilast is contraindicated in those with known hypersensitivity to apremilast or any of its formulation.[3]

Warnings and precautions

Treatment with apremilast increases the risk of depression. Significant weight loss (greater than 5%) has been shown to occur in a small number of patients, and regular patient weight monitoring should be performed.[3]

Adverse reactions

The most common adverse reactions include diarrhea, headache, and nausea, and these occur more frequently during the first few weeks of therapy. There is also an increased incidence of upper respiratory tract infections, vomiting, nasopharyngitis, and abdominal pain over placebo. The risk of developing or worsening depression and/or suicidal thoughts or behaviors are increased with apremilast.[3]

Drug interactions

Concomitant administration of apremilast with the strong CYP450 inducer, rifampin, decreased the effectiveness of apremilast; therefore, apremilast use with strong CYP450 inducers (such as rifampin, phenobarbital, carbamazepine, phenytoin) is not recommended.[3]

Clinical pearls

- Apremilast is a pregnancy category C medication
- Patients should have their weight monitored throughout therapy, and significant weight loss may warrant discontinuation of treatment
- Patients should be evaluated for depression or suicidal ideation before treatment and throughout therapy, as apremilast may cause or exacerbate depression or suicidal thoughts or behaviors
- Apremilast may be taken with or without food, and the drug should be swallowed whole and not chewed, split, or crushed.[3]

REFERENCES

1. Louie G. Psoriatic arthritis. 2014. http://www.hopkinsarthritis.org/arthritis-info/psoriatic-arthritis/.
2. Ibrahim G, Waxman R, Helliwell PS, et al. The prevalence of psoriatic arthritis in people with psoriasis. *Arthritis Rheum*. 2009;61(10):1373–1378.
3. Otezla® [package insert]. Summit, NJ: Celgene Corporation; 2014.

▼ Diabetes mellitus

Dapagliflozin (Farxiga)

Diabetes is a leading cause of amputations, kidney disease, and blindness, and is a contributing factor in stroke and myocardial infarction.[1]

Although there are many successful treatment options for diabetes, there is a relatively new class of drugs available for use, the sodium-glucose cotransporter 2 (SGLT2) inhibitors.[2] Drug treatment options up to now have focused on decreasing absorption of glucose from the GI tract,

improving glucose uptake in cells, promoting the natural release of insulin, or replacing insulin directly. The SGLT2 inhibitors work in the kidney by increasing the excretion of glucose in the urine.

Dapagliflozin is a new oral SGLT2 inhibitor, which was approved by the FDA for use in the treatment of diabetes in January, 2014. It is available in 5 mg and 10 mg oral tablets. It is currently marketed by AstraZeneca under the trade name Farxiga.

Indication

Dapagliflozin is indicated as an adjunct to diet and exercise for the treatment of type 2 diabetes mellitus in adults.[2] Dapagliflozin is not indicated for treatment of type 1 diabetes or diabetic ketoacidosis.[2]

Mechanism of action

Dapagliflozin inhibits sodium-glucose cotransporter 2 (SGLT2), an important mechanism in the reabsorption of filtered glucose from the renal tubular lumen. It also lowers the glucose renal threshold and increases glucose urinary excretion.[2]

Pharmacokinetics

Dapagliflozin is well absorbed orally and reaches maximum plasma levels in about 2 hours. Protein binding is significant (91%). Metabolism occurs via UGT1A9, and excretion occurs primarily through the kidneys. Terminal elimination half-life is about 13 hours.[2]

Dosing and administration

The recommended starting dose is 5 mg orally once per day given in the morning. Patients who tolerate this dose but do not achieve the desired therapeutic response may be increased to 10 mg orally once per day in the morning.[2]

Contraindications

Dapagliflozin is contraindicated in those with a history of serious hypersensitivity to the drug, in patients with severe kidney impairment, end-stage kidney disease, or those on dialysis.[2]

Warnings and precautions

Intravascular volume contraction may occur after use, and care should be taken when used in patients at risk for volume depletion.[2]

Adverse reactions

Although potentially severe adverse reactions are rare, they include kidney impairment, an increased risk of bladder cancer, and genital mycotic infections. Less severe adverse reactions include hypoglycemia, increased low density lipoprotein cholesterol, urinary tract infections, back pain, and increased urination.[2]

Drug interactions

Drug interactions are uncommon, include a possible increase in the plasma levels of bumetanide, and an increase in dapagliflozin when used with mefenamic acid.[2]

Clinical Pearls

- Dapagliflozin is a pregnancy category C drug
- It is important for patients to continue to follow their recommended diet, blood glucose testing, regular physical activity, and periodic A1c testing while on this medication

> ***Dapagliflozin reaches maximum plasma levels in about 2 hours.***

- If a dose is missed, patients should take it as soon as possible unless it is almost time for their next dose
  - In this case, they should skip the missed dose and continue with their regular dosing schedule.
- Instruct female patients to inform their HCP immediately if they become pregnant or if they are breastfeeding
- Educate patients on the signs and symptoms of hypotension and urinary tract infections, including yeast infections, and inform their HCP if any of these symptoms occur.[2]

REFERENCES

1. National Diabetes Statistics Report, 2014. 2014. http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf.
2. Farxiga® [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2014.

▼ Diabetes mellitus

Insulin human inhalation powder (Afrezza)

Insulin is the hormone responsible for the transport of glucose into muscle and adipose tissue. A deficiency of insulin leads to increased circulatory blood concentrations of glucose. Studies show that high blood glucose causes membrane deformations in red blood cells.[1] These deformed red blood cells lose their elasticity, resulting in microscopic deposits of cholesterol to build up in the blood vessels. The decreased circulation of red blood cells due to the narrowing of the

blood vessels eventually causes tissue around the damaged blood vessels to atrophy. The blood vessel damage results in microvascular and macrovascular complications of diabetes.[2]

Insulin is normally secreted by the beta cells in the pancreas in response to glucose elevations in the blood. Unfortunately, insulin is rapidly degraded in the gastrointestinal tract and is not absorbed orally. Up until now, the only avenue to replace insulin has been through injection into tissue. Insulin human inhalation powder is a new delivery method of insulin via oral inhalation and was recently approved by the FDA (June, 2014). The drug is marketed under the trade name Afrezza by MannKind Corporation.

Peak serum concentrations of Afrezza are reached in 12 to 15 minutes.

Indication

Afrezza is indicated to improve glycemic control in adult patients with diabetes mellitus, and those with type 1 diabetes must also be taking a long-acting insulin.[3] It is not recommended for treatment of diabetic ketoacidosis or in patients who smoke.[3]

Mechanism of action

Insulin is responsible for the uptake of glucose via skeletal muscle and fat and by inhibiting hepatic glucose production.

Pharmacokinetics

Orally inhaled Afrezza is rapidly absorbed with peak serum concentrations reached in 12 to 15 minutes. Despite this rapid absorption, median time to maximum effect is about 53 minutes with return to baseline levels by about 160 minutes.[3]

Dosing and administration

The drug is available in single-use cartridges of 4 units and 8 units. The individualized dose is administered using a single inhalation per cartridge at the beginning of a meal. Conversion from a subcutaneous, short-acting insulin can be done on a unit-to-unit basis and by rounding up to the closest combination of 4 unit and 8 unit cartridges. It is important to follow the guidelines for administration to avoid drug loss from the cartridge.[3]

Contraindications

Acute bronchospasm is a risk with insulin human inhalation powder, and the drug is contraindicated in patients with asthma or COPD. It is also contraindicated during episodes of hypoglycemia and in patients with a hypersensitivity to regular human insulin.[3]

Warnings and precautions

A complete physical exam of the patient, including spirometry, should be performed before initiating therapy. Long-term use is shown to decrease lung function as measured by FEV_1.[3]

Adverse reactions

Potentially serious adverse reactions include acute bronchospasm, hypoglycemia, decreased lung function, lung cancer, diabetic ketoacidosis, and severe allergic reactions. Less severe but more common adverse reactions include cough, throat irritation, headache, diarrhea, fatigue, and nausea.[3]

Drug interactions

The risk of hypoglycemia is increased when insulin human inhalation powder is used with the following: antidiabetic agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs, and sulfonamide antibiotics. In addition, the effects of insulin human inhalation powder may be lowered by atypical antipsychotics, corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, phenothiazines, protease inhibitors, somatropin, sympathomimetic agents, and thyroid hormones.[3]

Clinical pearls

- Insulin human inhalation powder is a pregnancy category C medication
- The drug should only be taken immediately before a meal
- Patients should be educated on the correct usage of the Afrezza inhaler
- As with all medications used to treat diabetes, it is important for patients to closely adhere to dietary instructions, exercise routines, glucose monitoring, and recognition of hypo- and hyper-glycemic reactions
- Patients should inform their HCP if they have a previous history of lung disease.[3]

REFERENCES

1. Traykov TT, Jain RK. Effect of glucose and galactose on red blood cell membrane deformability. *Int J Microcirc Clin Exp*. 1987;6(1):35-44.
2. National Diabetes Education Program. The Facts About Diabetes: A Leading Cause of Death in the U.S. http://ndep.nih.gov/diabetes-facts.
3. Afrezza® [package insert]. Danbuy, CT: Mannkind Corporation; 2014.

▼ Pulmonary hypertension

Riociguat (Adempas)

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially severe disease that can cause significant morbidity and mortality. If untreated, CTEPH patients with severe pulmonary hypertension have only a 20% survival rate over 2 years. It is, however, one of the only causes of severe pulmonary hypertension that is treatable without a lung transplant.[1] Approximately 3.8% of individuals who experience a pulmonary embolic event will eventually suffer from CTEPH.[2] Unfortunately, many individuals experience minor pulmonary emboli without being diagnosed. Over time, these patients are at an increased risk of developing CTEPH and right ventricular dysfunction.[3]

Riociguat (Adempas) is a new oral drug treatment for CTEPH. It is a soluble guanylate cyclase (sGC) agonist that shows an improvement in CTEPH by causing pulmonary vascular vasodilation.

On October 8, 2013, the FDA approved riociguat for the treatment of adults with persistent or recurrent CTEPH after surgery or in patients on inoperable surgery status to improve exercise capacity and the World Health Organization (WHO) functional class. Riociguat is marketed by Bayer Healthcare Pharmaceuticals Inc. under the trade name Adempas. It is available in 0.5 mg, 1 mg, 1.5 mg, 2 mg, and 2.5 mg tablets.

Indication

Riociguat has been approved for the treatment of adults with persistent or recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable status to improve exercise capacity and WHO functional class. It is also approved to improve exercise capacity, improve WHO functional class, and to delay clinical worsening in patients with pulmonary arterial hypertension (WHO Group 1).[4]

Mechanism of action

Riociguat stimulates sGC, a cardiopulmonary enzyme responsible for catalyzing the synthesis of cyclic guanosine monophosphate (cGMP) in response to nitric oxide (NO) binding. It also has a direct stimulating effect of sGC independent of NO binding. Both mechanisms result in increased generation of cGMP and subsequent vasodilation.[4]

Pharmacokinetics

Riociguat is readily absorbed from the gastrointestinal tract with peak plasma concentrations reached in about 1.5 hours.[4] The presence of food does not affect absorption time or extent. It is extensively bound to plasma proteins (albumin) and has a large volume of distribution. Metabolism occurs via liver enzyme systems with some metabolites being pharmacologically active. The terminal elimination half-life in patients is about 12 hours.[4]

Dosing and administration

The recommended starting oral dose is 1 mg taken three times a day, although patients prone to the hypotensive effect of riociguat may be started on 0.5 mg taken three times a day. If patients tolerate the starting dose, titration upward can be attempted every 2 weeks by increasing the dose by 0.5 mg taken three times a day. The maximum recommended dose is 2.5 mg taken three times a day.[4]

Contraindications

Riociguat is contraindicated in pregnant females due to the potential of fetal harm and is only available to females under a restricted Risk Evaluation and Mitigation Strategies (REMS) program.[4] Riociguat is also contraindicated for use with nitrates or any nitric oxide donors as well as with PDE inhibitors.[4]

Riociguat is a new oral drug treatment for CTEPH.

Warnings and precautions

Severe hypotension is a risk in patients with hypovolemia, severe left ventricular outflow obstruction, autonomic dysfunction, and in those taking antihypertensives or strong CYP and P-glycoprotein/breast cancer resistance protein (P-gp/BCRP) inhibitors. Serious bleeding can occur in patients; therefore, hemorrhagic events should be monitored. Riociguat should not be used in patients with pulmonary veno-occlusive disease.[4]

Adverse reactions

The most common adverse reactions (in order of frequency) include: headache, dyspepsia, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation.[4]

Drug interactions

Riociguat use is contraindicated in patients taking any form of nitrates or specific PDE-5 inhibitors (sildenafil, tadalafil, vardenafil) due to the risk of severe hypotension.[4] Patients who smoke have up to a 60% decrease in plasma concentra-

tions compared with nonsmokers. Since riociguat is metabolized by hepatic CYP enzyme systems, plasma concentrations may be increased by strong CYP inhibitors (ketoconazole, itraconazole, ritonavir) or decreased by strong CYP inducers (rifampin, phenytoin, carbamazepine, phenobarbital, St. John's Wort).[4]

Clinical pearls

- Riociguat is a Pregnancy Category X medication
- Female patients can only receive riociguat through the Adempas REMS Program, which requires regular pregnancy testing, use of contraceptives, and contraception education
- Educate patients on signs and symptoms of hemorrhagic events, and advise them to contact their HCP if they suspect a bleeding event has occurred
- Advise patients to inform their HCP and pharmacist of the use of any over-the-counter medications, including vitamins and herbal drugs
- Advise patients to keep on their regularly scheduled dosing regimen. If they miss a dose, they should take it as soon as they remember unless it is almost time for their next dose.[4]

REFERENCES

1. McNeil K, Dunning J. Chronic thromboembolic pulmonary hypertension (CTEPH). *Heart*. 2007;93(9):1152–1158.
2. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. 2004;350(22):2257–2264.
3. Ghofrani HA, D'Armini AM, Grimminger F, Hoeper MM, et al. Riociguat for the treatment of chronic thromboembolic pulmonary hypertension. *N Engl J Med*. 2013;369(4):319-329.
4. Adempas® [package insert]. Whippany, NJ: Bayer Healthcare Pharmaceutical Inc; 2014.

▼ Grass pollen allergic rhinitis

Timothy grass pollen extract (Grastek)

Allergic rhinitis is a chronic disorder that affects millions of Americans every year. Up to 60 million people are affected by this disease, which makes it the fifth-leading chronic disease in the United States.[1] Chronic allergic rhinitis may be seasonal or occur year-round and may be caused by any number of allergens. Common causes include dust mites, grass pollens, and tree pollens. Allergic rhinitis is manifested by sneezing, itching, nasal congestion, and rhinorrhea.[2]

Timothy grass pollen allergen extract was approved by the FDA for treatment of grass pollen-induced allergic rhinitis in April, 2014. It is also known as timothy grass pollen allergen extract tablets. It is available as 2,800 Bioequivalent Allergy Unit tablets. It is currently marketed for use in the United States under the trade name Grastek by Merck & Co.

Indication

Timothy grass pollen allergen extract is indicated for the treatment of allergic rhinitis caused by grass pollen when confirmed by a positive skin test or *in vitro* testing for pollen-specific IgE antibodies for timothy grass or cross-reactive grass pollens.[3]

Mechanism of action

Although the exact mechanism of action is unknown, it is thought to be due to an increase in the immune response to the ingested allergen.[3]

Dosing and administration

Timothy grass pollen allergen extract is given as a sublingual tablet once a day. The first dose must be given in a healthcare setting with appropriate tools and expertise to treat anaphylactic reactions. Patients should be observed for 30 minutes following the first dose. If the first dose is tolerated, patients may be instructed on how to take the tablets, and subsequent doses may be taken at home. Tablets are to be removed from the foil packet and placed under the tongue to dissolve. Patients should refrain from swallowing for 1 minute and no food or drink consumed for 5 minutes. Treatment is initiated 12 weeks prior to the start of the allergy season and continued throughout the season.[3]

Contraindications

Timothy grass pollen allergen extract is contraindicated in patients with severe, uncontrolled asthma, those with a history of any severe systemic allergic reaction or any local reaction to treatment with sublingual allergen immunotherapy, any patients with a history of eosinophilic esophagitis, or those with hypersensitivities to any components of the extract.[3]

Warnings and precautions

Timothy grass pollen allergen extract should not be used in patients with severe asthma, a previous severe allergic reaction, or a history of eosinophilic esophagitis. The extract can cause severe allergic reactions, including anaphylaxis.[3]

Drug interactions

Treatment should not be considered in patients who are taking medications that decrease the effectiveness of epinephrine. These include patients currently taking

beta-adrenergic blockers, alpha-adrenergic blockers, and ergot alkaloids.[3]

Adverse reactions

The most common adverse reactions found during treatment were ear, mouth, and tongue pruritus, mouth edema, and throat irritation. Rare cases of angioedema have been documented during initial treatment with timothy grass pollen allergen extract .[3]

Clinical pearls

- Timothy grass pollen allergen extract is a pregnancy category B medication
- Tablets are moisture-sensitive and must be kept in sealed foil packets until just prior to administration
- Patients should not swallow for 1 minute after placing the tablet under their tongue and no food or drink consumed for 5 minutes postdose
- Patients should have an unexpired, autoinjectable epinephrine syringe available to treat anaphylactic reactions, and they should be properly trained on its usage.[3]

REFERENCES

1. Schaffer F. National Impact of Allergies. 2014. http://www.aaapc.us/wp-content/uploads/2013/01/National-Impact-of-Allergies.pdf.
2. Skoner DP. Allergic rhinitis: definition, epidemiology, pathophysiology, detection, and diagnosis. *J Allergy Clin Immunol.* 2001;108(1 suppl):S2-S8.
3. Grastek® [package insert]. Whitehouse Station, NJ: Merck & Co. Inc.

▼ COPD

Umeclidinium and vilanterol (Anoro Ellipta)

Chronic obstructive pulmonary disease (COPD) is a major contributor to patient mortality and morbidity in the United States. In terms of incidence, it is estimated that in 2011, 12.7 million people in the United States suffered from COPD.[1]

COPD is the fourth leading cause of death worldwide.[2] It is a progressive disease associated with a chronic airway inflammatory response that results in parenchymal tissue destruction, air trapping, and persistent airflow limitation.[2] Cigarette smoking is the most common risk factor for COPD and smoking cessation should be encouraged for all patients who smoke.[2]

Umeclidinium and vilanterol is a new combination treatment approved for the treatment of COPD. It is the first product to combine an anticholinergic agent with a long-acting beta-2-adrenergic agonist (LABA). It is available as an inhaler containing two foil blisters per dose. One blister contains 62.5 mcg umeclidinium, and the other blister contains 25 mcg vilanterol.[3] The drug is currently marketed under the trade name Anoro Ellipta by GlaxoSmithKline.

Indication

The new combination drug is indicated for the long-term maintenance treatment of COPD. The drug is not indicated for the treatment of acute bronchospasm or asthma.[3]

Mechanism of action

Anoro Ellipta is composed of two medications with different mechanisms of action. Umeclidinium bromide is a long-acting anticholinergic agent that inhibits the M3 receptor on smooth muscle, resulting in bronchodilation. Vilanterol is a LABA, which selectively stimulates beta-2 receptors in bronchial smooth muscle. This stimulation causes bronchial smooth muscle to relax and inhibits the release of mediators of immediate hypersensitivity from mast cells.[3]

> ***Anoro Ellipta is indicated for the long-term maintenance treatment of COPD.***

Pharmacokinetics

Plasma levels of either drug may not predict therapeutic effect because both active ingredients are delivered directly to the lungs. Steady state levels are reached within 14 days after continuous use. Metabolism of umeclidinium occurs primarily in the liver by the CYP2D6. Vilanterol is metabolized in the liver by CYP3A4.[3]

Dosing and administration

The drug is dosed as one inhalation per day and at the same time every day. The maximum dose is one inhalation every 24 hours.[3]

Contraindications

The drug is contraindicated in those with severe hypersensitivity to milk proteins or any of the other drug ingredients.[3]

Warnings and precautions

LABAs should not be used in the treatment of asthma. Inhaled medications always run the risk of causing paradoxical bronchospasm, which may be life-threatening. A short-acting, inhaled bronchodilator should be available at all times. Beta-2 agonists should be used with caution in patients with underlying cardiovascular disorders, such as coronary insufficiency, cardiac dysrhythmias, and hypertension.[3] Use

with caution in patients with narrow-angle glaucoma, bladder-neck obstruction, or prostatic hyperplasia.[3]

Adverse reactions

Adverse reactions are rare and mimic those seen with placebo. Although very rare, exceptions include exacerbation of narrow-angle glaucoma, urinary retention, hypokalemia, and hyperglycemia.[2]

Drug interactions

Although umeclidinium and vilanterol are substrates for CYP2D6 and CYP3A4, respectively, no clinically relevant drug interactions exist with inhibitors or inducers of the CYP2D6 enzyme systems.[3] Use with caution with strong CYP3A4 inhibitors due to the potential for increased cardiovascular adverse reactions.[3] Do not use concomitantly with other anticholinergic drugs.[3] Beta-agonists should be used with extreme caution in patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QT interval or within 2 weeks of treatment with these agents.[3]

Vorapaxar inhibits platelet aggregation caused by thrombin.

Clinical pearls

- Anoro Ellipta is a pregnancy category C medication
- Patients should be cautioned that this medication is for maintenance of COPD, is not effective for acute symptoms, and acute symptoms should be treated with a rescue inhaler
- Tell patients to use this inhaler on a regular basis, but do not use it more often than prescribed
- Patients should be educated on the possibility of this medication aggravating the symptoms of narrow-angle glaucoma and urinary retention. Patients should report any eye pain or discomfort, blurred vision, or other visual effects, painful urination, and difficult urination to their HCP.[3]

REFERENCES

1. Chronic Obstructive Pulmonary Disease Fact Sheet. 2014. http://www.lung.org/lung-disease/copd/resources/facts-figures/COPD-Fact-Sheet.html.
2. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. 2014. http://www.goldcopd.org/uploads/users/files/GOLD_Report_2014_Jun11.pdf.
3. Anoro® Ellipta® [package insert]. Research Triangle Park, NC; 2013.

▼ Antithrombotic

Vorapaxar (Zontivity)

Coronary heart disease is the number one cause of death in the United States and is a major health concern.[1] Depending on the study reviewed, the incidence of myocardial infarction (MI) in adults ranges from 190 to 486 per 100,000. MI is almost twice as prevalent in men as it is in women.[1] According to the Worcester Heart Attack Study, death from MI over time can be as high as 18%.[1]

Vorapaxar is a platelet aggregation inhibitor approved by the FDA in May 2014 for the reduction of risk for thrombotic cardiovascular events in select patients. It is available in tablet form with each tablet containing 2.08 mg vorapaxar. It is marketed under the trade name Zontivity by Merck & Co.

Indication

Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of MI or with peripheral arterial disease. Treatment with vorapaxar is intended to reduce the risk of cardiovascular death, MI, stroke, and urgent coronary revascularization.[2]

Mechanism of action

Vorapaxar inhibits platelet aggregation caused by thrombin and thrombin receptor agonist peptide. Its mechanism of action is due to antagonism of platelet protease-activated receptor-1.[2]

Pharmacokinetics

Vorapaxar is almost completely absorbed following an oral dose with peak plasma levels reached in 1 hour. Distribution occurs throughout the body, and it is extensively bound (99%) to plasma proteins (albumin). Steady-state levels are seen within 21 days. Metabolism to active and inactive metabolites occurs in the liver via CYP3A4 and CYP2J2. The apparent terminal elimination half-life is about 8 days. Excretion occurs primarily in the feces. Clinical observation of inhibition of platelet aggregation is seen up to 4 weeks after discontinuation of therapy due to the long half-life of vorapaxar.[2]

Dosing and administration

The recommended dose is 2.08 mg given orally once daily in combination with aspirin and/or clopidogrel.[2]

Contraindications

Vorapaxar can increase the risk of bleeding events; therefore, it is contraindicated in patients with a history of stroke, transient ischemic attack, intracranial hemorrhage, or active pathologic bleeding.[2]

Warnings and precautions

Patients with positive risk factors for bleeding (advanced age, low body weight, renal or hepatic dysfunction, previous bleeding events, and concomitant use of medications that increase bleeding risks) are at an increased risk for bleeding events.[2]

Adverse reactions

An increase in bleeding events is the most severe, potentially adverse reaction to therapy. Other adverse reactions are rare and mild, including anemia, depression, and skin reactions (rash, eruptions, exanthemas).[2]

Drug interactions

Drugs that inhibit CYP3A4 and CYP2J2 may cause an increase in plasma levels. Avoid concomitant use of vorapaxar with strong CYP3A4 inhibitors, including the following drugs: ketoconazole, itraconazole, posaconazole, clarithromycin, telithromycin, nefazodone, conivaptan, ritonavir, saquinavir, nelfinavir, indinavir, boceprevir, and telaprevir.[2] Drugs that induce CYP3A4 and CYP2J2 may decrease plasma levels of vorapaxar. Avoid concomitant use of vorapaxar with strong CYP3A4 inducers, which include rifampin, carbamazepine, phenytoin, and St. John's Wort.[2]

Clinical pearls

- Vorapaxar is a Pregnancy Category B drug
- Advise patients to inform their HCP and pharmacist of the use of any over-the-counter medications, including vitamins and herbal drugs
- Advise patients to keep on their regularly scheduled dosing regimen. If they miss a dose, they should take it as soon as they remember unless it is almost time for their next dose
- Patients should contact their HCP if they experience any signs of abnormal bleeding, such as dark urine, dark stools, or sudden headache
- Inform patients to have their surgeon and dentist speak to their primary care HCP before they stop therapy.[2] NP

REFERENCES

1. Roger V. Epidemiology of myocardial infarction. 2014. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2537993.
2. Zontivity® [package insert]. Whitehouse Station, NJ: Merck & Co., Inc.; 2014.

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