New therapeutic agents marketed in 2022: Part 1

Daniel A. Hussar, PhD, is Dean Emeritus and Remington Professor Emeritus at the Philadelphia College of Pharmacy.

Four new therapeutic agents are considered in this review, the first in a series of articles on new therapeutic agents marketed in 2022: tirzepatide (Mounjaro–Eli Lilly and Company), daridorexant hydrochloride (Quviviq–Idorsia), tenapanor hydrochloride (Ibsrela–Ardelyx), and vonoprazan fumarate in co-packaging with amoxicillin, and amoxicillin and clarithromycin (Voquezna–Phathom Pharmaceuticals).

Following the review of each new therapeutic agent, the new drug is compared with the older medication(s) with which it is most similar in properties and uses, and its advantages and disadvantages are identified. (Advantages and disadvantages are identified at the time the new drug is first marketed and do not reflect approval of additional new drugs and/or changes that occur after the drug is initially marketed.)

Antidiabetic agent

Glucagon-like peptide-1 (GLP-1), a peptide hormone released soon after eating a meal, has multiple actions that include suppressing glucagon secretion, stimulating glucose-dependent insulin secretion, slowing gastric emptying, and promoting satiety. The class of GLP-1 receptor agonists includes exenatide (immediate-release formulation Byetta–AstraZeneca and the extended-release formulation Bydureon–AstraZeneca), liraglutide (Victoza–Novo Nordisk), dulaglutide (Trulicity—Eli Lilly and Company), and semaglutide (Ozempic–Novo Nordisk). These agents are administered subcutaneously as adjuncts to diet and exercise to improve glycemic control in patients with type 2 diabetes. Dulaglutide, semaglutide, and extended-release exenatide are administered once a week, whereas liraglutide is administered once a day and immediate-release exenatide is administered twice a day. An orally administered formulation of semaglutide (Rybelsus–Novo Nordisk) is also available; it is administered once a day.

GLP-1 receptor agonists have assumed an increasingly important role in the treatment of diabetes because in addition to their multiple actions that improve glycemic control, dulaglutide, semaglutide, and liraglutide have also been approved to reduce the risk of major adverse cardiovascular events (MACE) in patients

Learning objectives

At the conclusion of this knowledge-based activity, the pharmacist will be able to

- Identify the new therapeutic agents and explain their appropriate use.
- Identify the indications and mechanisms of action of the new agents.
- Identify the most important adverse events and other risks of the new therapeutic agents.
- State the route of administration for each new drug and the most important considerations regarding dosage and administration.
- Compare the new therapeutic agents with older medications to which they are most similar in properties and/or use and identify the most important advantages and disadvantages of the new drugs.

Preassessment questions

Before participating in this activity, test your knowledge by answering the following questions. These questions will also be part of the CPE assessment.

1. Which of the following agents should be administered immediately prior to a meal?

a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

2. Which of the following agents is administered subcutaneously?

a. Tirzepatide
b. Daridorexant
c. Tenapanor
d. Vonoprazan

3. Which of the following statements is correct regarding daridorexant?

a. It acts as an orexin receptor agonist.
b. In comparison with other drugs with a similar action, it is considered to have an intermediate duration of action.
c. It has been demonstrated to be more effective than eszopiclone.
d. It is eliminated in unchanged form in the urine.

with type 2 diabetes and established cardiovascular disease, and formulations of semaglutide (Wegovy–Novo Nordisk) and liraglutide (Saxenda–Novo Nordisk) have been approved as adjuncts to a reduced-calorie diet and increased physical activity for chronic weight management in patients with or without diabetes.

Tirzepatide is the most recent addition to the class of GLP-1 receptor agonists; however, unlike its predecessors, it is a dual-targeted treatment that also activates glucose-dependent insulinotropic polypeptide (GIP) receptors. It is a 39-amino acid modified peptide based on the GIP sequence, and it is administered subcutaneously as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Tirzepatide is administered subcutaneously in the abdomen, thigh, or upper arm, and the injection site should be rotated with each dose. As with dulaglutide, subcutaneous semaglutide, and extended-release exenatide, it is administered once a week. The recommended starting dosage is 2.5 mg injected once a week; however, it should be noted that this dosage is for treatment initiation and is not intended for glycemic control. After 4 weeks, the dosage is increased to 5 mg once a week. If additional glycemic control is needed, the dosage may be increased in 2.5 mg increments after at least 4 weeks on the current dose. The maximum dosage is 15 mg once a week. If the new drug is used concurrently with insulin, the products should be administered as separate injections and should not be mixed with tirzepatide.

Tirzepatide injection is available in prefilled single-dose pens containing 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL. The drug should be stored in a refrigerator in its original carton of 4 single-dose pens.

The effectiveness of tirzepatide was evaluated in five 40- or 52-week clinical trials as either a stand-alone therapy or as an add-on to other medications for diabetes. Three doses of the new drug (5 mg, 10 mg, 15 mg) were evaluated, and it was compared with placebo, semaglutide, insulin degludec (Tresiba–Novo Nordisk), and insulin glargine (e.g., Lantus–Sanofi). Patients receiving the maximum recommended dosage of 15 mg once a week of tirzepatide experienced, on average, a lowering of their hemoglobin A1C by 1.6% more than placebo, 0.5% more than semaglutide, 0.9% more than insulin degludec, and 1% more than insulin glargine.

Many patients with diabetes are overweight, and obesity was common among the participants in the clinical trials, with an average BMI of 32–34 kg/m^2 at the time of enrollment. Some antidiabetic agents (e.g., insulin, sulfonylureas) have been associated with weight gain during treatment, but those treated with a GLP-1 receptor agonist often experience weight loss. In patients treated with the maximum recommended dosage, the average weight loss with tirzepatide was 15 pounds more than with a placebo, 12 pounds more than semaglutide, 29 pounds more than insulin degludec, and 27 pounds more than insulin glargine.

Notwithstanding the likely greater weight loss with tirzepatide, chronic weight management is not a labeled indication for the new agent at present, as it is with semaglutide and liraglutide. It has not yet been determined whether tirzepatide reduces the risk of MACE, whereas this is a labeled indication for dulaglutide, semaglutide, and liraglutide in patients with diabetes and established cardiovascular disease.

The limitations of use for tirzepatide are similar to those of other agents with GLP-1 receptor agonist activity, and it should not be used in patients with type 1 diabetes. Acute pancreatitis has been infrequently reported with these agents, and they have not been studied

in patients with a history of pancreatitis. If pancreatitis is suspected, treatment with tirzepatide should be promptly discontinued. Other antidiabetic agents should be considered in patients with a history of pancreatitis.

In studies in rodents, tirzepatide and other GLP-1 receptor agonists have been reported to cause thyroid C-cell tumors, but it is not known whether they cause these tumors in humans. However, the labeling for these agents includes a boxed warning about this possibility and for contraindications in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2.

The most commonly reported adverse events in the studies of tirzepatide (and their incidence with the weekly dosage of 10 mg and 15 mg, respectively) include nausea (15%, 18%), diarrhea (13%, 17%), decreased appetite (10%, 11%), vomiting (5%, 9%), constipation (6%, 7%), dyspepsia (8%, 5%), and abdominal pain (5%, 5%). The new agent has not been studied in patients with severe GI disease, including severe gastroparesis, and its use is not recommended in these patients. Acute kidney injury and worsening of chronic renal failure have been infrequently reported in patients treated with GLP-1 receptor agonists; most of these events have occurred in patients who had experienced GI adverse events such as vomiting and diarrhea that resulted in dehydration. Renal function should be monitored when initiating or increasing the dosage of tirzepatide in patients with renal impairment who also report severe GI adverse events.

Additional risks associated with the use of tirzepatide and other GLP-1 receptor agonists include hypersensitivity reactions, complications in patients with a history of diabetic retinopathy, and acute gallbladder disease (e.g., cholelithiasis, cholecystitis). There are insufficient data to evaluate the safety of using tirzepatide during pregnancy or lactation, but based on animal studies its use during pregnancy may be associated with adverse developmental effects.

As with semaglutide, the effectiveness and safety of tirzepatide in patients younger than 18 years have not been established. However, dulaglutide, extended-release exenatide, and liraglutide are indicated for patients 10 years and older who have type 2 diabetes.

Following subcutaneous administration, the mean absolute bioavailability of tirzepatide is 80%. It is metabolized via proteolytic cleavage, beta-oxidation, and amide hydrolysis, and it is eliminated as metabolites in the feces and urine. Dosage adjustment is not necessary in patients with hepatic or renal impairment.

Tirzepatide and the other GLP-1 receptor agonists are not likely to cause hypoglycemia. However, there is an increased risk of hypoglycemia if they are used in combination with insulin or an insulin secretagogue, and a reduction in dosage of the latter agent may be necessary.

Because the GLP-1 receptor agonists delay gastric emptying, a potential exists for altered absorption and activity of concomitantly administered oral medications. The delay in gastric emptying caused by tirzepatide is greatest after the first dose and this effect diminishes over time. Patients who are concurrently treated with oral medications dependent on threshold concentrations for efficacy and/or with a narrow therapeutic index (e.g., warfarin) should be monitored for a potential change in activity. The labeling for tirzepatide advises that patients using oral hormonal contraceptives switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation and for 4 weeks after each dosage increase with tirzepatide.

Comparison of tirzepatide with dulaglutide and semaglutide

Advantages

- It is more effective in reducing hemoglobin A1C and causing weight loss than semaglutide, insulin degludec, and insulin glargine based on comparative clinical studies.
- It has dual-targeted mechanisms of action (i.e., it is an agonist of both GLP-1 and GIP receptors).

Disadvantages

- It is not indicated in pediatric patients, whereas dulaglutide is indicated for use in patients 10 years and older with type 2 diabetes.
- Labeled indications are more limited (i.e., it is not yet approved for chronic weight management, and it has not been determined whether it reduces the risk of MACE).

Hypnotic

Orexins are naturally occurring neuropeptides that act in a signaling mechanism as a central promoter of wakefulness. This wake-promoting action results from the binding of orexin A and orexin B to OX1R and OX2R receptors. Daridorexant hydrochloride (Quviviq–Idorsia) is the third orexin receptor antagonist to be approved for the treatment of patients with insomnia, joining suvorexant (Belsomra–Merck) and lemborexant (Dayvigo–Eisai Inc.). By blocking the binding of orexins to their receptors, these agents are thought to suppress the wake drive. Like its predecessors, daridorexant is indicated for the treatment of adult patients with insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Daridorexant hydrochloride is supplied in film-coated tablets in quantities equivalent to 25 mg and 50 mg of daridorexant.

The effectiveness of daridorexant was evaluated in 2 placebo-controlled trials in which the primary efficacy endpoints were the change from baseline to month 1 and month 3 in latency to persistent sleep (LPS, a measure of sleep induction) and wake after sleep onset (WASO, a measure of sleep maintenance). A secondary endpoint was patient-reported subjective total sleep time (sTST) that patients evaluated every morning at home using a sleep diary questionnaire.

In the first study, doses of 25 mg and 50 mg of daridorexant showed a statistically significant improvement compared with placebo on LPS, WASO, and sTST at months 1 and 3. In the second study, a dose of 25 mg of the new drug showed a statistically significant improvement compared with placebo on WASO and sTST but

not LPS at months 1 and 3. (The 50 mg dose was not evaluated in this study.) Patients treated with daridorexant in both studies reported longer total sleep time (about 10–20 minutes) and better sleep quality than those receiving a placebo.

The 3 orexin receptor antagonists as well as hypnotics such as eszopiclone and temazepam are considered to have an intermediate duration of action in comparison with agents such as triazolam and ramelteon, which have a short duration of action, and flurazepam, which has a long duration of action.

The loss of orexin receptors has been reported in individuals with narcolepsy, and antagonism of orexin receptors by daridorexant may be associated with signs of narcolepsy or cataplexy. Symptoms similar to mild cataplexy, such as periods of leg weakness, can occur with daridorexant and the other orexin receptor antagonists, and their use is contraindicated in patients with narcolepsy. Sleep paralysis—an inability to speak or move for several minutes during sleep-wake transitions—and hallucinations have also been infrequently reported.

Adverse events experienced most often with daridorexant (and their incidence with the 25 mg and 50 mg doses, respectively) include headache (6%, 7%) and somnolence or fatigue (6%, 5%). In a controlled study of the nighttime administration of daridorexant on next-morning driving performance, using a driving simulator, both doses of the drug caused a statistically significant impairment of next-day driving skills after the first dose. Although the mean effect on driving performance was not statistically significant after 4 consecutive nights of treatment with either dose, driving ability was impaired in some individuals. In view of the individual variation in sensitivity to daridorexant, patients should be cautioned about the potential for next-morning driving impairment. Patients should also be cautioned about central nervous system (CNS) depressant effects and related risks that increase with dosage and concurrent use with other CNS depressants. Patients should be advised not to consume alcohol because coadministration with daridorexant may result in additive effects on psychomotor performance.

The use of hypnotics, including daridorexant, has been associated with the occurrence of complex sleep behaviors, including sleepwalking, sleep-driving, and engaging in other activities while not fully awake (e.g., preparing and eating food, phone conversations) which patients do not usually remember. Treatment should be immediately discontinued if patients experience these effects.

Worsening of depression and suicidal ideation has been associated with the use of hypnotics. Appropriate precautions must be observed in evaluating, treating, and monitoring patients for these risks. Like suvorexant and lemborexant, daridorexant is classified as a schedule IV controlled substance. However, in clinical trials of chronic administration of the new drug, discontinuation of treatment was not associated with withdrawal signs or symptoms, and it appears unlikely to cause physical dependence.

The respiratory depressant effect of daridorexant was evaluated in patients with mild to moderate obstructive sleep apnea (OSA) not requiring continuous positive airway pressure (CPAP) and in patients with moderate chronic obstructive pulmonary disease (COPD); it was well-tolerated. However, it has not been studied in patients with severe OSA or those requiring CPAP, or in patients with severe COPD, and it must be used with caution in patients with compromised respiratory function.

Sufficient data are not available to assess the risk of daridorexant use during pregnancy and lactation. The risk of adverse events if used during pregnancy appears to be low, but those who are exposed to the drug during pregnancy are advised to register in the company's pregnancy registry by calling 1-833-400-9611. It is likely that daridorexant and its metabolites will be present in human milk, and infants exposed to the drug through breast milk should be monitored for excessive sedation. The effectiveness and safety of the new drug in pediatric patients have not been established.

Following oral administration, daridorexant has a prompt onset of action and it has an absolute bioavailability of 62%. It is extensively metabolized via the CYP3A4 pathway, and approximately 60% of a dose is recovered in the feces and 30% in the urine. Dosage adjustment is not necessary in patients with renal impairment, but it should be used in a lower dosage in patients with moderate hepatic impairment. The new agent has not been studied in patients with severe hepatic impairment, and its use in these patients is not recommended.

As with suvorexant and lemborexant, the activity of daridorexant is increased by drugs that are CYP3A4 inhibitors and decreased by CYP3A4 inducers. Concurrent use of daridorexant or suvorexant with a strong CYP3A4 inhibitor (e.g., clarithromycin, itraconazole) should be avoided, but the hypnotic may be used in a lower dosage in patients being treated with a moderate CYP3A4 inhibitor (e.g., diltiazem, fluconazole). The labeling for lemborexant recommends that concurrent use with a strong or moderate CYP3A4 inhibitor be avoided, and that it be used in a lower dosage in patients taking a weak CYP3A4 inhibitor. The use of daridorexant or lemborexant should be avoided in patients treated with a strong or moderate CYP3A4 inducer (e.g., carbamazepine, rifampin, St. John's wort), whereas the labeling for suvorexant cautions that its efficacy may be reduced by the concurrent use of a strong CYP3A4 inducer.

Unlike daridorexant and lemborexant, suvorexant is a P-glycoprotein (P-gp) inhibitor, and it may increase the serum concentration and activity of P-gp substrates such as digoxin.

The maximum concentration and time to sleep onset of daridorexant may be delayed if it is taken with or soon after a meal. The recommended dosage is 25 mg or 50 mg once per night, taken within 30 minutes before going to bed, with at least 7 hours remaining prior to planned awakening. In patients with moderate hepatic impairment

Comparison of daridorexant with suvorexant and lemborexant

Advantages

- It may be used in a lower dosage in patients treated concurrently with a moderate CYP3A4 inhibitor (compared with lemborexant).

Disadvantages

- Concurrent use with strong or moderate CYP3A4 inducers should be avoided compared with suvorexant, for which the labeling does not preclude concurrent use with a CYP3A4 inducer.
- It has not been directly compared with other hypnotics in clinical studies.

and in those also being treated with a moderate CYP3A4 inhibitor, the maximum recommended dosage is 25 mg once per night.

Agent for IBS

Irritable bowel syndrome (IBS) is a GI disorder in which abdominal pain is associated with constipation and/or diarrhea as well as sometimes other GI symptoms such as bloating. IBS with constipation (IBS-C) affects more than 11 million people in the U.S., many of whom do not experience adequate relief from dietary modification and use of laxatives. Medications that have been approved for the treatment of IBS-C include the secretagogues lubiprostone (indicated in women at least 18 years old), a chloride channel activator, and the guanylate cyclase-C agonists linaclotide (Linzess–AbbVie) and plecanatide (Trulance–Salix Pharmaceuticals). The serotonin-4 receptor agonist tegaserod (Zelnorm–Alfasigma) is effective in some patients with IBS-C; however, because it may cause cardiovascular adverse events, its use is restricted to women less than 65 years old who do not have a history of serious cardiovascular problems.

The sodium/hydrogen exchanger 3 (NHE3) is expressed on the apical surface of the small intestine and colon, and it is primarily responsible for the absorption of dietary sodium. Tenapanor hydrochloride (Ibsrela–Ardelyx) is the first NHE3 inhibitor to be approved and is administered orally. It is minimally absorbed and acts locally in the GI tract. By reducing the absorption of sodium, it causes an increase in water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency. In studies in animals, it has also been reported to reduce abdominal pain.

Tenapanor hydrochloride is supplied in tablets in a quantity equivalent to 50 mg of tenapanor. The labeling for linaclotide and plecanatide provides instructions for mixing the drugs with applesauce or water for patients who have difficulty swallowing capsules or tablets or who have a nasogastric or gastric feeding tube. However, such instructions are not provided for tenapanor.

The recommended dosage of tenapanor is 50 mg orally twice a day, and the drug should be administered immediately before breakfast or the first meal of the day and immediately before dinner. Linaclotide and plecanatide are administered once a day, and linaclotide should be administered at least 30 minutes prior to the first meal of the day.

The effectiveness of tenapanor was evaluated in 2 placebo-controlled clinical trials having identical designs during the first 12 weeks of treatment. The primary endpoint was the proportion of responders, which were defined as a patient achieving both the stool frequency and abdominal pain intensity criteria in the same week for at least 6 of the first 12 weeks of treatment. The stool frequency responder criterion was defined as a patient who experienced an increase of at least 1 complete spontaneous bowel movement (CSBM) in a weekly average from baseline, and the abdominal pain responder criterion was defined as a patient who experienced at least a 30% reduction in the weekly average of abdominal pain score compared with baseline. In one of the trials, 37% of the patients treated with tenapanor were responders, with 47% being CSBM responders and 50% being abdominal pain responders, compared with 24%, 33%, and 38%, respectively, of those receiving a placebo. In the other trial, the corresponding percentages of responders treated with tenapanor were 27%, 34%, and 44%, compared with 19%, 29%, and 33% of those receiving placebo.

Lubiprostone, linaclotide, and plecanatide are also indicated for the treatment of chronic idiopathic constipation in adults, and lubiprostone is also indicated for the treatment of opioid-induced constipation in adults with chronic noncancer pain. However, these are not labeled indications for tenapanor at present.

Tenapanor was approved by the FDA in 2019 but the company was also conducting studies of its use to control serum phosphorus in patients with chronic kidney disease (CKD) who are on dialysis, and it delayed marketing the drug with the hope that the additional indication for the drug would soon be approved. However, when the indication for patients with CKD (that was considered of greater importance) was still not approved by 2022, the drug was marketed for the treatment of IBS-C.

The effectiveness and safety of tenapanor, linaclotide, and plecanatide in patients less than 18 years have not been established. However, the 3 drugs are associated with a risk of serious dehydration in pediatric patients; in studies in juvenile mice and rats, the drugs have caused deaths due to dehydration. The labeling for each of the drugs includes a boxed warning regarding this risk. Tenapanor and plecanatide are contraindicated in patients less than 6 years, and the use of these agents should be avoided in patients aged 6–12 years and less than 18 years, respectively. Linaclotide is contraindicated in patients less than 2 years. All 3 drugs are also contraindicated in patients with known or suspected mechanical GI obstruction.

The adverse events most often reported in the studies of tenapanor include diarrhea (16%), abdominal distension (3%), flatulence (3%), and dizziness (2%). Severe diarrhea occurred in 2.5% of patients and, if severe diarrhea occurs, treatment should be suspended and the patient should be rehydrated. Tenapanor is minimally absorbed, and its use is not expected to cause risk during pregnancy or result in a clinically relevant

Comparison of tenapanor with linaclotide and plecanatide

Advantages

- It has a unique mechanism of action (i.e., it is a sodium/hydrogen exchanger 3 [NHE3] inhibitor).

Disadvantages

- It is administered more frequently (i.e., twice a day), whereas linaclotide and plecanatide are administered once a day.
- Instructions for use in patients with swallowing difficulties are not provided.
- It may reduce the effectiveness of OATP2B1 substrates (e.g., enalapril).
- It has not been directly compared with previous agents in clinical trials.
- Its labeled indications are more limited (linaclotide and plecanatide are also indicated for chronic idiopathic constipation).

exposure to breastfed infants.

Most of a dose of tenapanor is excreted in the feces as unchanged drug, with less than 10% recovered in the urine primarily as metabolites. Tenapanor is an inhibitor of intestinal uptake transporter organic anion transporter polypeptide 2B1 (OATP2B1), and concurrent use with a substrate of this transporter (e.g., enalapril) is likely to reduce exposure and effectiveness of the latter agent, possibly necessitating an increase in dosage of enalapril.

Gastric acid suppressant

Helicobacter pylori (*H. pylori*) is a gram-negative bacterium that is a common cause of infection in the stomach. It is estimated to affect more than 100 million people in the U.S. It does not usually cause symptoms but may cause inflammation and local tissue damage that result in gastritis and/or peptic ulcer, and an association with certain gastric cancers. Symptomatic *H. pylori* infections are most commonly treated with a combination of a gastric acid suppressant (e.g., omeprazole, lansoprazole) with one or more antimicrobial agents (e.g., amoxicillin, clarithromycin, metronidazole, tetracycline, rifabutin). There has been increased resistance of *H. pylori* to clarithromycin and (to a lesser extent) to metronidazole. Bismuth quadruple therapy with the combination product that contains bismuth subcitrate potassium, metronidazole, and tetracycline (Pylera–AbbVie) plus omeprazole or another PPI is usually considered the preferred treatment for *H. pylori* infection.

PPIs such as omeprazole block the final step of gastric acid production. Vonoprazan fumarate is a type of gastric PPI that is designated as a potassium-competitive acid blocker. It acts to suppress acid secretion at the surface of the gastric parietal cell by reducing potassium binding at the hydrogen-potassium-ATPase enzyme system (i.e., proton pump). It is the first gastric acid suppressant with this mechanism of action, and it provides a higher intragastric pH and has a longer half-life than the other PPIs.

Vonoprazan is not marketed as a single agent in the U.S., but rather as a copackaged product that includes the new drug with amoxicillin capsules (Voquezna Dual Pak–Phathom Pharmaceuticals) and as a copackaged product with amoxicillin capsules and clarithromycin tablets (Voquezna Triple Pak–Pharthom Pharmaceuticals).

The products have been approved for the treatment of *H. pylori* infection in adults and are used in a 14-day course of treatment.

The effectiveness of the 2 vonoprazan-containing copackaged products as well as a regimen of lansoprazole, amoxicillin, and clarithromycin (LAC) was evaluated in treatment-naive *H. pylori*–positive adult patients with at least one clinical condition (e.g., peptic ulcer, dyspepsia).

H. pylori eradication was confirmed with a negative ^{13}C urea breath test conducted at least 27 days following the completion of treatment. The vonoprazan triple and dual combination products were shown to be noninferior to LAC in patients who did not have a clarithromycin or amoxicillin resistant strain of *H. pylori* at baseline, with eradication rates of 85%, 79%, and 79%, respectively. However, the vonoprazan products were superior to LAC in patients who had a clarithromycin resistant strain of *H. pylori* at baseline, with eradication rates of 66%, 70%, and 32%, respectively. Although the regimens have not been directly compared in clinical trials, the results of the studies with the individual regimens suggest that the vonoprazan regimens are less effective than the bismuth quadruple therapy regimen.

The adverse events most often experienced in the clinical trial—and their incidence with the vonoprazan triple combination, vonoprazan dual combination, and LAC, respectively—include diarrhea (4%, 5%, 10%), dysgeusia (5%, 1%, 6%), vulvovaginal yeast infections (3%, 2%, 1%), and abdominal pain (2%, 3%, 3%). The properties and the risks of adverse events and drug interactions with amoxicillin and clarithromycin are

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Comparison of vonoprazan plus clarithromycin and/or amoxicillin with LAC

Advantages

- Regimens are more effective in patients who have a clarithromycin resistant strain of *H. pylori* at baseline.
- Vonoprazan has a unique mechanism of action (i.e., it is a potassium-competitive acid blocker).

Disadvantages

- It may be less effective than bismuth quadruple therapy (based on noncomparative studies of individual regimens);
- Vonoprazan is not available as a single agent.

well-recognized as a result of their long-term use, and most of the concerns (e.g., QT prolongation, hepatotoxicity) identified in the labeling of the new products pertain to the inclusion of clarithromycin in the triple combination product. The properties of vonoprazan that are relevant to its use in combination regimens are the primary focus in the following discussion.

There are insufficient data in patients who are pregnant or breastfeeding to determine if there are risks of developmental events or adverse effects in nursing infants. However, because of the risks with clarithromycin, the triple regimen including this agent should not be used during pregnancy. It is likely that vonoprazan will be present in human milk; based on concerns from studies in animals, breastfeeding is not recommended during treatment. A lactating patient can pump and discard breast milk during treatment and for 2 days after the completion of treatment, and the infant can be fed with stored human milk collected prior to treatment or with formula.

Although amoxicillin and clarithromycin are each indicated for treating infections in pediatric patients, the effectiveness and safety of the vonoprazan combination regimens have not been established in patients less than 18 years old.

Following oral administration and absorption, vonoprazan is metabolized via multiple pathways including CYP3A4/5 and CYP2C19. Approximately 67% of a dose is recovered in the urine and 31% in the feces, primarily as metabolites. Its use in combination with clarithromycin and/or amoxicillin should be avoided in patients with severe renal impairment and in patients with moderate and severe hepatic impairment.

As a CYP3A substrate, the activity of vonoprazan as well as that of clarithromycin may be reduced by strong or moderate CYP3A4 inducers (e.g., carbamazepine), and concurrent use should be avoided. Vonoprazan is a weak CYP3A inhibitor and clarithromycin is a strong inhibitor of this pathway; they may increase the exposure and risks of CYP3A substrates.

Concurrent use with CYP3A4 substrates—during which small changes in concentration may result in serious toxicity (e.g., cyclosporine, tacrolimus)—should be closely monitored.

Vonoprazan is a CYP2C19 inhibitor and may reduce the conversion of clopidogrel to its active metabolite via this pathway and possibly decrease its antiplatelet activity. However, it may increase exposure of drugs that are substrates for this pathway (e.g., citalopram, cilostazol).

Because vonoprazan reduces intragastric acidity, it may reduce the absorption and serum concentration of rilpivirine, and concurrent use is contraindicated. The new drug may also reduce the absorption of drugs such as itraconazole which are dependent on an acidic medium for optimum absorption. Conversely, the reduction in intragastric acidity increases chromogranin A levels and may cause false positive results in diagnostic investigations for neuroendocrine tumors.

Vonoprazan fumarate is supplied in tablets in an amount equivalent to 20 mg of vonoprazan. The Voquezna Dual Pak is copackaged containing vonoprazan tablets (20 mg) and amoxicillin capsules (500 mg); the recommended dosage is vonoprazan 20 mg twice a day (morning and evening) plus amoxicillin 1,000 mg 3 times a day (morning, midday, and evening) with or without food for 14 days. The Voquezna Triple Pak is copackaged containing vonoprazan tablets (20 mg), amoxicillin capsules (500 mg), and clarithromycin tablets (500 mg); the recommended dosage is vonoprazan 20 mg plus amoxicillin 1,000 mg plus clarithromycin 500 mg, each administered twice a day (morning and evening, 12 hours apart) with or without food for 14 days. ■

CPE information

To obtain 1 hour of CPE credit for this activity, complete the CPE exam and submit it online at www.pharmacist.com/education. A Statement of Credit will be awarded for a passing grade of 70% or better. You have two opportunities to successfully complete the CPE exam. Pharmacists and technicians who successfully complete this activity before March 1, 2026, can receive credit. Your Statement of Credit will be available online immediately upon successful completion of the CPE exam.

This policy is intended to maintain the integrity of the CPE activity. Learners who successfully complete this activity by the expiration date can receive CPE credit. Please visit CPE Monitor for your statement of credit/transcript.

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Assistance is available Monday through Friday from 8:30 am to 5:00 pm ET at APhA InfoCenter by calling 800-237-APhA (2742) or by e-mailing infocenter@aphanet.org.

CPE Assessment

This assessment must be taken online; please see "CPE information" in the sidebar on the previous page for further instructions. The online system will present these questions in random order to help reinforce the learning opportunity. There is only one correct answer to each question.

1. **Which of the following agents acts as a potassium-competitive acid blocker?**
   a. Tirzepatide
   b. Daridorexant
   c. Tenapanor
   d. Vonoprazan

2. **Which of the following agents is indicated for the treatment of patients with type 2 diabetes?**
   a. Tirzepatide
   b. Daridorexant
   c. Tenapanor
   d. Vonoprazan

3. **Which of the following agents should be administered immediately prior to a meal?**
   a. Tirzepatide
   b. Daridorexant
   c. Tenapanor
   d. Vonoprazan

4. **Which of the following agents is contraindicated in patients with narcolepsy?**
   a. Tirzepatide
   b. Daridorexant
   c. Tenapanor
   d. Vonoprazan

5. **Which of the following agents is administered subcutaneously?**
   a. Tirzepatide
   b. Daridorexant
   c. Tenapanor
   d. Vonoprazan

6. **Which of the following statements is correct regarding tirzepatide?**
   a. It is indicated for use in patients 10 years and older.
   b. Dizziness is the adverse event most often associated with its use.
   c. It is administered once a week.
   d. Following initiation of treatment, maintenance doses of 2.5 mg should be administered.

7. **Which of the following statements is correct regarding daridorexant?**
   a. It acts as an orexin receptor agonist.
   b. In comparison with drugs with a similar indication, it is considered to have an intermediate duration of action.
   c. It has been demonstrated to be more effective than eszopiclone.
   d. It is eliminated in unchanged form in the urine.

8. **Which of the following statements is correct regarding tenapanor?**
   a. It is extensively metabolized via hepatic CYP3A4 metabolic pathways.
   b. Nausea is the adverse event most often associated with its use.
   c. It is administered once a day.
   d. It acts as a sodium/hydrogen exchanger 3 inhibitor.

9. **Which of the following statements is correct regarding vonoprazan?**
   a. It is used in combination with omeprazole and metronidazole.
   b. It is indicated for use in the treatment of infections caused by *Clostridioides difficile*.
   c. Concurrent use with rilpivirine is contraindicated.
   d. It is administered once a day.

10. **Which of the following statements is correct regarding the comparison of tirzepatide and semaglutide?**
    a. Both agents have been demonstrated to reduce the risk of major adverse cardiovascular events.
    b. Hypoglycemia is the most important adverse event with the use of both agents.
    c. Both agents act as GLP-1 receptor agonists, but tirzepatide also acts as an SGLT-2 inhibitor.
    d. Tirzepatide has been demonstrated to cause greater weight loss than semaglutide in a comparative study.