December 2021

Focus on: Gastroenterologic Diseases

U.S. Pharmacist

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2 CE Credits

Pharmacist Review of Loperamide Abuse

Probiotic Use in
Gastrointestinal Disorders

Special Section: Cold & Flu

Comparing Oral Antivirals for
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Influenza in the Age of
COVID-19

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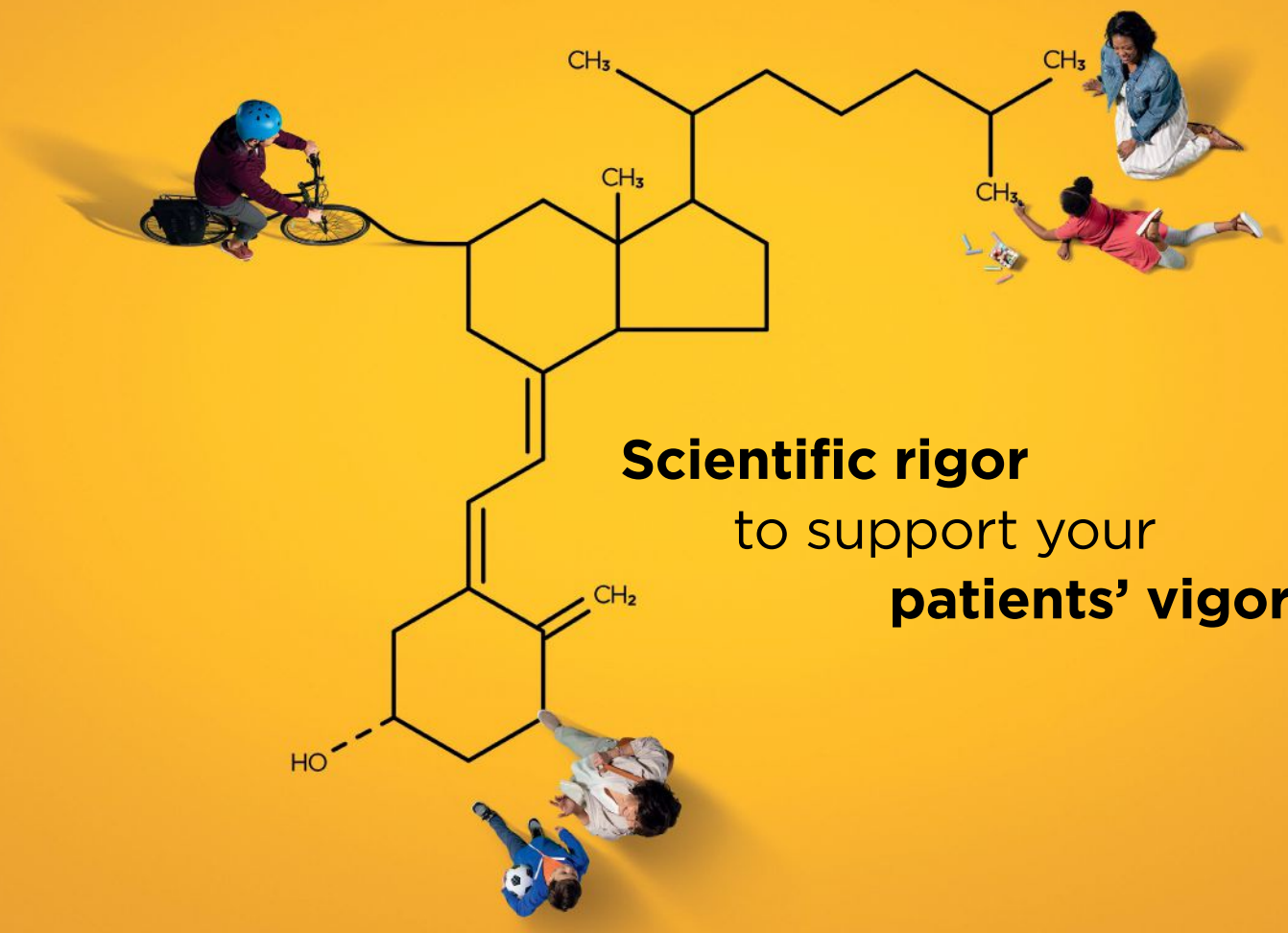
Health Systems Edition

Digesting the Updated *C difficile* Guidelines

Diabetes-Related GI Emergencies



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Digesting COVID's Impact on Gut Health

Most are familiar with COVID-19's hallmark symptoms of anosmia and difficulty breathing, but 60% of patients infected with SARS-CoV-2 also report gastrointestinal symptoms, such as nausea, diarrhea, and stomach pain.

Infection of the gut, which expresses high levels of the angiotensin-converting enzyme 2 (ACE2) receptor protein that SARS-CoV-2 uses to enter cells, is correlated with more severe cases of COVID-19, but the exact interactions between the virus and intestinal tissue are difficult to study in human patients.

To solve that problem, a team of scientists at the Wyss Institute for Biologically Inspired Engineering at Harvard University and several other organizations in Boston used a human intestine chip previously developed at the Institute to study coronavirus infection and potential treatments. The researchers infected the intestine chip with a coronavirus called NL63 that causes the common cold and, like SARS-CoV-2, uses the ACE2 receptor to enter cells.

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Next, they tested the effects of various drugs that have been proposed for treating SARS-CoV-2 infection, finding that a drug called nafamostat reduced infection while the drug remdesivir, which has been used to treat COVID-19 patients, did not reduce infection and actually damaged the intestinal tissue. This new preclinical model is described in *Frontiers in Pharmacology*.

Having established that their intestine chip could successfully model interactions between viruses, drugs, and the gut, the team tested a variety of other oral drugs, including toremifene, nelfinavir, clofazimine, and fenofibrate, all of which have been shown to inhibit infection by SARS-CoV-2 and other viruses in vitro. Of those, only toremifene showed similar efficacy to nafamostat in reducing NL63 viral load.

Because the immune system interacts with both pathogens and drugs via the inflammatory response, the researchers then introduced a mixture of human immune cells called peripheral blood mononuclear cells (PBMCs) into the blood vessel channel of the intestine chip. They found that more PBMCs attached themselves to the blood vessel wall in chips that had been infected with NL63 than in uninfected chips, and that the blood vessel cells were damaged.

Pretreating the intestine chip with nafamostat prior to the introduction of the virus and PBMCs reduced the secretion of some cytokines, but it did not mitigate the blood vessel damage or suppress the inflammatory response completely. Nafamostat pretreatment did, however, increase the production of an antimicrobial protein called lipocalin-2, implying that this type of protein could play a role in the cellular response to coronavirus infections.

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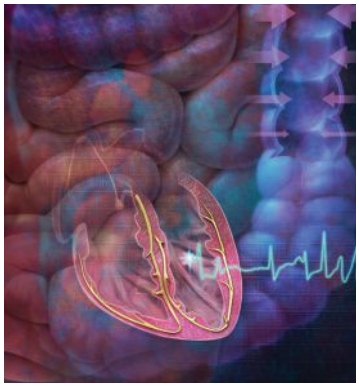
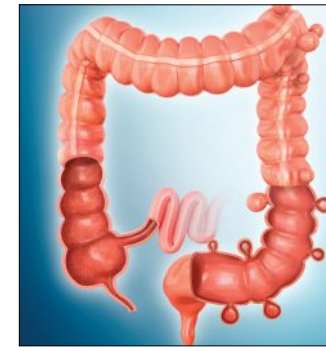


Loperamide, a commonly used OTC antidiarrheal medication, is a synthetic opioid agonist that lacks central nervous system effects when taken as directed. When supratherapeutic doses are ingested, however, this drug can cross the blood-brain barrier and result in a variety of adverse effects, including cardiovascular-related complications.



PATIENT TEACHING AID

Diverticular Disease.
See page 15

THIS MONTH
Editorial Focus:
Gastroenterologic Diseases

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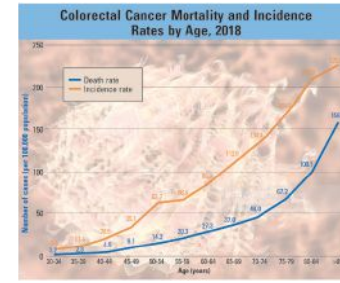

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binx health *io* CT/NG Assay

Chlamydia and gonorrhea are two of the most commonly reported bacterial sexually transmitted infections (STIs) in the United States. These STIs affect both men and women and can be associated with several long-term consequences if not treated properly. Chlamydia is often asymptomatic for both men and women, making it easily transmissible. However, untreated or incorrectly treated chlamydia infections can cause an array of complications, including cervicitis, proctitis, urethritis, epididymitis, pelvic inflammatory disease, pregnancy complications, and infertility or sterility.[1,2] Pregnant women who have chlamydia at the time of delivery can also pass the infection to their baby.

> It is estimated that one in five people in the U.S. has an STI, with the most recent data showing that there were 26 million new STIs in 2018. Chlamydia and gonorrhea are two of the most common STIs.

Gonorrhea infections are also sometimes asymptomatic, although less commonly. Symptoms of gonorrhea in men include discolored discharge from the penis, burning upon urination, or swollen testicles. Symptoms in women include burning upon urination, increased vaginal discharge, and abnormal spotting between periods.[3] Untreated gonorrhea complications include pelvic inflammatory disease in women and epididymitis in men, both of which could lead to infertility or sterility.

Both of these STIs can also increase the risk for HIV.[2,3] Coinfections with gonorrhea and chlamydia are also common, due to the often asymptomatic nature of these infections.

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Figure 1

The binx io *CT/NG assay, used to diagnose* C trachomatis *and* N gonorrhoeae.

Epidemiology

It is estimated that one in five people in the U.S. has an STI, with the most recent data showing that there were 26 million new STIs in 2018. Chlamydia and gonorrhea are two of the most common STIs, with chlamydia having a prevalence of 2.4 million and incidence of 209,000, and gonorrhea having an incidence of 4 million and a prevalence of 1.6 million. Nearly half (45.5%) of new STIs occur in teenagers and young adults, most commonly between the ages of 15 and 24 years. STIs continue to be a large financial burden for the U.S. healthcare system, with just chlamydia, gonorrhea, and syphilis accounting for over $1 billion in direct medical costs in 2018.[1]

Etiology and Transmission

Neisseria gonorrhoeae, a gram-negative bacterium, is the etiological agent for gonorrhea infections,

and *Chlamydia trachomatis*, also a gram-negative bacterium, is the etiological agent for chlamydia infections.[4] Both gonorrhea and chlamydia are STIs spread by having unprotected vaginal, oral, or anal sex. They can cause infections in the genital area, rectum, and throat. In women, infections can also spread to the cervix. Both of these infections can also be passed to a newborn via vaginal birth if a mother is infected at the time of delivery. Since these infections are often asymptomatic, they are easily transmissible. These infections can be prevented by abstaining from sex, being in a mutually monogamous relationship, or practicing safe sex practices, such as using a condom.

Diagnosis

There are different tests that may be utilized to diagnose chlamydia and gonorrhea. These tests include laboratory-based methods as well as point-of-care testing (POCT) that utilize nucleic acid amplification tests (NAAT) or polymerase chain reaction (PCR) methods.[5] Laboratory-based testing generally requires specific transportation and collection methods, which could potentially delay diagnosis and treatment of an STI. POCT methods, which are done at or near the site of care, are generally inexpensive, are rapid, and can provide accurate results during the patient visit. The World Health Organization considers the lack of POCT for STI to be an obstacle for global STI prevention.[6]

Management

Increasing rates of antimicrobial resistance led to the revision of the CDC update to the treatment for gonococcal infections in 2020. For the treatment of uncomplicated urogenital, anorectal, and pharyngeal gonorrhea, ceftriaxone given intramuscularly is recommended. If chlamydia infection has not been excluded, concurrent treatment with doxycycline administered for 7 days is also recommended.[7] For uncomplicated gonococcal infections of the pharynx, ceftriaxone is recommended, and if chlamydia coinfection exists, doxycycline is recommended for 7 days. There are no alternative treatment recommendations available for pharyngeal gonorrhea. Drug names and doses used in the treatment of chlamydia and gonorrhea are shown in **TABLE 1**.

> The binx *io* system assay uses a rapid polymerase chain reaction combined with a proprietary electrochemical detection to diagnose patients who have infections with chlamydia and gonorrhea.

Device

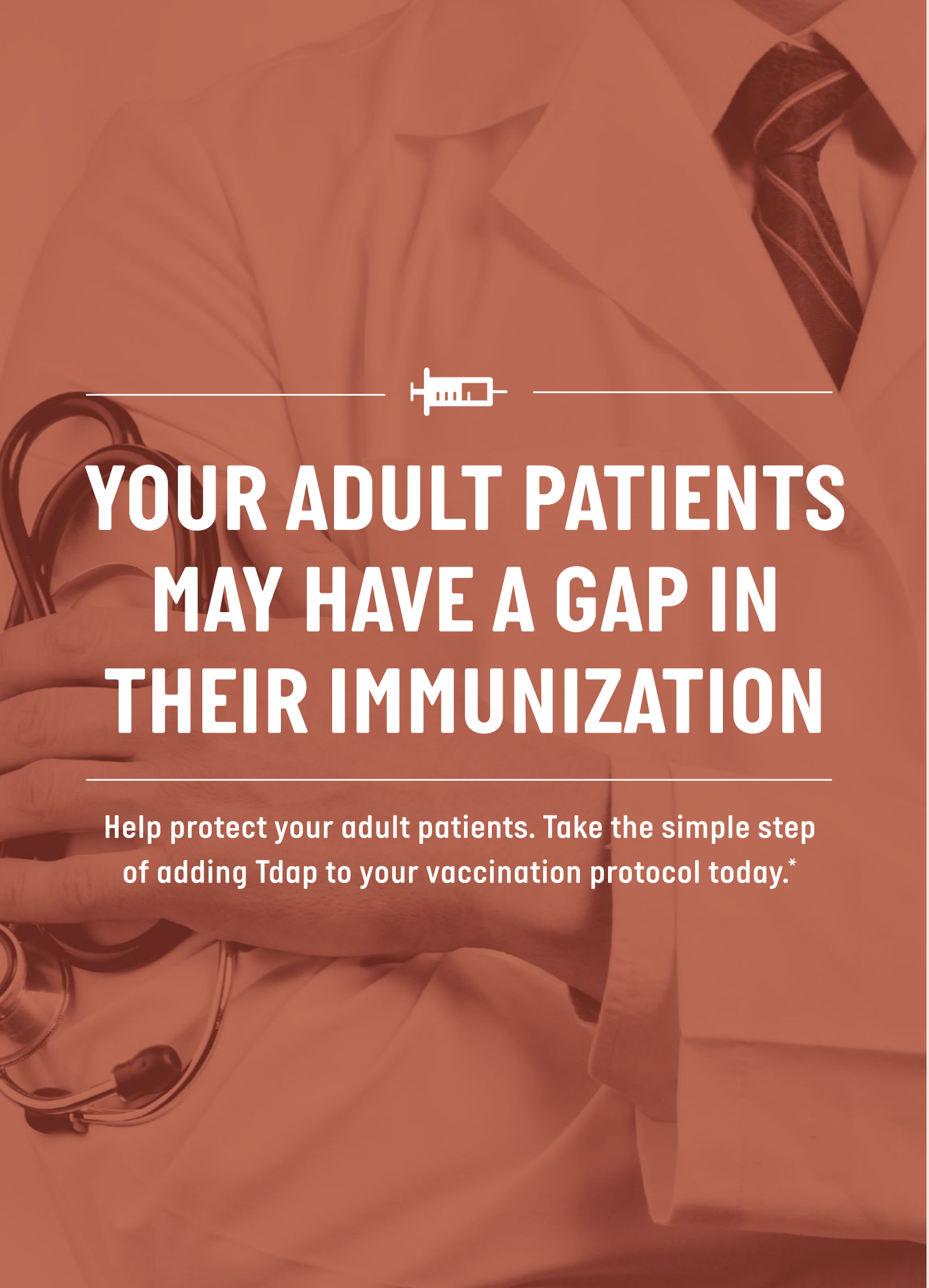
Designed by Binx Health Limited, the binx *io* CT/NG assay (**FIGURE 1**) is a clinical testing device used in the diagnosis of *C trachomatis* and *N gonorrhoeae*. In 2021, the FDA granted a clinical laboratory improvement amendment (CLIA) waiver for the binx *io* system to be used in physician offices, urgent care facilities, community health clinics, and retail settings with results in about 30 minutes.[8] The binx *io* system assay uses a rapid PCR combined with a proprietary electrochemical detection to diagnose patients who have infections with chlamydia and gonorrhea.[9] This device does not require manual manipulation, and the specimens may be obtained in a clinical setting or self-collected by a patient in a clinical setting. The binx *io* instrument processes the single-use, CT/NG cartridge that contains all reagents for use with no sample prep required. The results are easy to understand and

Table 1

Treatment for Gonococcal Infections

Drug	Ceftriaxone	Azithromycin	Cefixime[c]	Gentamicin[d]	Doxycycline[a]
Dose	Weight <150 kg: 500 mg IM Weight ≥150 kg: 1 g IM	2 g orally[d] 1 g orally[b]	800 mg orally	240 mg IM	100 mg orally twice a day

[a] Treatment for coinfection with Chlamydia trachomatis *when chlamydial infection has not been excluded. [b] Used in pregnancy to treat* C trachomatis. *[c] Alternative if ceftriaxone is not available. [d] Alternative if ceftriaxone is not available (used in combination). Source: Reference 7.*



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  - 46.1% of adults ≥19 years of age received an influenza vaccination in the 2017-2018 season.[2,†]
  - 69.0% of adults ≥65 years of age have ever received a pneumococcal vaccination as of 2018.[2,†]
- Although pertussis infection in adults is usually less severe than in babies and young children, complications can still occur. In one study, 91% of adults with pertussis (N=79) **experienced a cough for an average of 54 days**, and 61% of adults with pertussis (N=203) **missed an average of 10 days of work** in another study.[3,4]
- Depending on the vaccine, 79% to 85% of adult patients indicated they were **likely to get vaccinated if recommended by their healthcare provider.**[5]

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*For vaccine recommendations, please visit www.cdc.gov.

†Among adults for whom vaccination status could be assessed in the 2018 National Health Interview Survey.

CDC=Centers for Disease Control and Prevention; **Tdap**=tetanus, diphtheria, and acellular pertussis.

References: 1. Centers for Disease Control and Prevention. Vaccines and preventable diseases: diptheria, tetanus, and pertussis vaccine recommendations. https://www.cdc.gov/vaccines/vpd/dtap-tdap-td/hcp/recommendations.html. Updated January 22, 2020. Accessed June 23, 2021. **2.** Centers for Disease Control and Prevention (CDC). Surveillance of vaccination coverage among adult populations, United States, 2018. *MMWR*. 2021; 70(3);1–26. **3.** Postels-Multani S, Schmitt HJ, Wirsing von König CH, Bock HL, Bogaerts H. Symptoms and complications of pertussis in adults. *Infection*. 1995;23(3):139-142. **4.** Lee GM, Lett S, Schauer S, et al; for the Massachusetts Pertussis Study Group. Societal costs and morbidity of pertussis in adolescents and adults. *Clin Infect Dis*. 2004;39(11): 1572-1580. **5.** Johnson DR, Nichol KL, Lipczynski K. Barriers to adult immunization. *Am J Med*. 2008;121(7 Suppl 2):S28-S35.

Table 2

binx *io* CT/NG Assay Sensitivity and Specificity

	Female		Male	
Target	Sensitivity	Specificity	Sensitivity	Specificity
Chlamydia	96.1%	99.1%	92.5%	99.3%
Gonorrhea	100.0%	99.9%	97.3%	100%

Source: Reference 10.

displayed as detected or not detected. The device targets the chlamydia and gonorrhea genomic DNA. Sensitivity and specificity of the device can be found in **TABLE 2.**

> The development of the binx *io* CT/NG assay has paved the way for early accurate diagnosis and the subsequent effective management of chlamydia and gonorrhea at the point of care.

Efficacy

Several studies have demonstrated the efficacy of POCT in the treatment of STIs. In a study published in 2020 that was conducted by Van Der Pol and colleagues, the binx *io* CT/NG assay was compared with three FDA-approved NAAT devices. The study enrolled 1,523 women and 922 men conducted at 11 clinics throughout the U.S. It concluded that the binx *io* assay was associated with good performance compared with laboratory-based molecular diagnostics for vaginal swab samples and male urine samples.[10] Of note, 94.8% (2,318 of 2,445) of the tests were performed by non-laboratory personnel. In an earlier study conducted by Widdice and colleagues that compared the performance of the Atlas *io* diagnostic platform (binx *io* system) to Aptima Combo 2 and evaluated patient attitudes toward POCT by non–laboratory-trained personnel, the study concluded that the Atlas *io* device had higher sensitivity and specificity in women, 83.9% and 98.8%, respectively.[11] Most patients were willing to wait in the clinic for results if they could be treated before leaving.

Conclusion

Although laboratory-based diagnostic options are available, the development of the binx *io* CT/NG assay has paved the way for early accurate diagnosis and the subsequent effective management of chlamydia and gonorrhea at the point of care. This can decrease patients lost to follow-up and improve treatment success. More information can be found at https://mybinxhealth.com/point-of-care/.

The content contained in this article is for informational purposes only. The content is not intended to be a substitute for professional advice. Reliance on any information provided in this article is solely at your own risk.

REFERENCES

1. CDC. Sexually transmitted disease at a glance, 2020. www.cdc.gov/std/statistics/prevalence-2020-at-a-glance.htm. Accessed April 5, 2021.
2. CDC. Detailed STD facts—chlamydia. www.cdc.gov/std/chlamydia/stdfact-chlamydia-detailed.htm. Accessed April 5, 2021.
3. CDC. Detailed STD facts—gonorrhea. www.cdc.gov/std/gonorrhea/stdfact-gonorrhea-detailed.htm. Accessed April 5, 2021.
4. Hill SA, Masters TL, Wachter J. Gonorrhea—an evolving disease of the new millennium. *Microb Cell*. 2016;3(9):371-389.
5. CDC. Recommendations for the laboratory-based detection of *Chlamydia trachomatis* and *Neisseria gonorrhoeae*—2014. *MMWR Recommm Rep*. 2014;63(RR-02):1-19.
6. World Health Organization. Point-of-care diagnostic tests (POCTs) for sexually transmitted infections (STIs). www.who.int/reproductivehealth/topics/rtis/pocts/en/. Accessed April 13, 2021.
7. St. Cyr S, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1911-1916.
8. Binx Health press release. binx Health receives FDA CLIA waiver for chylamydia and gonorrhea test, expanding critical access to single-visit diagnoses. https://mybinxhealth.com/news/binx-health-receives-fda-clia-waiver-for-chlamydia-and-gonorrhea-test-expanding-critical-access-to-single-visit-diagnoses/. Accessed April 8, 2021.
9. Binx Health point-of-care testing. https://mybinxhealth.com/point-of-care. Accessed April 13, 2021.
10. Van Der Pol B, Taylor SN, Mena L, et al. Evaluation of the performance of a point-of-care test for chlamydia and gonorrhea. *JAMA Netw Open*. 2020;3(5):e204819.
11. Widdice LE, Hsieh YH, Silver B, et al. Performance of the Atlas rapid test for *Chlamydia trachomatis* and women's attitudes toward point-of-care testing. *Sex Transm Dis*. 2018;45(11):723-727.

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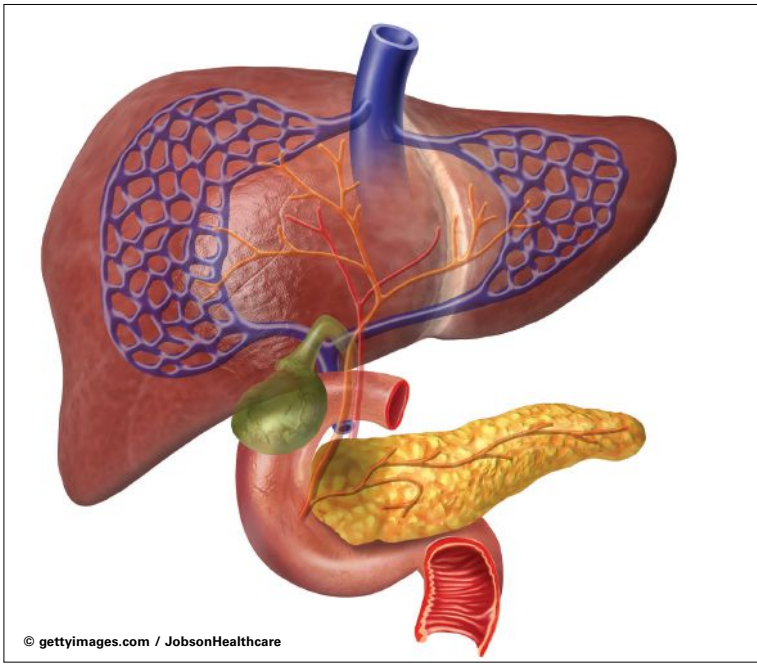
Health Systems Edition

December 2021

Diabetes-Related Gastrointestinal Emergencies: Gallstones and Acute Pancreatitis



ABSTRACT: Gastrointestinal (GI) diseases affect the alimentary tract, liver, biliary system, and pancreas. GI diseases are often encountered in the ICU setting, either as the major cause that prompted admission to the ICU or as a comorbid complication of another primary disease process. GI complications of diabetes have become increasingly prevalent as the rate of diabetes has risen. The most common and immediately life-threatening diabetes-related GI complications seen in emergency departments are gallstones and acute pancreatitis. Pharmacists in acute-care settings need to be aware of the prevalence, etiology, diagnosis, pathogenesis, and management of these two common complications of diabetes.

Gastrointestinal (GI) diseases affect the alimentary tract, liver, biliary system, and pancreas, and they are often encountered in the ICU setting, either as the major cause that prompted admission to the ICU or as a comorbid complication of another primary disease process.[1] Diabetes is a common condition, affecting 34.5 million people of all ages, or 10.5% of the U.S. population. The most common and immediately life-threatening diabetes-related GI complications seen in emergency departments are gallstones and acute pancreatitis.

In 2015, annual healthcare expenditures for GI diseases in the U.S. totaled $135.9 billion. Yearly, there were more than 54.4 million ambulatory visits with a primary diagnosis for a GI disease, 3.0 million hospital admissions, and 540,500 all-cause 30-day readmissions.[1] GI complications of diabetes have become increasingly prevalent as the rate of diabetes has risen. Up to 75% of patients with diabetes may experience GI symptoms, leading to a significant decrement in quality of life and an increase in healthcare costs. In fact, at some point in their lives, diabetic patients will develop a GI problem, such as ulcers, gallstones, irritable bowel syndrome, or another GI disorder. Both type 1 and type 2 diabetes can affect a patient's entire GI tract, from the esophagus to the anus. No data are available as to how many of the 3 million patients who are hospitalized annually for GI disease have diabetes.[2,3]

GALLSTONES

Gallstones, formally known as *cholelithiasis*, are one of the most common and costly GI diseases. These hard, pebble-like deposits that form in the gallbladder are typically composed of cholesterol or bilirubin. Gallstones can be as small as a grain of salt or as large as a golf ball. The gallbladder can make one large gallstone, hundreds of tiny stones, or both small and large stones. Gallstones can also travel from the gallbladder to the common bile duct, which is the largest of the ducts in the liver. Blockage of bile ducts by gallstones may cause sudden, severe pain in upper right portion of the abdomen. Common bile duct stones are much less common than gallstones.[4]

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Consultant Pharmacist
Rockville, Maryland

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  - 2 min onset
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  - 1-hour offset
- **No dosage adjustment for renal or hepatic impairment**[1]

Pharmacology:
>98% inhibition
of platelet aggregation in whole blood impedance aggregometry[3]

*In a post-hoc analysis of CHAMPION PHOENIX, the absolute benefit of KENGREAL increased progressively with the number of high-risk lesion features treated and was greatest for patients with ≥3.[4]

Indication

KENGREAL® (cangrelor) for Injection is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) to reduce the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

Important Safety Information

KENGREAL® (cangrelor) for Injection is contraindicated in patients with significant active bleeding.

KENGREAL® is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to cangrelor or any component of the product.

Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL®, increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

The most common adverse reaction is bleeding.

Please see Brief Summary on adjacent page.

Chiesi
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Brief Summary

KENGREAL® (cangrelor) for injection, for intravenous use

Brief Summary of Prescribing Information

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INDICATIONS AND USAGE

KENGREAL is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

CONTRAINDICATIONS

Significant Active Bleeding: KENGREAL is contraindicated in patients with significant active bleeding [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Hypersensitivity: KENGREAL is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to KENGREAL or any component of the product [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS

Bleeding: Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL, increase the risk of bleeding.

In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL than with clopidogrel [see Adverse Reactions (6.1)]. Bleeding complications with KENGREAL were consistent across a variety of clinically important subgroups [see Figure 1 in Clinical Trials Experience (6.1)].

Once KENGREAL is discontinued, there is no antiplatelet effect after an hour [see Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling: Bleeding [see Warnings and Precautions (5.1)].

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of KENGREAL has been evaluated in 13,301 subjects in controlled trials, in whom, 5,529 were in the CHAMPION PHOENIX trial.

Bleeding

There was a greater incidence of bleeding with KENGREAL than with clopidogrel. No baseline demographic factor altered the relative risk of bleeding with KENGREAL [see Table 1 and Figure 1 in Clinical Trials Experience (6.1)].

Table 1. Major Bleeding Results in the CHAMPION PHOENIX Study (Non-CABG related bleeding)[a]

CHAMPION PHOENIX	KENGREAL (N=5529)	CLOPIDOGREL (N=5527)
Any GUSTO bleeding, n (%)	857 (15.5)	602 (10.9)
Severe/life-threatening[b]	11 (0.2)	6 (0.1)
Moderate[c]	21 (0.4)	14 (0.3)
Mild[d]	825 (14.9)	582 (10.5)
Any TIMI bleeding, n (%)	45 (0.8)	17 (0.3)
Major[e]	12 (0.2)	6 (0.1)
Minor[f]	33 (0.6)	11 (0.2)

Abbreviations: GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI: Thrombolysis in Myocardial Infarction

[a]Safety population is all randomized subjects who received at least one dose of study drug

[b]intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment

[c]requiring blood transfusion but not resulting in hemodynamic compromise

[d]all other bleeding not included in severe or moderate

[e]any intracranial hemorrhage, or any overt bleeding associated with a reduction in hemoglobin of ≥5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit ≥15%)

[f]any overt sign of bleeding (including observation by imaging techniques) that is associated with a reduction in hemoglobin of ≥3 g/dL and <5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit of ≥9% and <15%)

Drug Discontinuation

In CHAMPION PHOENIX, the rate of discontinuation for bleeding events was 0.3% for KENGREAL and 0.1% for clopidogrel. Discontinuation for non-bleeding adverse events was low and similar for KENGREAL (0.6%) and for clopidogrel (0.4%). Coronary artery dissection, coronary artery perforation, and dyspnea were the most frequent events leading to discontinuation in patients treated with KENGREAL.

Non-Bleeding Adverse Reactions

Hypersensitivity - Serious cases of hypersensitivity were more frequent with KENGREAL (7/13301) than with control (2/12861). These included anaphylactic reactions, anaphylactic shock, bronchospasm, angioedema, and stridor.

Decreased renal function - Worsening renal function was reported in 3.2% of KENGREAL patients with severe renal impairment (creatinine clearance <30 mL/min) compared to 1.4% of clopidogrel patients with severe renal impairment.

Dyspnea - Dyspnea was reported more frequently in patients treated with KENGREAL (1.3%) than with control (0.4%).

DRUG INTERACTIONS

Thienopyridines: Clopidogrel or prasugrel administered during KENGREAL infusion will have no antiplatelet effect until the next dose is administered. Therefore, administer clopidogrel or prasugrel after KENGREAL infusion is discontinued [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

(cont'd on next page)

Brief Summary for KENGREAL® (cangrelor) for injection, for intravenous use (cont'd)

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on cangrelor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Untreated myocardial infarction can be fatal to the pregnant women and fetus [see Clinical Considerations (8.1)].

In animal reproduction studies, continuous infusion of cangrelor in pregnant rats and rabbits throughout organogenesis at dose approximately 2-times the maximum recommended human dose (MRHD) did not result in fetal malformations [see Data (8.1)].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Myocardial infarction is a medical emergency in pregnancy which can be fatal to the pregnant woman and fetus if left untreated. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of cangrelor on the fetus.

Labor or delivery

Cangrelor use during labor and delivery may increase the risk for maternal bleeding and hemorrhage. Performance of neuraxial blockade procedures is not advised during cangrelor use due to potential risk of spinal hematoma. When possible, discontinue cangrelor 1 hour prior to labor, delivery, or neuraxial blockade [see Clinical Pharmacology (12.2)].

Data

Animal Data

A prenatal and postnatal development study in female rats demonstrated a slight increase in the incidence of maternal mortality in dams treated at doses up to 30 mcg/kg/min (approximately 7.5 times the MRHD) cangrelor continuous infusion from Day 6 of gestation up to Day 23 post-partum. Pregnancy rates, gestation index, length of gestation, numbers of live, dead and malformed pups, sex ratio, live birth index, and lactation of the maternal animals were unaffected.

Cangrelor administered at dose levels of ≥3 mcg/kg/min in pregnant rats from Day 6 to 17 post-coitum resulted in dose-related fetal growth retardation characterized by increased incidences of incomplete ossification and unossified hind limb metatarsals.

An embryo-fetal development study in rabbits administered 4, 12, or 36 mcg/kg/min cangrelor continuous IV infusion from Day 6 to Day 19 post-coitum resulted in increased incidences of abortion and intrauterine losses at ≥12 mcg/kg/min (3 times the MRHD). Fetal growth retardation occurred at 36 mcg/kg/min (9 times the MRHD) and was characterized by decreased fetal weights, slight reduction in ossification, and a slight increase in skeletal variants.

Cangrelor did not produce malformations in either the rat or rabbit embryo-fetal development studies and is not considered to be a teratogen.

Lactation:

Risk Summary

There are no data on the presence of cangrelor in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. However, due to its short half-life, cangrelor exposure is expected to be very low in the breastfed infant.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In CHAMPION PHOENIX, 18% of patients were ≥75 years. No overall differences in safety or effectiveness were observed between these patients and those patients <75 years [see Clinical Studies (14.1)].

Renal Impairment: No dosage adjustment is required for patients with mild, moderate, or severe renal impairment [see Clinical Pharmacology (12.3)].

Hepatic Impairment: KENGREAL has not been studied in patients with hepatic impairment. However, the metabolism of KENGREAL is not dependent on hepatic function, so that dosage adjustment is not required for patients with hepatic impairment [see Clinical Pharmacology (12.3)].

OVERDOSAGE

There is no specific treatment to reverse the antiplatelet effect of KENGREAL but the effect is gone within one hour after the drug is discontinued.

In clinical trials, 36 patients received an overdose of KENGREAL, ranging from 36 to 300 mcg/kg (bolus dose) or 4.8 to 13.7 mcg/kg/min (infusion dose). The maximum overdose received was 10 times the PCI bolus dose or 3.5 times the PCI infusion dose in 4 patients. No clinical sequela were noted as a result of overdose following completion of KENGREAL therapy.

Please see Full Prescribing Information at www.KENGREAL.com.

References: 1. KENGREAL® (cangrelor) Prescribing Information. 2019. **2.** Bhatt DL, Stone GW, Mahaffey KW, et al; CHAMPION PHOENIX Investigators. *N Engl J Med.* 2013;368(14):1303-1313. **3.** Data on file. Chiesi USA, Inc. **4.** Stone GW, Généreux P, Harrington RA, et al. *Eur Heart J.* 2018;39(46):4112-4121.

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(cangrelor) for injection

Prevalence and Etiology

Gallstones are a significant health problem in developed societies, affecting 10% to 15% of the adult population; in the U.S., 20 million to 25 million people have or will develop gallstones. The resultant direct and indirect costs of gallbladder disease in the U.S. are calculated at roughly $6.2 billion annually, constituting a major health burden that has increased more than 20% over the past 3 decades. With an estimated 1.8 million ambulatory-care visits for this condition each year, gallstone disease is a leading cause of hospital admissions related to GI problems.[5]

Gallstones are encountered more frequently in patients with diabetes, which is not surprising given that risk factors for the development of stones, such as intestinal dysmotility, obesity, and hypertriglyceridemia, are more common in this population (particularly patients with type 2 diabetes). In addition, impairment of gallbladder motility and autonomic neuropathy, as well as elements such as cholesterol supersaturation and crystal nucleation–promoting factors, are considered important in the development of gallstones.[6]

In the general U.S. population, both men and women with a diabetes diagnosis were more than 50% more likely to have gallstone disease compared with persons without a diabetes diagnosis after adjustment for multiple shared risk factors. Men and women with undiagnosed diabetes (fasting plasma glucose 126 mg/dL or greater) were approximately twice as likely to have gallstone disease as those with normal fasting glucose (<110 mg/dL [<6.11 mmol/L]).

This relationship reached statistical significance only among women. Impaired fasting glucose (110-125 mg/dL) was unrelated to gallstone disease in women or men.[6]

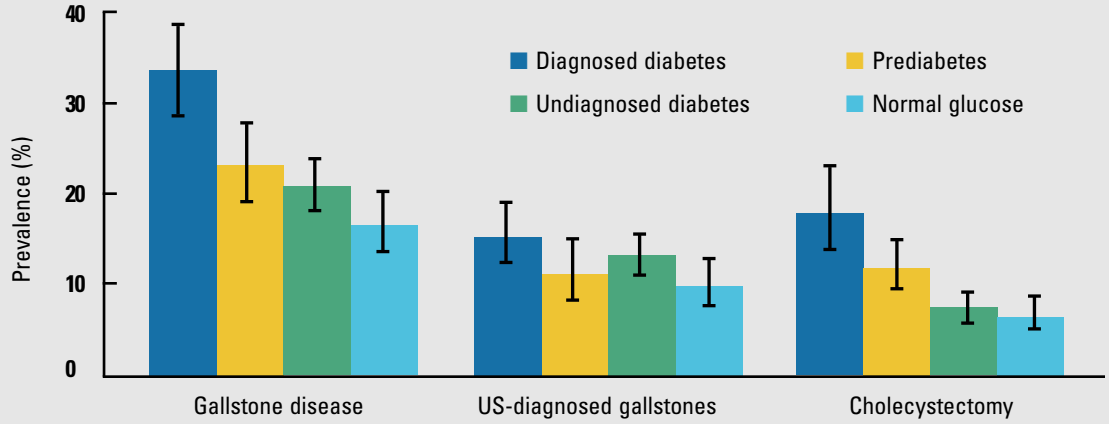
To further assess the relationship between diabetes and gallstone disease in the general U.S. population, new analyses for the publication *Diabetes in America* were conducted using gallbladder ultrasonography data on adults aged 20 to 74 years from the Third National Health and Nutrition Examination Study (NHANES III). In these analyses, gallstone-disease prevalence and odds ratios may not be identical to those in previously published NHANES III reports because of differences in definitions of diabetes and adjustment only for age (prevalence) or for age, ethnicity/race, or sex. NHANES III defines diabetes as *diagnosed* (i.e., self-reported healthcare provider diagnosis) and—in patients without a diagnosis—as *undiagnosed* (A1C 6.5% or greater, or fasting glucose 126 mg/dL or greater), prediabetes (A1C 5.7%-6.4% or fasting glucose 100-125 mg/dL), or normal glucose (A1C <5.7% and fasting glucose <100 mg/dL). The prevalence (± standard error) of gallstone disease was 33.3% ± 2.6% among patients with diagnosed diabetes, 23.3% ± 2.2% among those with undiagnosed diabetes, 20.8% ± 1.5% among those with prediabetes, and 16.7% ± 1.7% among those with normal glucose (FIGURE 1).[7]

Pathogenesis

Five primary defects play a critical role in the pathogenesis of cholesterol gallstones: *Lith* genes and genetic factors; hepatic hypersecretion of cholesterol, resulting in supersaturated gallbladder bile; rapid

Figure 1

Age-Standardized Prevalence of Gallstone Disease, US-Diagnosed Gallstones, and Cholecystectomy by Diabetes Status



[a] *U.S. data for the period 1988–1994. US: ultrasound. Source: Reference 7.*

Table 1

Complications of Gallstones

Diagnosis	Pain Site and Character	Recommended Diagnostic Tests	Laboratory Tests
Acute cholecystitis	Right-upper-quadrant pain that is steady and lasts >6 h, right-upper-quadrant tenderness, fever, chills, Murphy sign[a]	US or hepatobiliary iminodiacetic acid scan, CT if complications suspected	WBC may be elevated
Obstructive cholangitis secondary to choledocholithiasis	Right-upper-quadrant pain, exquisitely tender right upper quadrant, fever, jaundice	Endoscopic retrograde cholangiopancreatography	Leukocytosis, elevated liver enzymes
Gallstone pancreatitis	Epigastric pain, diffuse and constant	Endoscopic retrograde cholangiopancreatography	Elevated amylase and lipase

[a] *Inspiratory arrest during deep right-upper-quadrant palpation. US: ultrasound. Source: Reference 12.*

phase transitions of cholesterol in bile, with the precipitation of solid cholesterol crystals; impaired gallbladder motility with hypersecretion and accumulation of mucin gel in the gallbladder lumen and immune-mediated gallbladder inflammation; and intestinal factors involving absorption of cholesterol, slow intestinal motility, and altered gut microbiota. The principal gallbladder pathologic feature in diabetic patients is a functional deficit of uncertain etiologic factors, leading to a large, flaccid, poorly emptying organ. Bile acid and lipid composition are usually increased in diabetic patients.[8,9]

Diagnosis

The occurrence of right-upper-quadrant abdominal pain, nausea, or vomiting suggests a diagnosis of gallstones. The location, duration, and character of the pain (i.e., gnawing, cramping, or stabbing) help the clinician determine the likelihood of gallstones. The patient may exhibit abdominal tenderness and abnormally high liver-function tests. Abdominal ultrasound (US) is a sensitive, quick, and fairly inexpensive method of detecting gallstones in the gallbladder or common bile duct, and it is the test most often employed.[10]

CT should be considered in patients with negative or ambiguous US results or if complications of gallstones are suspected. Magnetic resonance cholangiopancreatography is a noninvasive screening method with high sensitivity and specificity for detecting gallstones. According to the 2010 American College of Radiology guidelines, MRI is recommended as a secondary imaging study if US does not result in a clear diagnosis of acute cholecystitis or gallstones.[11]

See TABLE 1 for more information on complications of gallstones.

Management

Surgery: *Cholecystectomy* (removal of the gallbladder), whether open or minimally invasive, remains the primary means of managing symptomatic gallstone disease; it is safe, has the lowest risk of recurrence, and provides 92% of patients with complete relief from biliary pain. Laparoscopic cholecystectomy remains the surgical choice for symptomatic and complicated gallstones, replacing open cholecystectomy as the standard of care. Laparoscopic cholecystectomy is associated with a shorter hospital stay and a shorter convalescence period than open cholecystectomy. Laparoscopic cholecystectomy continues to have numerous advantages over the open technique, and the laparoscopic approach to treating gallstone disease in various patient populations is gaining clinical acceptance based on its safety. Percutaneous cholecystostomy is an alternative for patients who are critically ill with gallbladder empyema and sepsis. Diabetic patients with symptomatic gallbladder disease usually require surgery. The cholecystectomy risk in patients with diabetes is similar to that in patients without diabetes. Formerly, prophylactic cholecystectomy was recommended for diabetic patients with silent gallstones based on an apparent high risk of cholecystitis.[11]

Nonsurgical Treatments: For asymptomatic pigmented or calcified gallstones, no medical therapy other than pain prophylaxis is recommended. For cholesterol-containing gallstones, litholysis with oral agents is a historical option not often used in current clinical practice. Symptomatic patients who are not candidates for surgery or those who have small gallstones (5 mm or smaller) in a functioning gallbladder with a patent cystic duct are candidates for *dissolution*

therapy. Options include oral ursodeoxycholic acid (ursodiol [Actigall]) and chenodeoxycholic acid (chenodiol [Chenodal]). Both agents reduce hepatic secretion of biliary cholesterol, cause formation of unsaturated bile, and promote dissolution of cholesterol crystals and gallstones. After 6 to 12 months, dissolution therapy may eventually result in dissolution of small gallstones, but the recurrence rate exceeds 50%. Oral dissolution has several disadvantages, including the lengthy time frame of observation (up to 2 years). Gallstone recurrence is another disadvantage of this treatment, as approximately 25% of patients develop recurrent gallstones within 5 years. Fewer than 10% of patients with symptomatic gallstones are candidates for this therapy. Presently, bile acid therapy is indicated only for patients unfit for or unwilling to undergo surgery. When surgery is to be avoided, extracorporeal shock wave lithotripsy is a noninvasive therapeutic alternative for symptomatic patients. Although serious adverse effects (e.g., biliary pancreatitis, liver hematoma) are rare, stone recurrence is a limitation of the procedure. Complications of gallstones include acute cholecystitis, obstructive cholangitis secondary to choledocholithiasis, and gallstone pancreatitis.[11,12]

ACUTE PANCREATITIS

Chronic pancreatitis is a continuing inflammatory disease of the pancreas that is characterized by irreversible morphological changes. These changes typically cause pain and loss of exocrine and endocrine pancreatic function. Acute pancreatitis is a condition that typically presents with abdominal pain and is usually associated with raised pancreatic enzymes in blood or urine due to inflammatory disease of the pancreas. Acute pancreatitis is an unpredictable and potentially lethal disease, and its prognosis depends mainly on the development of organ failure and secondary infection of pancreatic or peripancreatic necrosis. Despite improvements in treatment and critical care, severe acute pancreatitis is still associated with high mortality rates.[13,14]

Prevalence and Etiology

Pancreatitis is common in the U.S., with a yearly incidence of 40 per 100,000 persons; it leads to more than 300,000 inpatient admissions and 20,000 deaths annually, with costs exceeding $2.2 billion per year. From 35% to 55% of pancreatitis cases are related to gallstones.[15] Acute pancreatitis is the more common form of pancreatitis, accounting for about 275,000 hospital stays each year in the U.S.[1] The reason for the increase in acute pancreatitis is unknown. However, a concurrent trend has been the rapid worldwide increase in type 2 diabetes and obesity. Several clinical factors associated with type 2 diabetes and obesity (in particular, abdominal obesity) are known risk factors for acute pancreatitis (e.g., gallstone disease). Therefore, it can be hypothesized that in type 2 diabetic patients the risk of acute pancreatitis may be higher than that occurring in the general population.

Several clinical factors associated with type 2 diabetes and obesity (in particular, abdominal obesity) are known risk factors for acute pancreatitis (e.g., gallstone disease).

A case-control study concluded that sulfonylurea glyburide increased the risk of acute pancreatitis, but neither insulin nor metformin seemed to lower the risk. In fact, there are reports of cases of acute pancreatitis in patients using metformin after an episode of acute renal failure. Although acute pancreatitis has numerous causes, the two most common factors are alcohol abuse and biliary tract obstruction related to cholelithiasis. These two conditions account for 60% to 80% of all cases of acute pancreatitis. The incidence of gallstone pancreatitis is higher in white women older than 60 years, and it is highest in patients with small gallstones (<5 mm in diameter) or microlithiasis.[16]

In general, patients with gallstone pancreatitis tend to have a higher mortality rate than patients with alcoholic pancreatitis. In addition, the presence of type 2 diabetes significantly increases the risk of complications and death. In patients with multiorgan involvement, the mortality rate is as high as 20%. Most deaths are due to multiorgan failure and hypotensive shock.[17]

Pathogenesis

The pathogenesis of acute pancreatitis relates to inappropriate activation of trypsinogen to trypsin (the key enzyme in the activation of pancreatic zymogens) and a lack of prompt elimination of active trypsin inside

the pancreas. Activation of digestive enzymes causes pancreatic injury and results in an inflammatory response that is out of proportion to the response of other organs to a similar insult. The acute inflammatory response itself causes substantial tissue damage and may progress beyond the pancreas to a systemic inflammatory response syndrome, multiorgan failure, or death.[18]

Diagnosis

The diagnosis of acute pancreatitis is established by the presence of at least two of the following: stereotypical abdominal pain, serum amylase and/or lipase more than three times the upper limit of normal (ULN), and/or characteristic findings on abdominal imaging. Patients with acute pancreatitis typically present with midepigastric or right-upper-quadrant pain that is constant, is stabbing in character, and radiates to the back or flank.[19]

Serum pancreatic enzymes (amylase and lipase) remain the gold standard for diagnosing acute pancreatitis. If a diagnosis of acute pancreatitis is established by the presence of abdominal pain and increases in serum pancreatic enzyme activity, CT is not usually required for diagnosis in the emergency department or upon hospital admission. The onset of pancreatitis is considered to coincide with the first day of pain, not the day on which the patient presents for care or the day of hospital admission.[20]

Serum amylase and lipase are the two blood tests most commonly used to confirm a diagnosis of acute pancreatitis. Serum amylase increases in 6 to 12 hours and remains elevated for 3 to 5 days in uncomplicated acute pancreatitis. Serum lipase is elevated on the initial day and remains elevated slightly longer than amylase. If the cutoff of three times the ULN is used, the specificity of both enzymes is high. It is recommended to measure blood lipase because it is reported to be superior to all other pancreatic enzymes in terms of sensitivity and specificity.[20]

Contrast-enhanced CT and MRI of the pancreas should be reserved for patients in whom diagnosis is uncertain from clinical and laboratory assessment alone or for patients who fail to improve clinically within the first 72 hours of hospitalization. US may be useful for evaluating gallstones or biliary ductal dilation. MRI with gadolinium provides the same information about the pancreas as CT scanning; however, it provides better information regarding the biliary tree.[20]

Management

Fluid Therapy: The American College of Gastroenterology clinical guideline for initial management of acute pancreatitis states that aggressive hydration (defined as 250-500 mL/h of isotonic crystalloid solution) should be provided to all patients, unless cardiovascular or renal comorbidities exist. Early aggressive IV hydration is most beneficial in the first 12 to 24 hours but may have little benefit beyond that (strong recommendation, moderate quality of evidence). In a patient with severe volume depletion manifesting as hypotension and tachycardia, more rapid repletion (i.e., bolus) may be needed (conditional recommendation, moderate quality of evidence). Fluid requirements should be reassessed at frequent intervals within 6 hours of admission and for the next 24 to 48 hours. The goal of aggressive hydration should be to reduce blood urea nitrogen (strong recommendation, moderate quality of evidence).[21] Surgical intervention is indicated in patients with infected necrosis.

Symptom Control: The role of antibiotics in the management of early acute pancreatitis is controversial. Although some studies have shown reduced mortality with the use of antibiotics, the severity of complications makes it difficult to perform unblinded studies. Control patients who decompensate receive more surgical procedures, which may contribute to infection and bias the studies. However, the use of IV or gut-sterilizing oral antibiotics is recommended in patients with acute necrotizing pancreatitis. Antibiotics that show promising results include imipenem-cilastatin (Primaxin), cefuroxime (Zinacef), and ceftazidime (Ceptaz).[22]

CONCLUSION

GI disorders in patients with diabetes are quite common but are not typically diagnosed in the community medical practice. In the U.S., gallstones and acute pancreatitis are two leading causes of GI-related hospitalization in patients with diabetes, and their frequency continues to rise worldwide. Pharmacists in acute-care settings need to be aware of the prevalence, etiology, diagnosis, pathogenesis, and management of these two common complications of diabetes.

References available online at www.uspharmacist.com.

Updated Clinical Practice Guidelines for *C difficile* Infection in Adults

ABSTRACT: Guidelines for the management of adults with *Clostridioides difficile* infection (CDI) were recently published by the American College of Gastroenterology, followed by a focused update by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA-SHEA). Recommended treatment is based on the type of episode (primary or recurrent) as well as the number of previous recurrences and/or presence of fulminant infection. The IDSA-SHEA guidelines suggest fidaxomicin as the preferred agent for treating initial CDI, with oral vancomycin considered an acceptable alternative. For a first recurrence, standard or extended-pulsed dosing of fidaxomicin is suggested, with oral vancomycin considered an acceptable alternative. Pharmacists are in a key position to recommend appropriate antimicrobial therapy and preventive measures for CDI management.

Clostridioides difficile (formerly known as *Clostridium difficile*) is an anaerobic, gram-positive, spore-forming rod that causes up to 25% of cases of antibiotic-associated diarrhea.[1-3] The CDC has classified *C difficile* as an *urgent threat*, defined as a public-health threat that requires aggressive action.[3] Although there has been a decline in healthcare-associated *C difficile* infection (CDI), an estimated 223,900 cases in hospitalized patients and 226,400 cases of community-associated CDI were reported in the United States in 2017.[3,4] In 2021, clinical practice guidelines for CDI were updated by the American College of Gastroenterology (ACG), and the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America (IDSA-SHEA) published clinical practice guidelines focusing on the use of fidaxomicin and bezlotoxumab in adults.[5,6] This article includes information from these guidelines, with an emphasis on the IDSA-SHEA treatment recommendations.

RISK FACTORS

A number of risk factors for CDI have been identified (**TABLE 1**).[5,7-12] The main risk factors for development of CDI are exposure to the healthcare environment, advanced age (65 years or older), and exposure to antibiotics.[5,7] Receipt of an antimicrobial agent is the most significant modifiable risk factor for initial or recurrent CDI.[13] Although most antibiotics can disrupt normal intestinal gut flora, thereby creating an environment that enables growth and colonization of *C difficile*, carbapenems, clindamycin, fluoroquinolones, piperacillin-tazobactam, and third- and fourth-generation cephalosporins have been shown to confer the highest risk of infection.[8,13] Patients are at highest risk for CDI during antimicrobial therapy and within the first month after its discontinuation, and they continue to be at risk for 3 months after completion of therapy.[14]

It is unclear whether the use of acid-suppressing medications such as proton pump inhibitors (PPIs) increase a patient's risk for CDI, as some studies have shown an epidemiologic association but others have

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Table 1

Risk Factors for CDI

Initial CDI	Recurrent CDI
Antibiotic exposure	Antibiotic exposure after prior episode of CDI
Advanced age (≥65 years)	Advanced age (≥65 years)
Hospitalization (especially if long duration) or residence in long-term-care facility	Prolonged or recent stay in healthcare facility
Acid-suppression therapy (conflicting data)	Acid-suppression therapy
Immunosuppression	Infection with a hypervirulent strain
Abdominal surgery/ nasogastric tube	Prior episode of CDI
Diabetes mellitus	
End-stage renal disease	
Inflammatory bowel disease	

CDI: Clostridioides difficile *infection.*
Source: References 5, 7-12.

Table 2

Criteria for Determining CDI Severity

Definition	Supportive Data
Nonsevere infection	WBC count ≤15,000 cells/ mL and SCr <1.5 mg/dL
Severe infection	WBC count ≥15,000 cells/ mL or SCr >1.5 mg/dL
Fulminant infection	Hypotension or shock, ileus, or megacolon

CDI: Clostridioides difficile *infection; SCr: serum creatinine. Source: References 5, 13.*

not; additional studies are needed to confirm causality.[8,9,11-13] The guidelines state that unnecessary PPIs should always be discontinued but that there is not enough evidence to discontinue a PPI for prevention of CDI.[5,13]

Recurrent CDI may occur after completion of treatment, and approximately 25% of patients with a first episode of CDI will have a recurrent infection.[10,13,15,16] The risk of recurrence increases with the number of CDI episodes, with up to 45% of patients experiencing recurrent CDI after the second episode and more than 60% having a recurrence after three or more episodes.[10,16]

CLINICAL PRESENTATION AND CLASSIFICATION

Clinical manifestations of CDI vary from asymptomatic carriage of the organism to mild or moderately acute watery diarrhea to severe colitis; potential life-threatening complications include sepsis, renal failure, toxic megacolon, and bowel perforation.[7,8] Criteria for the definitions of nonsevere, severe, and fulminant CDI are presented in TABLE 2.[5,13]

DIAGNOSIS

Because colonization with *C difficile* is common, it is recommended that testing be performed only in patients with symptoms consistent with active CDI, which is characterized by unexplained new-onset diarrhea (i.e., three or more unformed stools within 24 hours).[5,13] A two-step testing algorithm should be used to increase the accuracy of diagnosis of active CDI.[5] The ACG guidelines recommend starting with a sensitive test, such as nucleic acid amplification testing (NAAT) or glutamate dehydrogenase (GDH). If the initial test is negative, then the patient does not have active CDI. If the initial test is positive, additional testing is recommended owing to limitations in the use of NAAT or GDH. Although NAAT is sensitive for detecting the presence of toxigenic strains of *C difficile,* it cannot distinguish between colonization and active production of toxin. The absence of GDH is strongly predictive of the absence of CDI; however, this enzyme may be produced by other clostridial species as well as by non–toxin-producing strains of *C difficile*. Therefore, if the result of one of these initial tests is positive, then a highly specific test, such as an enzyme immunoassay (EIA) that detects *C difficile* toxins A and B, should be used. If that result is also positive, the patient is diagnosed with active CDI. Discordant results (i.e., the initial sensitive test is positive and the EIA is negative) require further clinical evaluation to determine whether the patient has active CDI.[5]

TREATMENT

The IDSA-SHEA recommendations for CDI treatment and dosing regimens, selected adverse effects, and considerations for the use of CDI agents are presented in TABLE 3.[6,13,17-20] The antimicrobial agent(s) that may have led to CDI should be discontinued, if possible, in order to decrease the risk of CDI recurrence; additionally, any fluid or electrolyte imbalances occurring as a result of CDI should be corrected.[9,13,21]

First Episode

The IDSA-SHEA guidelines state that fidaxomicin for 10 days at a standard dosing regimen is the preferred treatment for an initial episode of CDI; this recom-

Table 3

IDSA-SHEA Treatment Recommendations for CDI in Adults

Type of Infection	Preferred Regimen[a]	Alternative Regimen[a]	Additional Recommendations	Selected ADRs/ Considerations for Use
Initial episode[b]	Fidaxomicin (standard dosing): 200 mg po bid for 10 days	Vancomycin (standard dosing): 125 mg po qid for 10 days	For nonsevere CDI, metronidazole 500 mg po tid for 10-14 days is an alternative if other agents are not available	**Fidaxomicin:** minimal systemic absorption; hypersensitivity potential in patients with macrolide allergy. **Oral vancomycin:** minimal systemic absorption; consider monitoring trough levels owing to potential for systemic absorption and drug accumulation in patients with renal failure, prolonged duration of use (≥10 days), and/or altered integrity of intestinal mucosa. **Metronidazole:** avoid repeated or prolonged courses owing to risk of neurotoxicity; avoid alcohol during treatment and for 3 days after therapy completion
First recurrence	Fidaxomicin (standard dosing): 200 mg po bid for 10 days or Fidaxomicin (extended-pulsed dosing): 200 mg po bid for 5 days, then once every other day for 20 days	Vancomycin (standard dosing): 125 mg po qid for 10 days or Vancomycin (example of tapered and pulsed regimen): 125 mg po qid for 10-14 days, then bid for 7 days, then once daily for 7 days, then q2-3d for 2-8 wk	Adjunctive bezlotoxumab 10 mg/kg IV given once during antibiotic therapy (in selected patients)[b]	**Bezlotoxumab:** use only in patients with history of CHF when benefit outweighs risk; limited data on its use with fidaxomicin
Second or subsequent recurrence	Fidaxomicin (standard dosing): 200 mg po bid for 10 days or Fidaxomicin (extended-pulsed dosing): 200 mg po bid for 5 days, then once every other day for 20 days or Vancomycin 125 mg po qid for 10 days followed by rifaximin 400 mg po tid for 20 days or Vancomycin (example of tapered and pulsed regimen): 125 mg po qid for 10-14 days, then bid for 7 days, then once daily for 7 days, then q2-3d for 2-8 wk or FMT		Reserve FMT for patients who have received appropriate antibiotic treatment for ≥2 episodes of recurrence (or 3 CDI episodes). Adjunctive bezlotoxumab 10 mg/kg IV given once during antibiotic therapy (in selected patients)[b]	**Rifaximin:** minimal systemic absorption; concerns about rates of *Clostridioides difficile* resistance. **FMT:** risk for infection

Continued >>

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Table 3

IDSA-SHEA Treatment Recommendations for CDI in Adults (cont.)

Type of Infection	Preferred Regimen[a]	Alternative Regimen[a]	Additional Recommendations	Selected ADRs/ Considerations for Use
Fulminant	Vancomycin 500 mg po or via nasogastric tube qid and metronidazole 500 mg IV q8h. If patient has ileus, consider adding vancomycin rectal enema (created by combining 500 mg of vancomycin with 100 mL of normal saline) given q6h as retention enema		Surgical intervention may be necessary	**Rectal vancomycin:** may be systemically absorbed in the case of inflamed intestinal mucosa

[a] Dosing in adults with normal renal and hepatic function. [b] Consider adjunctive use of bezlotoxumab (based on logistics/ resources such as insurance coverage) in patients with an initial or recurrent CDI episode who have risk factors for recurrent infection; suggested for use in patients with a CDI recurrence within the previous 6 months. ADR: adverse drug reaction; CDI: Clostridioides difficile *infection; CHF: congestive heart failure; FMT: fecal microbiota transplantation; IDSA-SHEA: Infectious Diseases Society of America and Society for Healthcare Epidemiology of America. Source: References 6, 13, 17-20.*

mendation is conditional, with a moderate certainty of evidence. Oral vancomycin for 10 days at a standard dosing regimen is an acceptable alternative.[6]

Recurrent CDI

First Recurrence: The IDSA-SHEA guidelines suggest using fidaxomicin as a standard or extended-pulsed dosing regimen over vancomycin in patients with a first recurrence of CDI; this is a conditional recommendation with a low certainty of evidence. The guidelines also state that vancomycin (either standard dosing or a tapered and pulsed regimen) is an acceptable alternative.[6]

Multiple Recurrences: The IDSA-SHEA guidelines include several treatment options for patients with multiple (i.e., two or more) recurrences of CDI. Additionally, fecal microbiota transplantation (FMT) is an option for those with multiple recurrences; however, it is recommended that FMT be reserved for patients who have received appropriate antibiotic treatment for at least two episodes of recurrence (or three CDI episodes). This is because of the potential for adverse events such as transmission of pathogenic organisms, including *Escherichia coli* and severe acute respiratory syndrome coronavirus 2.[6]

Fulminant CDI

Recommended treatment of *fulminant CDI* (characterized by hypotension or shock, ileus, or megacolon) has not changed from the previous version of the guidelines.[6,13] Importantly, there is no current evidence to support the use of fidaxomicin for fulminant infections, so this agent is not recommended for fulminant CDI.[6] Patients with fulminant CDI may also require surgical management.[6,8]

ADJUNCTIVE AGENTS

Bezlotoxumab

Bezlotoxumab is a humanized monoclonal antibody that binds to and neutralizes *C difficile* toxin B.[6,20] It was approved in 2016 as a single-dose infusion in conjunction with antibiotic therapy for CDI to reduce recurrent CDI in adults at high risk for recurrence.[6,20] The IDSA-SHEA guidelines suggest the addition of bezlotoxumab to antibiotic therapy (given at any time during antibiotic therapy) in patients who had a CDI recurrence within the previous 6 months.[6] Patients with a first episode of CDI who have additional risk factors (particularly those with multiple risk factors) for recurrence, such as age 65 years or older, immunocompromised status, or severe CDI, may benefit from the addition of bezlotoxumab to antibiotic therapy in settings with available resources for its use.[6,15]

It is important to note that bezlotoxumab carries a warning of heart failure based on higher rates of heart failure reported in patients taking bezlotoxumab compared with placebo; this adverse event occurred primarily in patients with a history of congestive heart failure (CHF).[20] Therefore, in patients with a history of CHF, bezlotoxumab should be used only when the benefit outweighs the risk.[6,20] The IDSA-SHEA guidelines acknowledge that most studies of bezlotoxumab with antibiotics used vancomycin or metronidazole and that data on its combination with fidaxomicin are limited.[6] Additionally, the use of this agent may be limited by logistical factors

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such as insurance coverage, particularly in patients with a first episode of CDI.[6]

Probiotics

According to the 2020 American Gastroenterological Association (AGA) guidelines on the role of probiotics in managing gastrointestinal (GI) disorders, probiotics should be used only in the context of a clinical trial on the treatment of patients with CDI. This is based on a knowledge gap, and standardized studies are needed in order to more clearly identify which specific probiotics are beneficial and which populations are most appropriate for their use.[22]

MONITORING

Patients should be monitored for resolution of signs and symptoms of infection, and they should be counseled regarding the risk of infection recurrence.[13,16] Repeat testing (within a 7-day period) of stool during the same episode of diarrhea or after treatment to confirm infection eradication is not recommended.[13] However, recurrent infection should be considered (with appropriate testing performed) in patients who develop new or worsening diarrhea after completing successful treatment for CDI.[13,16] Selected side effects and usage considerations for agents used to treat CDI are listed in TABLE 3.[6,13,17-20]

PREVENTION

A multifactorial approach is recommended for the prevention of CDI. This includes infection prevention measures (e.g., hand hygiene, isolation precautions, contact precautions, and appropriate environmental cleaning and disinfection) as well as implementation of antimicrobial stewardship programs that restrict high-risk antibiotics and focus on minimizing the use and duration of unnecessary antimicrobial agents.[5,13,21]

Vancomycin for Suppression or Prophylaxis

The updated ACG guidelines state that the use of oral vancomycin as prophylaxis (to prevent recurrence) may be considered in patients with a recent history of CDI who require antibiotic treatment and are at high risk for recurrent infection (i.e., aged 65 years or older or significantly immunocompromised and hospitalized within the previous 3 months for severe CDI); this is a conditional recommendation with a low quality of evidence. The suggested dosage of vancomycin for prophylaxis is 125 mg orally once daily, continued for 5 days after completion of antibiotic therapy.[5]

Additionally, long-term suppression with oral vancomycin may be used in patients with recurrent CDI who are not candidates for FMT, developed a recurrence after FMT, or require antibiotics (either ongoing use or frequent courses); this recommendation is conditional with a very low quality of evidence. The suggested dosage of vancomycin for chronic suppression is 125 mg orally once daily.[5]

Recommendations on Probiotics

The ACG guidelines advise against the use of probiotics for primary prevention in patients receiving antibiotics or for secondary prevention of CDI recurrence.[5] However, regarding their role in managing GI disorders, the AGA guidelines suggest that probiotics may be used in patients receiving antibiotics in order to prevent CDI; this is a conditional recommendation with a low quality of evidence.[22] The AGA guidelines recommend using specific strains and combinations of strains (over no probiotics or other probiotic agents), including *Saccharomyces boulardii*; a combination of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R; a 3-strain combination of *L acidophilus, Lactobacillus delbrueckii* subspecies *bulgaricus,* and *Bifidobacterium bifidum*; or a combination of the previously listed 3-strain probiotics plus a fourth agent, *Streptococcus salivarius* subspecies *thermophilus*. Acknowledging that the beneficial effects of probiotics were demonstrated mainly in patients at very high risk for developing CDI, the AGA guidelines state that it is reasonable to not use probiotics for CDI prevention in patients (especially those in the outpatient setting) who have a low risk of CDI or those (particularly if they are immunocompromised) who want to avoid either the cost or the potential harms of probiotics.[22]

THE PHARMACIST'S ROLE

Pharmacists are in a key position to educate patients and healthcare providers about risk factors for CDI, as well as to collaborate with clinicians to ensure appropriate treatment of initial or recurrent infection based on patient-specific factors. Pharmacists are also integral to establishing and implementing antimicrobial stewardship programs that focus on appropriate antibiotic use in order to decrease the risk of CDI.

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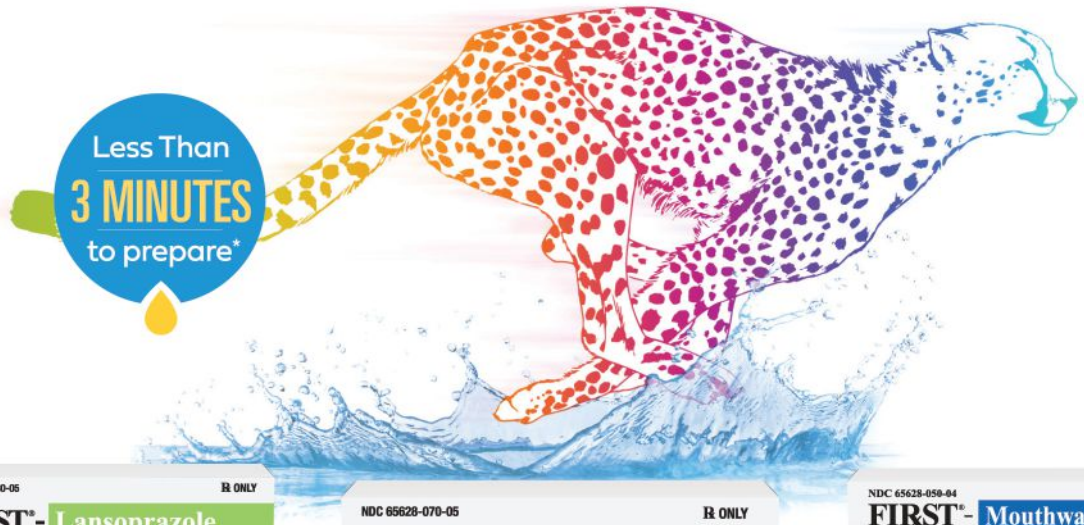

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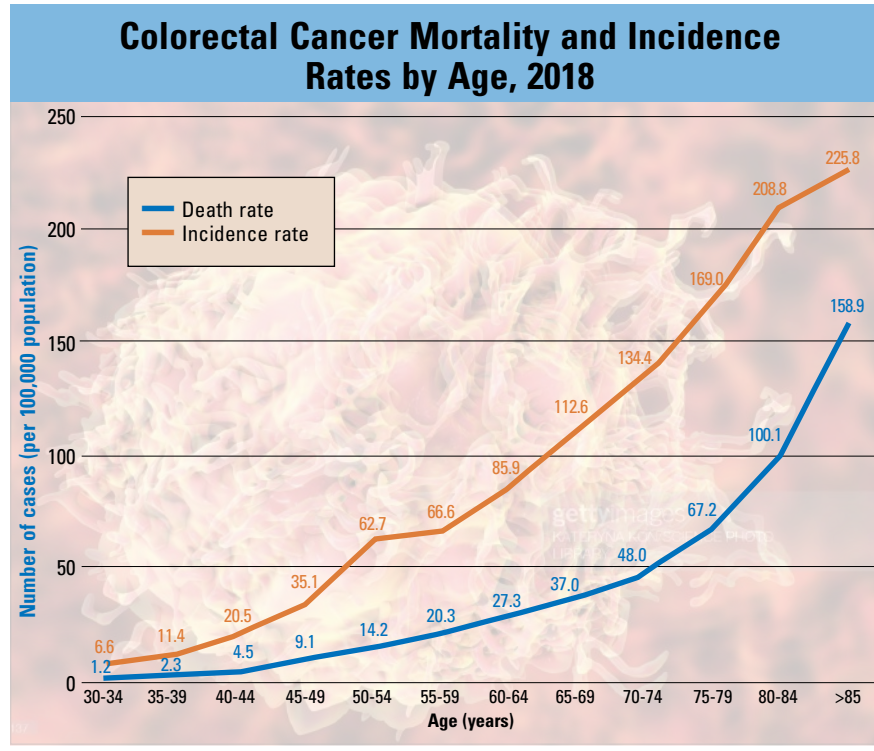
Incidence, Survival, and Mortality Rates for Colorectal Cancer

According to *U.S. Cancer Statistics* data for 2018, the incidence of colorectal cancer was 30.3% higher in men (41.7 per 100,000 population) than in women (32 per 100,000 population). The highest incidence was among African Americans (40.4), and there were 11.4% fewer cases among whites (35.8). In addition, 16% more cases occurred among Hispanics (32.3) compared with Asian/Pacific Islanders (27.8); this rate was slightly higher than that for American Indian/Alaska Natives (25.7). Although the incidence rate exceeded the mortality rate across races and ethnicities, the smallest difference was among African Americans, whose incidence rate was approximately 1.4 times higher than the mortality rate, and the largest difference was among Asian/Pacific Islanders, whose incidence rate was 2.1-fold higher than their mortality rate.



Incidence by Age: Incidence rates of colorectal cancer rose with age progression. For persons in the age ranges of 30 to 34 years and 50 to 54 years, there was a mean increase of 75.6% in the number of new cases of colorectal cancer per 100,000 population. Among persons older than 54 years, the rate of increase was significantly less, varying between 23% and 31%. The lowest increase in incidence rate (8%) occurred between the age groups 80 to 84 years and 85 years or older.

Five-Year Survival: The 5-year survival rate for colorectal cancer was greater for females (64.5%) than for males (62.6%). However, from the ages of 55 to 74 years and 45 to 54 years, 5-year survival increased to 65.5% and 70.7%, respectively. White persons (63.8%) had an 8.3% increased 5-year survival rate compared with African American persons (58.9%). There was an 6.8% increased 5-year survival among white females (64.7%) compared with African American females (60.6%), and the rate was 10.2% greater for white males (62.9%) than for African American males (57.1%).

Mortality by Race/Ethnicity and Sex: Even though mortality rates for colorectal cancer were approximately 45% more common among males of all racial backgrounds, African American men had the highest mortality rate. Whereas 54% more deaths occurred in African American males (21.3 per 100,000) than in their female counterparts (13.8 per 100,000), the greatest difference (66.7%) between males (14 per 100,000) and females (8.4 per 100,000) occurred among Hispanic persons. The smallest difference (36%) in mortality rates was between male (11.7 per 100,000) and female (8.6 per 100,000) Asian/Pacific Islanders.

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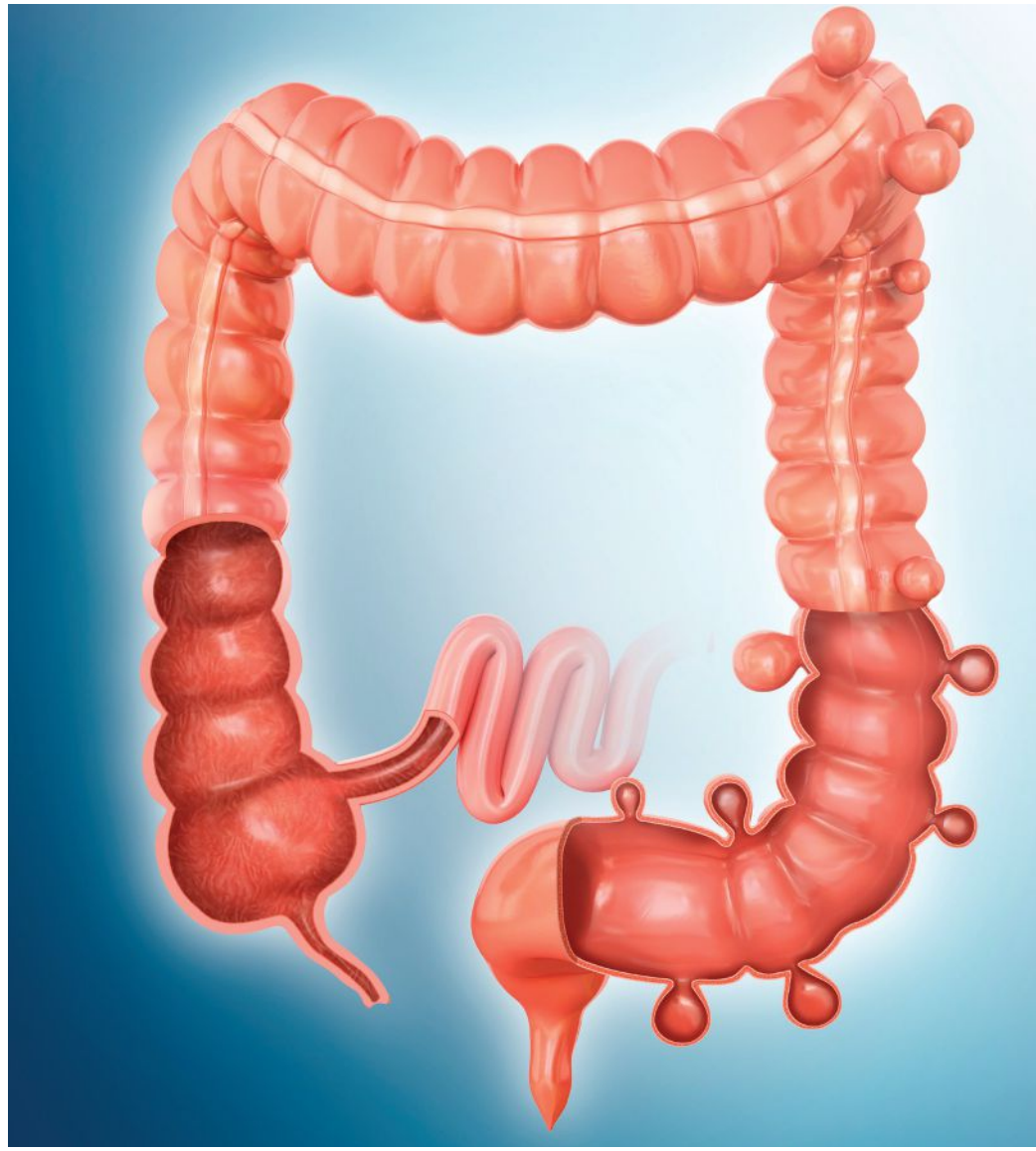
Diverticular Disease

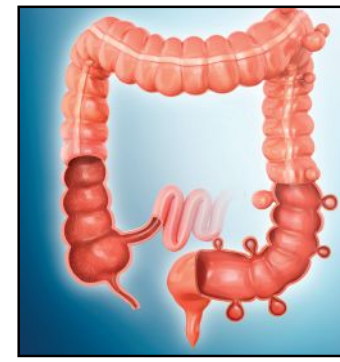


Small Pouches in Digestive Tract

Diverticular disease *is a widespread gastrointestinal condition where small pouches form in the lining of the digestive tract. Each one of these pockets or sacs is called a* diverticulum. *It is present in 70% of people aged 80 years or older, with similar rates for men and women. For some, these sacs can be present in the intestine and not cause any noticeable symptoms. For others, however, the symptoms can be severe, and further dangerous complications can arise.* Diverticulosis *is the presence of diverticula without associated complications and is the most common finding during a routine colonoscopy. However, when these pouches become inflamed, it is called* diverticulitis.

continued

Genetic and Environmental Causes



A diverticulum happens when the inside lining of the intestine pushes through a weak spot in the outer lining.

A diverticulum happens when the inside lining of the intestine pushes through a weak spot in the outer lining, causing a herniation. For many individuals in the United States, diverticulosis mainly affects the lower-left portion of the large intestine. However, they can be found anywhere in both the small and large intestines. The cause of diverticular disease is not fully understood. Still, many factors can contribute to the development of the condition. These factors include a genetic predisposition, diet and fiber intake, obesity, and low physical activity. Of these, genetics likely contributes the most, or 40% to 50% of the risk, to diverticular disease. Many do not have noticeable symptoms, but some do experience chronic symptoms similar to irritable bowel syndrome, including persistent bloating and discomfort in the lower abdomen and changes in bowel habits. Diagnosis typically occurs during a routine colonoscopy screening.

Diverticulitis Is an Acute Complication

Diverticulitis, or inflammation of the diverticulum, can occur when fecal matter becomes trapped in the pouch and the intestinal lining becomes irritated and inflamed. Approximately 25% of people with diverticula will experience symptomatic diverticulitis. Diverticulitis can lead to severe complications if left untreated or unnoticed, including abscesses, fistulas, bowel obstruction, or bowel rupture. The symptoms of diverticulitis can vary, with some individuals experiencing pain or discomfort in the left-lower abdomen, bloating, nausea or vomiting, severe constipation, or diarrhea. Medications, such as oral steroids and nonsteroidal anti-inflammatories (including ibuprofen), are associated with a higher risk of diverticulitis.

To diagnose diverticulitis, doctors perform a CT scan of the abdomen. The CT scan can identify inflamed or infected pouches and help assess the severity of diverticulitis to guide treatment.

Emerging Evidence About Prevention and Treatment

In the past, individuals with diverticulosis were advised to avoid foods with indigestible pieces, such as popcorn, or fruits and vegetables with small seeds, such as tomatoes. However, more recent studies have shown that those who avoid such foods do not lower their risk of diverticulitis, so avoidance is no longer recommended. Eating a high-fiber diet, reducing red meat in the diet, losing weight, and exercising all can help lower the risk of diverticulitis. Doctors may use laxatives in people prone to constipation to prevent hard stools from developing. For others who have painful spasms, antispasmodics or muscle relaxants may be used to improve symptoms.

There are no specific treatments for diverticulitis or for preventing and treating diverticular disease. Most medications only manage the symptoms and complications that may arise. Antibiotics can be prescribed to eliminate infections for some individuals with complicated diverticulitis. Routine use of antibiotics for uncomplicated diverticulitis is no longer recommended. Some studies suggest improved symptoms with the use of probiotics for uncomplicated diverticulitis. Vigorous activity has been proven to reduce the risk of acute diverticulitis and bleeding.

Elective surgery to remove part of the intestine was previously used to manage diverticulitis in people after their second acute episode. It was thought that after two or more acute bouts with diverticulitis, the risk of complications was higher. More recently, studies have supported other additional criteria to be used, such as age and severity, to determine the need for surgery. Surgery may be required if a severe complication, such as an obstruction, abscess, or perforation, is present.

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BRIEF SAFETY STATEMENT

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Probiotic Use in Gastrointestinal Disorders

ABSTRACT: Probiotics are live microorganisms that are available without a prescription for use as dietary supplements. In the United States, millions of adults have taken some form of probiotic to treat or prevent a variety of conditions, most commonly gastrointestinal (GI) disorders. Based on the widespread use of these products specifically for improvement of GI health, in 2020 the American Gastroenterological Association published clinical practice guidelines with evidence-based recommendations for probiotics in the treatment and/or prevention of prioritized disorders. Pharmacists should incorporate these recommendations into patient care and educational activities as appropriate, and they should understand the variations in available probiotic formulations and combinations as well as the need for more research to determine the safety and potential health benefits of different probiotic strains.

The human gut is thought to contain trillions of microbial cells of different species that are responsible for various metabolic functions, protect against disease-causing bacteria, and maintain overall intestinal health. Disruptions to the gut environment, often caused by bacterial infections, dietary changes, or antibiotic use, can contribute to the development of various chronic diseases. Reintroducing beneficial bacteria, which are present in probiotic products, has been found instrumental in restoring gut microbial homeostasis.[1]

Probiotics

The Food and Agriculture Organization and the World Health Organization define *probiotics* as "live microorganisms which when administered in adequate amounts confer a health benefit on the host."[2] Probiotics, which are available without a prescription, are added to a variety of food sources, such as cultured milk products, breakfast cereals, and infant formula, and are in some cosmetic products. For nutritional purposes, probiotics are available in both tablet and powder formulations. Over the past two decades, interest in the role of probiotics in improving various conditions has greatly increased, particularly among persons with gastrointestinal (GI) disorders.[3,4] In 2012, a National Health Interview Survey found that approximately 4 million U.S. adults (1.6%) had used a probiotic product in the previous 30 days, making probiotics one of the most-used dietary supplements other than vitamins and minerals.[5]

Mechanisms of Action

The mechanisms of action for the benefits of probiotics are multifactorial, complex, and not entirely understood. In addition, it is difficult to find commonality with probiotics, as they are all not alike. Benefits seen with one species of probiotic cannot be generalized and assumed to occur with another. Some general mechanisms include 1) immunomodulation through induction of protective cytokines and suppression of proinflammatory cytokines in the GI mucosa; 2) displacement of pathogenic bacteria, thereby inhibiting invasion, adherence, and proliferation in the epithelium; 3) improvement of intestinal-barrier function; 4) protection from physiological stress through increased gamma-aminobutyric acid receptor expression in the brain; and 5) analgesic effects through mu-opioid and cannabinoid receptor induction in intestinal epithelial cells.[3,6]

Probiotic Qualifications

The most common microorganisms used in probiotics

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belong to the *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces* genera; other genera include *Streptococcus*, *Enterococcus*, *Escherichia*, and *Bacillus*.[5] For a microorganism to be considered a probiotic, several criteria must be met. First, the organism must be properly categorized through accurate strain identification and genus and species naming. The probiotic must also be deemed safe for human consumption in foods and supplements, and it must be free of pathogenic bacteria and not contain any transferable antibiotic-resistant genes. The probiotic must be able to survive transit through the intestinal tract and must endure the acid and bile contents in the upper-GI tract before reaching the small intestine and colon; it also must adhere to the intestinal mucosa and colonize for a brief time in the intestines. Additionally, the probiotics must demonstrate positive effects on a person's health, with this benefit documented in at least one phase II study. Finally, the probiotic must maintain stability during processing and while stored. Throughout its shelf life, the product should contain sufficient levels of the probiotic strain to deliver its claimed health benefit.[6]

Regulation

In the U.S., probiotics are sold primarily as dietary supplements (capsules, powders, liquids, etc.) and do not require FDA approval before they become available on the market. These products are regulated as vitamins and food, and they often contain various strains at different quantities. Probiotics are referred to by their genus, species, and strain and are measured in colony-forming units (CFU). CFU indicate an estimate of the number of live and active microbial cells in one serving of a probiotic supplement. Probiotic CFU counts may be included on product labels (e.g., 1 × 109 for 1 billion CFU, 1 × 1010 for 10 billion CFU). Many probiotic supplements contain 1 billion to 10 billion CFU per dose, but some products contain up to 50 billion or more CFU. However, a higher CFU count does not necessarily increase a product's claimed health benefit.[7]

Current labeling regulations require manufacturers to list only the total weight of the microorganisms on a probiotic product's Supplement Facts label. This weight includes both live and dead microorganisms and does not correlate to the actual number of viable microorganisms in the product. Manufacturers may voluntarily list a product's CFU—ideally, for each strain—along with total microorganism weight on the Supplement Facts label, provided that it is not misleading. Because probiotics must be consumed live to have health benefits and can die during their shelf life, consumers should seek products that are labeled with the number of CFU at the end of the product's shelf life, not at the time of manufacture.[8] Consumers should also be aware of the storage instructions for products; some require refrigeration, whereas others may be stored at room temperature.[7,8]

Probiotics and GI Health

Some of the more commonly recommended probiotics available commercially are Align (*Bifidobacterium longum* subsp. *infantis* 35624), Bacid (*Lactobacillus acidophilus*), Culturelle (*Lactobacillus rhamnosus* GG), Florastor (*Saccharomyces boulardii*), and VSL#3 (*L acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus delbrueckii* subsp. *bulgaricus, Bifidobacterium breve, B longum, Bifidobacterium infantis, Streptococcus thermophilus*). Probiotic interventions have shown promise in various areas of medicine, most notably with regard to GI disorders.[9] In 2020, the American Gastroenterological Association (AGA) published evidence-based clinical practice guidelines on the role of probiotics in managing 1) *Clostridioides difficile*–associated diseases; 2) inflammatory bowel disease; 3) irritable bowel syndrome; 4) infectious gastroenteritis; and 5) necrotizing enterocolitis. The aforementioned were prioritized for review by the AGA based on data suggesting that probiotics are most commonly considered for these particular GI disorders and on the lack of sufficient evidence for other GI conditions.[4]

AGA 2020 Clinical Practice Recommendations

C difficile–Associated Diseases: The AGA recommends the use of probiotics in patients with *C difficile* infection only in the context of a clinical trial.[4] For adults and children on antibiotic treatment, *S boulardii* or the combinations of *L acidophilu*s CL1285 plus *L casei* LBC80R or *L acidophilus* plus *L delbrueckii* subsp. *bulgaricus* plus *Bifidobacterium bifidum* with or without *Streptococcus salivarius* subsp. *thermophilus* are recommended over no or other probiotics in order to prevent *C difficile*. It is important to note that the benefit effect for prevention of *C difficile* was driven by patients at high risk (>15%) for developing the infection.[4]

Inflammatory Bowel Disease: In adults and children with Crohn's disease or ulcerative colitis, the AGA recommends probiotic use only in the context of a clinical trial.[4] Studies evaluating probiotics' role in the induction or maintenance of remission of inflammatory bowel disease were determined to be of low quality, consisted of small sample sizes, were heterogeneous, and included

variable strains of probiotics. However, the AGA does suggest the use of an eight-strain combination (*Lacticaseibacillus paracasei* subsp. *paracasei* DSM 24733, *L plantarum* DSM 24730, *L acidophilus* DSM 24735, *L delbrueckii* subsp. *bulgaricus* DSM 24734, *B longum* subsp. *longum* DSM 24736, *B breve* DSM 24732, *B longum* subsp. *infantis* DSM 24737, and *S salivarius* subsp. *thermophilus* DSM 24731) over no or other probiotics for the treatment of pouchitis in adults and children with inflammatory bowel disease.[4]

Irritable Bowel Syndrome: In adults and children with symptomatic irritable bowel syndrome, the AGA recommends probiotic use only in the context of a clinical trial.[4] Although 76 randomized, controlled trials were identified and reviewed for probiotic use in irritable bowel syndrome, these trials used 44 different probiotic strains or combinations of strains for various durations. These trials were also found to have significant heterogeneity in study design and outcomes.[4]

Infectious Gastroenteritis: The use of probiotics in children with acute infectious gastroenteritis is not recommended by the AGA.[4] The majority of studies have been conducted outside of the U.S. and Canada and used various probiotics and combination products. Two high-quality studies from the U.S. and Canada failed to demonstrate any benefit in this patient population.[4]

Necrotizing Enterocolitis: In preterm (gestational age <37 weeks) and low-birthweight infants, the AGA recommends the use of the following to prevent necrotizing enterocolitis over no or other probiotics: combination *Lactobacillus* and *Bifidobacterium* spp. (*L rhamnosus* ATCC 53103 and *B longum* subsp. *infantis*; or *L casei* and *B breve*; or *L rhamnosus*, *L acidophilus*, *L casei*, *B longum* subsp. *infantis*, *B bifidum*, and *B longum* subsp. *longum*; or *L acidophilus* and *B longum* subsp. *infantis*; or *L acidophilus* and *B bifidum*; or *L rhamnosus* ATCC 53103 and *B longum* Reuter ATCC BAA-999; or *L acidophilus*, *B bifidum*, *Bifidobacterium animalis* subsp. *lactis*, and *B longum* subsp. *longum*), or *B animalis* subsp. *lactis* (including DSM 15954), or *Limosilactobacillus reuteri* (DSM 17938 or ATCC 55730), or *L rhamnosus* (ATCC 53103 or ATC A07FA or LCR 35).[4] Findings from 63 studies that compared probiotics (single and combination products) against placebo in infants with necrotizing enterocolitis revealed overall reductions in severe necrotizing enterocolitis, number of days to reach full enteral feeds, duration of hospitalizations, and all-cause mortality.[4]

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease is a chronic condition in which contents from the stomach flow back into the esophagus and may cause patients to experience esophageal irritation, difficulty swallowing, chest pain, and other symptoms. Although the 2020 AGA clinical practice guidelines on probiotics' role in managing of GI disorders did not include this particular GI condition, a systematic review of the 13 available prospective studies was conducted to examine the efficacy of probiotics in adults with gastroesophageal reflux disease.[10] Eleven (79%) of these studies reported positive benefits of probiotics for symptoms of gastroesophageal reflux disease, including reduced regurgitation and improvements in reflux or heartburn, dyspepsia, and other upper-GI symptoms (e.g., nausea, abdominal pain, belching, gurgling, burping). It was concluded that probiotics may have a place in the treatment of symptoms of gastroesophageal reflux disease; however, additional placebo-controlled, randomized, double-blind clinical trials with a greater number of participants and longer durations are necessary to confirm the overall role and safety of these products in gastroesophageal reflux disease.[10]

The Pharmacist's Role

Pharmacists remain the most accessible and frequently visited healthcare professionals in the U.S., as nearly 90% of Americans live within 5 miles of a community pharmacy.[11,12] With an estimated 4 million adults having used probiotics as a dietary supplement, it is imperative that pharmacists are aware of evidence-based recommendations for their proper use. Additionally, all healthcare professionals should understand the variations in available probiotic formulations and combinations, as well as the need for more research to determine the safety and potential health benefits of the different probiotic strains in various patient populations.

Conclusion

Probiotics are one of the most-used dietary supplements in the U.S. Millions of adults have taken some form of probiotic to treat or prevent various conditions. In 2020, the AGA published clinical practice guidelines with evidence-based recommendations for probiotic use in selected GI disorders. Healthcare professionals should be aware of these recommendations in order to properly care for and educate patients with these disorders.

References available online at www.uspharmacist.com.

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Comparing Oral Antiviral Agents for Seasonal Influenza

ABSTRACT: The annual influenza vaccine is the best way to reduce the risk of seasonal influenza illnesses. However, due to the limitations of the influenza vaccine and influenza-related complications, antiviral medications were developed to overcome these challenges and serve as an additional line of defense. There are four FDA-approved antiviral drugs recommended by the CDC to treat influenza, two of which are available orally: oseltamivir phosphate and baloxavir marboxil. Differences exist in their uses, dosing, and how they work. Appropriate use of these agents in both treatment and prophylaxis should be carefully considered.

In a post-COVID world, seasonal influenza has been effectively dethroned. Masking mandates, increased vaccination rates, and quarantines might have diluted the global effect of the influenza virus; however, it still poses a significant threat to public health.[1-4] The most effective treatment of the virus is prevention through annual vaccination, although that is not without caveats.[3,5] The influenza vaccine is majorly limited by the virus' constant mutation, requiring annual reformulations and what are essentially "best guesses" with regard to targeted strains. Development of the vaccine and medications are significantly handicapped by both the nature of the virus and increasing resistance rates, leading to a call for new drug therapies as well.[1,3,4,6] Maintenance of influenza surveillance has also suffered during the pandemic, leading to less evidence characterizing the influenza virus and, consequently, limitations in the development of the 2021-22 flu vaccine.[2] While focus and funding of research have understandably been targeted toward COVID-19 in recent months, it is imperative that healthcare professionals remain vigilant toward the virus that once held much more attention. Considering the limitations of the flu vaccine and the imminence of the current flu season, a review of treatment options for seasonal influenza is vital; and increasing resistance rates call for increased stewardship of our currently available therapies. This review article will focus on the oral influenza therapies commonly prescribed in the community.

Overview of Oral Influenza Therapies

Antiviral therapies for influenza were developed to shorten the disease duration, improve recovery, and reduce the risk of influenza-associated complications. Currently, three antiviral classes of medications exist in the treatment of influenza: adamantane antivirals (M2 inhibitors), neuraminidase inhibitors (NAIs), and nucleoprotein inhibitors.[1] Adamantane antivirals (amantadine and rimantadine) fell out of favor almost 2 decades ago due to increased resistance, limitation to influenza A viruses, and poor tolerability; thus, they are no longer recommended.

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Three NAIs are currently approved for and used in the treatment of influenza in the United States, including zanamivir (Relenza), oseltamivir (Tamiflu), and peramivir (Rapivab). NAIs are the only drug class recommended in the 2018 Infectious Diseases Society of America (IDSA) clinical practice guidelines.[7] NAIs work by inhibiting neuraminidase, the enzyme that cleaves glycosidic bond of sialic acid, which ultimately allows the new virion to be released from the host cell and consequently infect other cells.[1] Oseltamivir is the only NAI with sufficient oral bioavailability to be formulated as capsules and liquid, and it targets both influenza strains A and B. The single nucleoprotein inhibitor baloxavir (Xofluza) is an oral anti-influenza agent that was approved by the FDA in 2018, and thus it is not included in the most current IDSA guidelines. This cap-dependent endonuclease inhibitor works by inhibiting transcription of viral mRNA through targeting the viral polymerase, thus inhibiting viral replication.[1,8] By targeting different parts of the viral life span, release and replication, these two agents can be uniquely efficacious.

Oseltamivir phosphate is a phosphate prodrug of oseltamivir, which is rapidly absorbed and extensively metabolized to oseltamivir carboxylate (OC) by esterases found throughout the body.[1] With this rapid absorption, detectable levels of OC are present in plasma within 30 minutes of dosing, and time to maximum concentration (Tmax) is reached after 3 to 4 hours.[9] Rapid absorption is a very desirable trait when discussing oseltamivir, as it is most effective when administered within 48 hours of onset of symptoms. Without this phosphate salt formulation, oseltamivir has low lipophilicity and oral bioavailability, which would render it ineffective as an oral treatment option.

Oseltamivir and OC are well distributed throughout the body and, therefore, are able to reach therapeutic levels in the lungs, sinuses, and nasal mucosa, making it an ideal agent for a susceptible respiratory virus.[9] As mentioned, oseltamivir phosphate is extensively metabolized, around 75%, to OC by first-pass metabolism from hepatic esterases. Neither the phosphate prodrug nor OC is metabolized through CYP-mediated interactions, and therefore there are no CYP-mediated drug interactions associated with them. OC and oseltamivir phosphate are primarily cleared by renal elimination through both glomerular filtration and renal tubular secretion via anionic transport process.[9]

Baloxavir marboxil is a prodrug that is rapidly metabolized to baloxavir acid by hydrolysis.[10] Baloxavir has a similar Tmax to oseltamivir, roughly 3.5 hours.[10] In contrast to oseltamivir, baloxavir demonstrated a half-life of 49 to 91 hours, which is favorable for dosing regimen as baloxavir is administered as a single-dose regimen with no follow-up doses required.[10] Fed-state or before-meals administration of baloxavir were found to have a significant impact on drug concentrations, as they resulted in a decreased AUC of 37% to 47% compared with administration in the fasted state.[10]

Safety and Efficacy

When considering an oral flu regimen, it is also important to consider the safety data, particularly in patients with underlying diseases, younger children and infants, elderly patients, and pregnant patients, as these special populations are still at risk of complications associated with influenza. While oseltamivir has plenty of data supporting its safety in younger populations and pregnancy, one study targeted further assessment of these safety findings at standard and higher doses of oseltamivir in healthy adults aged 18 to 65 years. In this particular study, participants were given one of four treatment regimens (placebo, 75 mg twice daily, 225 mg twice daily, or 450 mg twice daily each for 5 days).[11]

The most frequently reported adverse events were headache, nausea/vomiting, dizziness, and hot flushes.[11] Of these, headache was the most common; it was noted in about 17% to 24% of participants and did not show any relationship to increasing dosages of oseltamivir.[11] Nausea and vomiting did appear to be dose-related, but most cases occurred on Day 1 and resolved within 24 hours.[11] Hot flushes also appeared to be dose-related and occurred in a few patients from each of the three oseltamivir groups. Out of 391 participants, there were seven withdrawals, three of which were from the placebo group, and no withdrawals from the 450-mg bid group. Of the other four withdrawals, only two were due to adverse events, both of which were in the 225-mg bid group.[11] As evidenced by this study, oseltamivir has been proven safe even at doses much higher than that currently indicated for influenza treatment or prophylaxis. As previously alluded to, oseltamivir has also been studied in various special populations with well-documented safety data.

Baloxavir is a newer influenza agent and, therefore, does not have the overwhelming safety data

from trials compared with oseltamivir. Regardless, the results from the phase III clinical trial show baloxavir to have fewer adverse events compared with oseltamivir.[12] Two serious adverse events did occur in the baloxavir treatment group, but neither were considered to be related to the trial regimen.[12] The adverse events observed in the phase III clinical trial that were considered to be related to the trial regimen were diarrhea and nausea.[12] Diarrhea occurred more often in the baloxavir group (1.8% vs. 1.4%), while nausea occurred more often in the oseltamivir group (0.3% vs. 1.6%).[12] Given the results of this clinical trial, while there are not as much safety data for baloxavir as there are for oseltamivir, both treatment options have established safety data to support their use in current influenza infections.

Baloxavir is perhaps the newest widely used influenza agent, despite its absence from the IDSA guidelines. Its single-dose formula has quickly made it a desirable option in the treatment of influenza.

While the safety of these drugs is established, the efficacy has generally been held under closer inspection. Viruses pose unique challenges in drug development—as evident in the paucity of antiviral therapy relative to other antimicrobials and especially in those specifically directed at influenza. Though the virus is responsible for over 30 million cases annually, there are only two available oral options, oseltamivir and baloxavir, which are quickly gaining resistance.[13] NAIs are heralded as agents that can limit the severity and duration of influenza, which is essentially the reach of their efficacy. Oseltamivir has been well studied in multiple, specific populations, including pregnant women and adolescents. Notably, its effects are also time-dependent, where trials found that receipt of the drug within 48 hours of symptom onset greatly improved clinical outcomes. A meta-analysis estimated the reduction in time to first alleviation of symptoms to be approximately 16 to 18 hours upon administration of oseltamivir.[14] These results are limited to uncomplicated disease, as efficacy of oseltamivir in severe cases of influenza is inconclusive, especially with regard to hospitalization and mortality. Additionally, resistance to agents such as oseltamivir has increased, best exhibited by the drug-resistant H274Y/H1N1 influenza virus, or "swine flu" strain responsible for the 2009 pandemic.[3,4]

Baloxavir is perhaps the newest widely used influenza agent, despite its absence from the IDSA guidelines. Its single-dose formula has quickly made it a desirable option in the treatment of influenza. Additionally, trials also found it to have better efficacy against the strains resistant to NAIs. In the CAPSTONE-1 phase III trial, patients older than age 12 years treated with baloxavir had a median time to alleviation of symptoms of ~54 hours compared with ~80 hours with placebo. In this trial, baloxavir had similar results to oseltamivir in time to alleviation of symptoms but did have greater reductions in viral load 1 day after administration compared with placebo and oseltamivir. Though baloxavir displayed similar clinical efficacy to oseltamivir in this trial with regard to influenza A, it did display superiority to oseltamivir when treating influenza B.[8] These results were confirmed by the CAPSTONE-2 trial.[15] Unfortunately, while no resistant strains had been identified at the time of approval, some resistance to baloxavir has emerged. It lacks evidence in special populations as well. Baloxavir, like oseltamivir, does not have evidence supporting use in complicated or severe cases. Monitoring of resistance, as well as research in these complicated populations, is warranted in order to fully understand the extent of efficacy oseltamivir and baloxavir have against influenza.[4]

Other Considerations

As with many medications, oseltamivir and baloxavir may cause a severe skin reaction and/or a serious allergic reaction, including anaphylaxis.[16] In either case, the patient should be counseled to stop the medication immediately and seek medical attention right away. While rare, oseltamivir also carries the risk of neuropsychiatric events, and any patient experiencing abnormal behavior should be instructed to stop the medication and contact their physician.[16] If a dose of oseltamivir is missed, the patient should be instructed to take the dose as soon as they remember, unless it is within 2 hours of their next scheduled dose.[16] While baloxavir does not carry the same risks as oseltamivir, patients should be advised to avoid milk, calcium-rich beverages, antacids, or supplements around the time that they take their single dose of baloxavir.[17]

Place in Therapy

Rising resistance rates and a potential surge in demand for influenza medications this flu season warrants a closer look at their appropriate use and place in therapy. Oseltamivir and baloxavir are both commonly inappropriately prescribed.[18] The unique timing criteria for both agents and general lack of options create a perfect storm for misuse. Baloxavir has not been studied in patients presenting after 48 hours of symptom onset, and oseltamivir studies have revealed a decline in efficacy after 48 hours of symptom onset, with no evidence suggesting any clinical utility thereafter.[18,19] Guidelines recommend against using these medications after this time period unless the illness is severe and progressing in a hospitalized patient, which is supported only by observational studies.[13] Inappropriate prescribing has been associated with a lack of

Table 1

Oral Oseltamivir and Baloxavir Comparisons

	Oseltamivir	Baloxavir
Treatment dose	• **Adult and Adolescent (age 13 years and older):** 75 mg twice daily usually for 5 days • **Pediatric (age 1 to 12 years):** weight-based twice daily for 5 days • **Pediatric (age 2 weeks to age <1 year):** 3 mg/kg twice daily for 5 days **Timing of initiation:** Initiate ≤48 hours following illness onset. Patients with complicated or progressive illness, initiate as soon as possible even if >48 hours have elapsed since onset; do not delay for laboratory confirmation	• **Adult (age 12 years and older):** <80 kg: 40 mg as a single dose within 48 hours of onset of influenza symptoms ≥80 kg: 80 mg as a single dose within 48 hours of onset of influenza symptoms • **Pediatric:** not FDA approved
Prophylaxis dose	• **Adult and Adolescent (age 13 years and older):** 75 mg once daily for at least 10 days • **Pediatric (age 1 to 12 years):** Based on weight once daily for 10 days • **Considerations:** *Pre-exposure prophylaxis:* during widespread outbreaks for persons at very high risk for influenza complications or not protected by vaccination, continue for the duration of influenza activity or for 2 weeks following vaccination *Postexposure prophylaxis:* for patients at high risk of complications and the influenza vaccination is contraindicated, unavailable, or expected to have low efficacy who have had close contact within the past 48 hours with a person with confirmed or suspected influenza during that person's infectious period, continue for 1 week after last exposure (if previously vaccinated) or 2 weeks (if unvaccinated) *Institutional outbreaks:* all, regardless of vaccination status, for at least 2 weeks and 1 week after the last known case	• **Adult (age 12 years and older):** <80 kg: 40 mg as a single dose within 48 hours of influenza exposure ≥80 kg: 80 mg as a single dose within 48 hours of influenza exposure • **Pediatric:** not FDA approved
Renal dose adjustments	• Treatment (CrCl 10-30 mL/min): reduce to 75 mg once daily for 5 days • Prophylaxis (CrCl 10-30 mL/min): reduce to 75 mg once every other day or 30 mg once daily	No adjustments necessary
Interactions	LAIV should not be administered within 2 weeks before or 48 hours after administration	LAIV should not be administered within 2 weeks before or 48 hours after administration Avoid use with polyvalent cation–containing products and dairy products

CrCl: creatinine clearance; LAIV: live attenuated influenza vaccine. Source: References 1, 7, 8, 13, 16, 17, 21.

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INDICATION

OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use:

Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

IMPORTANT SAFETY INFORMATION

SERIOUS INFECTIONS

Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death. Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with anactive, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled. Carefully consider the benefits and risks of treatment prior to initiating OPZELURA in patients with chronic or recurrent infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA.

No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

MORTALITY

Higher rate of all-cause mortality, including sudden cardiovascular death, has been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions.

MALIGNANCIES

Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Non-melanoma skin cancers, including basal cell and squamous cell carcinoma, have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

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IMPORTANT SAFETY INFORMATION (continued)

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)

Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

THROMBOSIS

Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed in patients treated with oral Janus kinase inhibitors forinflammatory conditions. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.

Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia

Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations

Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

Adverse Reactions

The most common adverse reactions (≥1%) are nasopharyngitis (3%), diarrhea (1%), bronchitis (1%), ear infection (1%), eosinophil count increased (1%), urticaria (1%), folliculitis (1%), tonsillitis (1%), and rhinorrhea (1%).

Pregnancy

There will be a pregnancy registry that monitors pregnancy outcomes inpregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 855-4MEDINFO or 855-463-3463.

Lactation

Advise women not to breastfeed during treatment with OPZELURA and for four weeks after the last dose (approximately 5 elimination half-lives).

Please see Brief Summary of Full Prescribing Information for OPZELURA™ on the following pages.

BSA, body surface area; FDA, Food and Drug Administration; JAK, Janus kinase.

Reference: OPZELURA™ (ruxolitinib) cream. Prescribing Information. Incyte Corporation, 2021.

Incyte

Opzelura™ (ruxolitinib) cream 1.5%

OPZELURA™ (ruxolitinib) cream, for topical use

Brief Summary of FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE: OPZELURA is indicated for the topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.

Limitation of Use: Use of OPZELURA in combination with therapeutic biologics, other JAK inhibitors or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

WARNING: SERIOUS INFECTIONS, MORTALITY, MALIGNANCY, MAJOR ADVERSE CARDIOVASCULAR EVENTS, AND THROMBOSIS

SERIOUS INFECTIONS
Patients treated with oral Janus kinase inhibitors for inflammatory conditions are at risk for developing serious infections that may lead to hospitalization or death *[see Warnings and Precautions and Adverse Reactions]*.

Reported infections include:

- **Active tuberculosis, which may present with pulmonary or extrapulmonary disease.**
- **Invasive fungal infections, including candidiasis and pneumocystosis.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. If a serious infection develops, interrupt OPZELURA until the infection is controlled.

The risks and benefits of treatment with OPZELURA should be carefully considered prior to initiating therapy in patients with chronic or recurrent infection.

Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with OPZELURA *[see Warnings and Precautions]*.

MORTALITY
Higher rate of all-cause mortality, including sudden cardiovascular death have been observed in patients treated with oral Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MALIGNANCIES
Lymphoma and other malignancies have been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

MAJOR ADVERSE CARDIOVASCULAR EVENTS (MACE)
Higher rate of MACE (including cardiovascular death, myocardial infarction, and stroke) has been observed in patients treated with Janus kinase inhibitors for inflammatory conditions *[see Warnings and Precautions]*.

THROMBOSIS
Thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to placebo. Many of these adverse reactions were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS

Serious Infections: Serious and sometimes fatal infections due to bacterial, mycobacterial, invasive fungal, viral, or other opportunistic pathogens have been reported in patients receiving oral janus kinase inhibitors. Serious lower respiratory tract infections were reported in the clinical development program with topical ruxolitinib. Avoid use of OPZELURA in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating OPZELURA in patients: with chronic or recurrent infection; with a history of a serious or an opportunistic infection; who have been exposed to tuberculosis; who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or with underlying conditions that may predispose them to infection. Closely monitor patients for the development of signs and symptoms of infection during and after treatment with OPZELURA. Interrupt OPZELURA if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume OPZELURA until the infection is controlled.

Tuberculosis: No cases of active tuberculosis (TB) were reported in clinical trials with OPZELURA. Cases of active TB were reported in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider evaluating patients for latent and active TB infection prior to administration of OPZELURA. During OPZELURA use, monitor patients for the development of signs and symptoms of TB.

Viral Reactivation: Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical trials with Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA. If a patient develops herpes zoster, consider interrupting OPZELURA treatment until the episode resolves.

Hepatitis B and C: The impact of Janus kinase inhibitors used to treat inflammatory conditions including OPZELURA on chronic viral hepatitis reactivation is unknown. Patients with a history of hepatitis B or C infection were excluded from clinical trials.

Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking oral ruxolitinib. OPZELURA initiation is not recommended in patients with active hepatitis B or hepatitis C.

Mortality: A higher rate of all-cause mortality, including sudden cardiovascular death was observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA.

Malignancy and Lymphoproliferative Disorders: Malignancies, including lymphomas, were observed in clinical trials of oral Janus kinase inhibitors used to treat inflammatory conditions. Patients who are current or past smokers are at additional increased risk. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA, particularly in patients with a known malignancy (other than successfully treated non-melanoma skin cancers), patients who develop a malignancy, and patients who are current or past smokers.

Non-melanoma Skin Cancers: Non-melanoma skin cancers including basal cell and squamous cell carcinoma have occurred in patients treated with OPZELURA. Perform periodic skin examinations during OPZELURA treatment and following treatment as appropriate.

Major Adverse Cardiovascular Events (MACE): Major adverse cardiovascular events (MACE) defined as cardiovascular death, non-fatal myocardial infarction (MI), and non-fatal stroke were observed in clinical trials of Janus kinase inhibitors used to treat inflammatory conditions. Consider the benefits and risks for the individual patient prior to initiating or continuing therapy with OPZELURA particularly in patients who are current or past smokers and patients with other cardiovascular risk factors. Patients should be informed about the symptoms of serious cardiovascular events and the steps to take if these symptoms occur.

Thrombosis: Thrombosis, including deep venous thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis, has been observed at an increased incidence in patients treated with oral Janus kinase inhibitors for inflammatory conditions compared to patients treated with placebo. Many of these adverse reactions were serious and some resulted in death. Thromboembolic events were observed in clinical trials with OPZELURA. There was no clear relationship between platelet count elevations and thrombotic events. OPZELURA should be used with caution in patients who may be at increased risk of thrombosis.

Thrombocytopenia, Anemia and Neutropenia: Thrombocytopenia, anemia and neutropenia were reported in the clinical trials with OPZELURA. Consider the benefits and risks for individual patients who have a known history of these events prior to initiating therapy with OPZELURA. Perform CBC monitoring as clinically indicated. If signs and/or symptoms of clinically significant thrombocytopenia, anemia, and neutropenia occur, patients should discontinue OPZELURA.

Lipid Elevations: Treatment with oral ruxolitinib has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides.

ADVERSE REACTIONS

Clinical Trials Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two double-blind, vehicle-controlled clinical trials (Trials 1 and 2), 499 subjects 12 years of age and older with atopic dermatitis were treated with OPZELURA twice daily for 8 weeks. In the OPZELURA group, 62% of subjects were females, and 71% of subjects were White, 23% were Black, and 4% were Asian. The adverse reactions reported by ≥ 1% of OPZELURA-treated subjects and at a greater incidence than in the vehicle arm through week 8 are as follows for OPZELURA (N=499) vs Vehicle (N=250), respectively: Subjects with any treatment emergent adverse event (TEAE) 132 (27%) vs 83 (33%), Nasopharyngitis 13 (3%) vs 2 (1%), Bronchitis 4 (1%) vs 0 (0%), Ear infection 4 (1%) vs 0 (0%), Eosinophil count increased 4 (1%) vs 0 (0%), Urticaria 4 (1%) vs 0 (0%), Diarrhea 3 (1%) vs 1 (<1%), Folliculitis 3 (1%) vs 0 (0%), Tonsillitis 3 (1%) vs 0 (0%), and Rhinorrhea 3 (1%) vs 1 (<1%).

Adverse reactions that occurred in Trials 1 and 2 in < 1% of subjects in the OPZELURA group and none in the vehicle group were: neutropenia, allergic conjunctivitis, pyrexia, seasonal allergy, herpes zoster, otitis externa, Staphylococcal infection, and acneiform dermatitis.

DRUG INTERACTIONS

Drug interaction studies with OPZELURA have not been conducted. Ruxolitinib is known to be a substrate for cytochrome P450 3A4 (CYP3A4). Inhibitors of CYP3A4 may increase ruxolitinib systemic concentrations whereas inducers of CYP3A4 may decrease ruxolitinib systemic concentrations.

Strong Inhibitors of CYP3A4: Avoid concomitant use of OPZELURA with strong inhibitors of CYP3A4 as there is a potential to increase the systemic exposure of ruxolitinib and could increase the risk of OPZELURA adverse reactions.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There will be a pregnancy registry that monitors pregnancy outcomes in pregnant persons exposed to OPZELURA during pregnancy. Pregnant persons exposed to OPZELURA and healthcare providers should report OPZELURA exposure by calling 1-855-463-3463.

Risk Summary: Available data from pregnancies reported in clinical trials with OPZELURA are not sufficient to evaluate a drug-associated risk for major birth defects, miscarriage, or other adverse maternal or fetal outcomes. In animal reproduction studies, oral administration of ruxolitinib to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes at doses associated with maternal toxicity.

The background risks of major birth defects and miscarriage for the indicated populations are unknown. All pregnancies carry some risk of birth defects, loss, or other adverse outcomes. The background risk in the U.S. general population of major birth defects and miscarriage is 2-4% and 15-20%, respectively.

Data

Animal Data: Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations at any dose. A decrease in fetal weight of approximately 9% was noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 22 times the clinical systemic exposure at the maximum recommended human dose (MRHD); the clinical systemic exposure from ruxolitinib cream, 1.5% applied twice daily to 25-40% body surface area is used for calculation of multiples of human exposure. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose resulted in systemic exposure approximately 70% the MRHD clinical systemic exposure. In a pre-and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse effects on embryofetal survival, postnatal growth, development parameters or offspring reproductive function at the highest dose evaluated (3.1 times the MRHD clinical systemic exposure).

Lactation

Risk Summary: There are no data on the presence of ruxolitinib in human milk, the effects on the breastfed child, or the effects on milk production. Ruxolitinib was present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because of the serious adverse findings in adults, including risks of serious infections, thrombocytopenia, anemia, and neutropenia, advise women not to breastfeed during treatment with OPZELURA and for approximately four weeks after the last dose (approximately 5 elimination half-lives).

Data: Lactating rats were administered a single dose of [14C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13 times the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma.

Pediatric Use: The safety and effectiveness of OPZELURA for the topical treatment of atopic dermatitis have been established in pediatric patients aged 12 to 17 years of age with mild-to-moderate atopic dermatitis. Use of OPZELURA in this age group is supported by evidence from Trials 1 and 2 which included 92 subjects aged 12 to 17 years. No clinically meaningful differences in safety or effectiveness were observed between adult and pediatric subjects. The safety and effectiveness of OPZELURA in pediatric patients younger than 12 years of age have not been established.

Juvenile Animal Toxicity Data: Oral administration of ruxolitinib to juvenile rats resulted in effects on growth and bone measures. When administered starting at postnatal day 7 (the equivalent of a human newborn) at doses of 1.5 to 75 mg/kg/day, evidence of fractures occurred at doses ≥ 30 mg/kg/day, and effects on body weight and other bone measures [e.g., bone mineral content, peripheral quantitative computed tomography, and x-ray analysis] occurred at doses ≥ 5 mg/kg/day. When administered starting at postnatal day 21 (the equivalent of a human 2-3 years of age) at doses of 5 to 60 mg/kg/day, effects on body weight and bone occurred at doses ≥ 15 mg/kg/day, which were considered adverse at 60 mg/kg/day. Males were more severely affected than females in all age groups, and effects were generally more severe when administration was initiated earlier in the postnatal period. These findings were observed at systemic exposures that are at least 40% the MRHD clinical systemic exposure.

Geriatric Use: Of the 1249 total subjects with atopic dermatitis in clinical trials with OPZELURA, 115 were 65 years of age and older. No clinically meaningful differences in safety or effectiveness were observed between patients less than 65 years and patients 65 years and older.

PATIENT COUNSELING INFORMATION

Advise the patient or caregivers to read the FDA-approved patient labeling (Medication Guide).

Infections: Inform patients that they may be at increased risk for developing infections, including serious infections, when taking Janus kinase inhibitors. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of an infection. Advise patients that Janus kinase inhibitors increase the risk of herpes zoster, and some cases can be serious.

Malignancies and Lymphoproliferative Disorders: Inform patients that Janus kinase inhibitors may increase the risk for developing lymphomas and other malignancies including skin cancer. Instruct patients to inform their health care provider if they have ever had any type of cancer. Inform patients that periodic skin examinations should be performed while using OPZELURA.

Major Adverse Cardiovascular Events: Advise patients that events of major adverse cardiovascular events (MACE) including non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death, have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct all patients, especially current or past smokers or patients with other cardiovascular risk factors, to be alert for the development of signs and symptoms of cardiovascular events.

Thrombosis: Advise patients that events of DVT and PE have been reported in clinical studies with Janus kinase inhibitors used to treat inflammatory conditions. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of a DVT or PE.

Thrombocytopenia, Anemia and Neutropenia: Advise patients of the risk of thrombocytopenia, anemia, and neutropenia with OPZELURA. Instruct patients to tell their healthcare provider if they develop any signs or symptoms of thrombocytopenia, anemia or neutropenia *[see Warnings and Precautions]*.

Administration Instructions: Advise patients or caregivers that OPZELURA is for topical use only *[see Dosage and Administration]*.

Advise patients to limit treatment to 60 grams per week.

Pregnancy: Inform patients to report their pregnancy to Incyte Corporation at 1-855-463-3463 *[see Use in Specific Populations]*.

Lactation: Advise a patient not to breastfeed during treatment with OPZELURA and for four weeks after the last dose *[see Use in Specific Populations]*.

Manufactured for:
Incyte Corporation
1801 Augustine Cut-off
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Issued: September 2021 PLR-ONA-00004

knowledge of their appropriate use, the belief that they might have some efficacy after 48 hours, or the desire to ensure patient satisfaction by providing a prescription. Evidence suggests there is, in fact, a gap in provider knowledge, and increased education might be warranted.[18]

> The IDSA guidelines include only NAIs in their recommendations. However, the advantages found with baloxavir, as well as its presumed efficacy, have given it an established place in therapy.

IDSA guidelines include only NAIs in their recommendations, of which oseltamivir is recommended as first line.[7] However, the advantages found with baloxavir, as well as its presumed efficacy, have given it an established place in therapy. Baloxavir is not approved for use in chemoprophylaxis like oseltamivir, but rather only in treatment. Guidelines ultimately suggest, however, that the influenza vaccine is the primary recommended means of prevention.[7] Recently, combination therapy using the two agents has been studied, and a benefit over monotherapy in mice was found, although more research is needed in to confirm this.[20] Further details regarding appropriate use of oseltamivir and baloxavir can be found in **TABLE 1.**

Conclusion

A review of oral influenza therapy is necessary and timely given the expected severity of the current flu season, the questions surrounding the current flu vaccine, and rising resistance rates towards agents. Oseltamivir and baloxavir are the only two oral agents available, and they are most commonly seen in the community. Fortunately, their safety is well established, and other concerns such as adverse effects or drug interactions are relatively mild. Unfortunately, efficacy is not as curative as desired but rather reduces duration and symptom severity. Importantly, clinical utility is only seen when administered within 48 hours of symptom onset, and no evidence exists to suggest efficacy thereafter. Appropriate use of these agents in both treatment and prophylaxis should therefore be carefully considered. Education of providers might be warranted to preserve the already limited arsenal of influenza agents and to provide optimal care to patients in the community.

REFERENCES

1. Shie JJ, Fang JM. Development of effective anti-influenza drugs: congeners and conjugates—a review. *J Biomed Sci*. 2019;26:84.
2. Rubin R. Influenza's unprecedented low profile during COVID-19 pandemic leaves experts wondering what this flu season has in store. *JAMA*. 2021;326(10):899-900.
3. Yin H, Jiang N, Shi W, et al. Development and effects of influenza antiviral drugs. *Molecules*. 2021;26:810.
4. Principi N, Camilloni B, Alunno A, et al. Drugs for influenza treatment: is there significant news? *Front Med (Lausanne)*. 2019;6:109.
5. Gavin PJ, Thomson RB Jr. Review of rapid diagnostic tests for influenza. *Clin Applied Immunol Rev*. 2004;4:151-172.
6. Treanor J. Influenza challenge and the challenge of drug development. *J Infect Dis*. 2019;219:171-172.
7. Uyeki TM, Bernstein HH, Bradley JS, et al. Clinical practice guidelines by the Infectious Diseases Society of America: 2018 update on diagnosis, treatment, chemoprophylaxis, and institutional outbreak management of seasonal influenza. *Clin Infec Dis*. 2019;68:895-902.
8. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med*. 2018;379(10):913-923.
9. Davies BE. Pharmacokinetics of oseltamivir: an oral antiviral for the treatment and prophylaxis of influenza in diverse populations. *J Antimicrob Chemother*. 2010;65(Suppl 2):ii5-ii10.
10. Koshimichi H, Ishibashi T, Kawaguchi N, et al. Safety, tolera¬bility, and pharmacokinetics of the novel anti-influenza agent bal¬oxavir marboxil in healthy adults: phase I study findings. *Clin Drug Investig*. 2018;38:1189-1196.
11. Dutkowski R, Thakrar B, Froehlich E, et al. Safety and phar¬macology of oseltamivir in clinical use. *Drug Saf*. 2003;26:787-801.
12. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir marboxil for uncomplicated influenza in adults and adolescents. *N Engl J Med*. 2018;379:913-923.
13. CDC. Influenza antiviral medications: summary for clinicians. Updated September 22, 2021. https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm?web=1&wdLOR=c07FAF0A5-A982-E640-8BFF-3987955EC0FA. Accessed September 25, 2021.
14. Dobson J, Whitley RJ, Pocock S, et al. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials [published correction appears in *Lancet*. 2015;385(9979):1728]. *Lancet*. 2015;385(9979):1729-1737.
15. Ison MG, Portsmouth S, Yoshida Y, et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. *Lancet Infect Dis*. 2020;20(10):1204-1214.
16. Tamiflu (oseltamivir) [package insert]. South San Francisco, CA: Genentech, Inc. August 2019.
17. Xofluza (baloxavir marboxil) [package insert]. South San Francisco, CA: Genentech, Inc. March 2021.
18. Kazempoor D. Healthcare provider education on oseltamivir resistance and Centers for Disease Control and Prevention prescrip¬tion guidelines of oseltamivir for influenza. UCLA. ProQuest ID: Kazempoor_ucla_0031D_19742. Merritt ID: ark:/13030/m5wt4rp9. Retrieved from https://escholarship.org/uc/item/5hs3h7bh.
19. McLean HQ, Belongia EA, Kieke BA, et al. Impact of late oseltamivir treatment on influenza symptoms in the outpatient setting: results of a randomized trial. *Open Forum Infect Dis*. 2015;2:ofv100.
20. Fukao K, Noshi T, Yamamoto A, et al. Combination treatment with the cap-dependent endonuclease inhibitor baloxavir marboxil and a neuraminidase inhibitor in a mouse model of influenza A virus infection. *J Antimicrob Chemother*. 2019;74(3):654-662.
21. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir marboxil for prophylaxis against influenza in household contacts. *N Engl J Med*. 2020;383(4):309-320.

Influenza in the Age of COVID-19

ABSTRACT: Very little data are available on how the coronavirus disease 2019 (COVID-19) pandemic will affect influenza, and although new information is emerging daily, much remains to be learned. Infection-control measures undertaken as a result of the COVID-19 pandemic have significantly impacted the annual influenza season, with a substantial drop in positive influenza cases compared with previous years. Despite the lack of influenza circulation, data suggest that coinfection with influenza and severe acute respiratory syndrome coronavirus 2 worsens disease severity and worsens prognosis. Although the spread of influenza decreased, misinformation has widely increased. Pharmacists have proven to be essential in the community, offering support not only in vaccine administration and point-of-care testing but also in combating misinformation through education.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the resultant coronavirus disease 2019 (COVID-19) have captured the world's attention for the past 2 years. The COVID-19 pandemic has significantly impacted every country, industry, and person while irreparably changing not only healthcare but life on a global scale. The influenza virus typically disrupts life each season, and despite extensive research it remains responsible for thousands of deaths per season and has caused multiple pandemics. However, very little data are available on how the COVID-19 pandemic will affect influenza, and although new information is emerging daily, much remains to be learned. The objective of this article is to provide a general review of the effect the COVID-19 pandemic has had on seasonal influenza.

Background

Compared with SARS-CoV-2, influenza has circulated for hundreds of years and has caused multiple pandemics.[1] The 1918–1919 influenza pandemic, also known as the "Spanish flu," infected more than 500 million people and caused an estimated 50 million deaths, whereas the most recent H1N1 influenza pandemic (in 2009) caused an estimated 500,000 deaths worldwide.[2] From 2010 to 2020, an estimated 9 million to 45 million influenza cases per year, with 12,000 to 61,000 deaths, have been reported.[3] On December 12, 2019, initial cases of what came to be known as COVID-19 were identified in Wuhan, China; not long thereafter, on March 11, 2020, COVID-19 was declared a pandemic by the World Health Organization.[4] In circumnavigating the globe, COVID-19 has resulted in more than 256 million cases and 5.1 million deaths as of November 22, 2021.[5] TABLE 1 compares the characteristics of influenza and SARS-CoV-2.

COVID-19's Impact on Influenza

Infection-control measures undertaken during the COVID-19 pandemic have significantly impacted the annual influenza season. The 2019–2020 influenza season was considered a moderate one, with roughly 38 million cases and 22,000 deaths.[3] In

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Table 1

Characteristics of Influenza and SARS-CoV-2

	Influenza	SARS-CoV-2
Viral taxonomy	Family: Orthomyxoviridae	Family: Coronaviridae
	Species: *influenza A* (infectious in humans), *influenza B* (infectious in humans), *influenza C*, *influenza D*	Genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, *Deltacoronavirus*
Binding site	Sialic acid	Angiotensin-converting enzyme 2
Infectivity	Less contagious	More contagious
Incubation	1-4 days	2-14 days
Tissues affected	Upper respiratory tract, lower respiratory tract	Upper respiratory tract, lower respiratory tract, intestinal tract, cardiovascular system, kidneys, nervous system
Risk factors	Age ≥65 years, age <2 years, asthma, heart disease, immunocompromising conditions	Age ≥65 years, chronic lung conditions, cancer, chronic kidney disease, diabetes, Down syndrome, obesity, immunocompromising conditions
Typical symptoms	Fever, chills, headache, sore throat, cough, nasal congestion, fatigue, myalgia	Fever, chills, cough, shortness of breath, fatigue, myalgia, headache, anosmia
Severe symptoms	Difficulty breathing, altered mental status, seizures	Difficulty breathing, persistent pain, pressure in the chest, new confusion, inability to wake or stay awake
Morbidity	Lower (5.8%)	Higher (16.9%)
Treatment	Oseltamivir phosphate, zanamivir, peramivir, baloxavir marboxil	Dexamethasone, remdesivir, baracitanib
Vaccines	Multiple vaccines approved[a]	Pfizer, BioNTech (mRNA), Moderna (mRNA), J&J (viral vector)
Typical vaccine side effects	Injection-site swelling, soreness, redness; fever, nausea, muscle aches, fatigue	Injection-site swelling, pain, redness; fatigue, headache, muscle pain, chills, fever, nausea
Severe vaccine side effects	Severe reactions, which are rare, include life-threatening anaphylactic allergic reactions and Guillain-Barré syndrome (extremely rare; 1-2 cases per million immunizations)	Severe reactions, which are extremely rare, include life-threatening anaphylactic allergic reactions, thrombosis with thrombocytopenia (47 confirmed cases with J&J vaccine, 2 cases with Moderna vaccine), Guillain-Barré syndrome (210 reported cases with J&J vaccine), and myocarditis and pericarditis (892 confirmed cases with mRNA-based vaccines)

[a] 2021–2022 strains include egg-based vaccines: A/Victoria/2570/2019 (H1N1) pdm09-like virus, A/Cambodia/e0826360/2020 (H3N2)-like virus, B/Washington/02/2019-like virus (B/Victoria lineage), and B/Phuket/3073/2013-like virus (B/Yamagata lineage) and cell- or recombinant-based vaccines: A/Wisconsin/588/2019 (H1N1) pdm09-like virus, A/Cambodia/e0826360/2020 (H3N2)-like virus, B/Washington/02/2019-like virus (B/Victoria lineage), and B/Phuket/3073/2013-like virus (B/Yamagata lineage).
J&J: Johnson & Johnson; mRNA: messenger RNA; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2.
Source: References 17, 27-36.

March 2020, around the same time that mask mandates and stay-at-home orders were enacted, a reduction in influenza infections occurred. Although infection-control measures may have influenced this decrease, the typical influenza season lasts until May, and the drop in influenza infections may have been due to the arrival of the end of the season.

The 2020–2021 influenza season saw a drastic drop in both positive influenza cases and the rate of hospitalizations compared with previous influenza

seasons. Of the 1,081,671 clinical samples tested for influenza between 2020 and 2021, only 1,899 samples were positive for either influenza A or influenza B.[6] This is a considerable change from previous influenza seasons: An estimated 38 million people were infected with influenza in the 2019–2020 season, and 35.5 million were infected in the 2018–2019 season.[3] The rate of influenza-associated hospitalizations for the 2020–2021 season was the lowest ever reported, with 0.8 influenza-associated hospitalizations per 100,000 persons infected.[7] Comparatively, in the past 10 years, the rate of influenza-associated hospitalizations per 100,000 persons infected varied widely, from 8.7 in 2011–2012 to 102.9 in 2017–2018 to 66.2 in 2019–2020.[7] The drastic reduction in positive influenza cases and hospitalizations may be attributable to the increased infection-control measures used worldwide because of the COVID-19 pandemic.

The 2020–2021 influenza season also saw an increase in the number of influenza vaccines distributed.[8] During the 2020–2021 influenza season, 193.8 million influenza vaccines were distributed, more than in any single previous influenza season. In the past 20 years, the number of influenza vaccines distributed ranged from 57 million during the 2004–2005 season to 174.5 million during the 2019–2020 season.

With significant infection-control measures in place and influenza vaccine administration increased, the 2020–2021 influenza season was all but nonexistent. From September 2020 through May 2021, only 0.2% (1,675/818,393) of evaluated respiratory specimens were positive for an influenza virus.[6] Although social distancing and mask mandates may have eliminated the 2020–2021 influenza season, COVID-19 persists, underscoring its significant infectivity and the need for increased infection-control measures and vaccine acceptance.

Coinfection With Influenza and COVID-19

Despite the lack of influenza circulation during the 2020–2021 influenza season, data suggest that coinfection with influenza and SARS-CoV-2 impacts disease severity. Current evidence is primarily based on cell studies, animal models, and retrospective studies. Interestingly, human alveolar basal epithelial cells infected with influenza A virus have a threefold increase in expression of angiotensin-converting enzyme 2. This enzyme is the receptor in which the spike protein of the SARS-CoV-2 virus binds for entry into a host cell.[9]

Compared with cells infected only with SARS-CoV-2, cells preinfected with influenza A virus increased SARS-CoV-2 infectivity more than fivefold, whereas cells preinfected with another respiratory virus (i.e., respiratory syncytial virus, parainfluenza, or rhinovirus 3) showed no change.[9] Mice with SARS-CoV-2 preinfected with influenza A virus had significantly higher SARS-CoV-2 viral loads and greater lung damage compared with mice without influenza A virus preinfection.[9] Research in hamsters preinfected with SARS-CoV-2 or influenza A virus, either together or sequentially, showed that coinfected hamsters had significantly more weight loss, severe lung damage, higher cytokine expression, and a longer clinical course compared with those infected with a single virus.[10] Moreover, hamsters initially infected with influenza A virus and then with SARS-CoV-2 virus demonstrated lower SARS-CoV-2 viral loads but greater lung damage than those infected with SARS-CoV-2 virus alone. Additionally, hamsters initially infected with influenza A virus and then with SARS-CoV-2 virus had higher influenza A viral loads than hamsters infected with influenza A virus alone.[10] Therefore, coinfection with influenza A virus appears to augment lung damage caused by SARS-CoV-2 alone, and if it is established before SARS-CoV-2, influenza A appears to enhance the disease.

Early data in humans shows that coinfection may worsen prognosis. A review of 307 patients with SARS-CoV-2 infection hospitalized in Wuhan, China, from January through February 2020 showed that 49.8% were coinfected with influenza A virus and 7.5% with influenza B virus.[11] Patients coinfected with influenza B virus were more likely to have severe disease characterized by fatigue upon presentation, abnormal chest CT, and decreased lymphocytes and eosinophils. Furthermore, patients with influenza B virus coinfection were more likely to present with a poor prognosis (30.4%) compared with patients with SARS-CoV-2 only (7.6%) or coinfection with influenza A virus (5.9%).

According to the National Institutes of Health guideline for management of COVID-19 and current CDC guidelines, hospitalized patients with acute respiratory illnesses should be tested for both SARS-CoV-2 and influenza viruses when both viruses are circulating.[12,13] However, testing for influenza A virus in outpatients with acute respiratory illness is

Making a case for IV KENGREAL® (cangrelor)

Addition of this $P2Y_{12}$ inhibitor to formulary at a hospital system

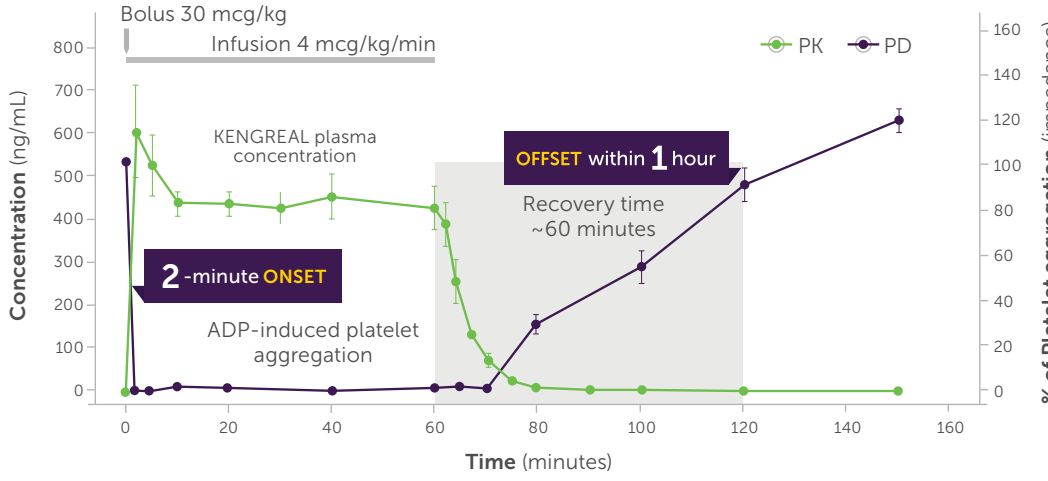
Hannah Pope, PharmD, MHA, BCPS, has been a practicing clinical pharmacy specialist for over a decade. Over the last 8 years she has worked at Barnes Jewish Hospital in Missouri alongside a team of physicians that manage patients in the cardiovascular intensive care unit, many presenting with STEMI and high-risk NSTEMI, as well as in the cardiac catheterization laboratory to provide pharmacy support surrounding selection of medications and dosing, operational procedures, formulary changes, protocol development, and drug education for hospital staff.

How did the opportunity to add IV KENGREAL® (cangrelor) to formulary present itself?
There was so much excitement surrounding KENGREAL that the day it received FDA-approval, I was approached by two interventional cardiologists (ICs) who asked me if I could have it available at the pharmacy the very next day. At that time, because our institution was part of a larger health system with about 10–12 hospitals in its network, formulary approval had to be granted by representatives from all its affiliates. As the clinical pharmacy specialist dedicated to the catheterization lab, my responsibilities include partnering with physicians to facilitate formulary updates and protocol development, so I became the primary champion tasked with making that happen.

What were the steps in the process of adding KENGREAL to formulary?
I approached the Pharmacy and Therapeutics (P&T) committee, which is responsible for all matters related to medication use in our network, and requested KENGREAL be added to formulary and available for use as soon as possible in the cardiac catheterization lab. The P&T committee denied the original request

What was the unmet need KENGREAL could fill at your hospital?
As a parenteral antiplatelet agent with a favorable pharmacokinetic and pharmacodynamic profile, KENGREAL offered multiple benefits. From a pharmacy standpoint, the rapid onset within 2 minutes[1], half-life of ~3–6 minutes[1], and offset within 1 hour[1] really stood out to me. KENGREAL could be used in a variety of clinical situations such as emergent cases, cases with high angiographic risk, when there is an inability to administer or reliably absorb oral medication, in patients who may need to proceed to surgery, and many others.[1] KENGREAL also offers potent platelet inhibition with a pharmacodynamic effect of >98% inhibition of platelet aggregation demonstrated in whole blood impedance aggregometry.[2] Furthermore, since KENGREAL is not renally cleared and its metabolism is independent of hepatic function, no dosage adjustments are required in patients with renal or hepatic impairment.[1] As a large academic institution, we perform a high volume of PCI procedures, many considered complicated, so there was definitely a role for KENGREAL in our hospital's antiplatelet armamentarium based on its profile and the types of cases we see.

KENGREAL pharmacology[1,3]



Phase I study in healthy volunteers (n=9); dose: 30 mcg/kg IV bolus + 4 mcg/kg/min IV infusion. KENGREAL blood levels and platelet activity were assessed over 150 minutes by whole blood impedance aggregometry in response to 20 µM of ADP.[3]

Infusion should be continued for at least 2 hours or the duration of the procedure, whichever is longer.[1]

Important Safety Information
Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL®, increase the risk of bleeding. In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL® than with clopidogrel. Bleeding complications with KENGREAL® were consistent across a variety of clinically important subgroups. Once KENGREAL® is discontinued, there is no antiplatelet effect after an hour.

Please see Important Safety Information continued on next page.

and asked to establish and resubmit with prespecified criteria for use. In collaboration with several ICs within the hospital system, we identified target patient populations that present to the cardiac catheterization lab that could benefit from the use of KENGREAL. The initial use criteria were largely derived from the KENGREAL Prescribing Information and AHA/ACC Guidelines regarding use of $P2Y_{12}$ inhibitors in PCI.*[4] We also took into consideration results from CHAMPION PHOENIX, the pivotal trial of KENGREAL vs clopidogrel.[5] The criteria defined three subsets of patients in the catheterization lab undergoing PCI at a level specific enough to limit use, but also broad enough to give the treating physician an opportunity to consider KENGREAL for a range of patients within each category.

Once KENGREAL was available on formulary, was there validation required by the hospital system to justify and maintain its addition?

After the P&T committee granted formulary approval, I was tasked with performing a 6-month drug use evaluation (DUE) of every patient who received KENGREAL. It was intended to validate whether the appropriate population was correctly identified and if new criteria should be added; it did not evaluate patient outcomes. The DUE ended up taking 1.5 years, which was encouraging in a way, because it suggested there was no excessive use of KENGREAL and indicated that our pharmacy budget was not significantly impacted by its availability. Ultimately, the vast majority of patients fell within the defined parameters—a successful result. If that were not the case, the P&T committee would likely have asked me to narrow the criteria.

How have the criteria changed since initial approval?

There were no revisions following the first use evaluation, but over time, the criteria have continued to evolve due to identification and validation of additional cases from physicians or as a result of subsequent DUEs that showed other patient types that could benefit from KENGREAL. After the last changes to the use criteria, KENGREAL is well positioned for a variety of PCI cases as defined, and is now a part of the antiplatelet regimen at our hospital.

Predefined use criteria for KENGREAL†:

1. **STEMI:** patients in whom glycoprotein IIb/IIIa inhibitor use is not planned; bivalirudin or heparin will be used; patients not loaded with an oral $P2Y_{12}$ inhibitor prior to PCI.
2. **NSTEMI/Unstable Angina:** patients who were not loaded with an oral $P2Y_{12}$ inhibitor and planned to go to catheterization lab within 2 hours from presentation for PCI.
3. **Elective PCI:** in high-risk, stable patients with complex anatomy undergoing elective PCI who have not been loaded with an oral $P2Y_{12}$ inhibitor.

†These criteria are for illustrative purposes only and are more specific than the FDA-approved indication.

In addition to any industry-supported education, was it necessary to educate the staff following formulary approval?

Continued staff education is very important, and while I present an annual antiplatelet therapy review, I also wanted to provide focused outreach to physicians, fellows, and nurses following KENGREAL's availability on formulary. Education was not only targeted to the catheterization lab staff, but it also included other departments. This was because patients receiving KENGREAL may be transferred to other locations in the hospital outside of the catheterization lab, such as the ICU or another floor while the drug is still being administered. With KENGREAL being a newly available antiplatelet agent at our hospital, these informational presentations and the resources provided by the manufacturer were vital to controlling responsible uptake and familiarizing the staff with KENGREAL use. Ensuring safe administration was also an important education component given the need to transition patients to an oral $P2Y_{12}$ inhibitor to maintain platelet inhibition once the KENGREAL infusion is stopped.

For other clinical pharmacy specialists or institutions looking to add KENGREAL to formulary, what is the best advice you could share? What about for a non-pharmacy specialist who hopes to have it available at their hospital?

Ultimately, it's most important to not lose sight of your institution's required formulary process. Some institutions may require an assessment of potential direct cost benefits related to improved outcomes, as well as indirect cost benefits, such as decreased length of stay. At our hospital, gaining formulary approval for KENGREAL required evaluating its clinical benefits[5] and pharmacologic profile[1], and then identifying appropriate patients and situations for KENGREAL. Establishing use criteria, providing continued education, and performing periodic DUEs helps reassure the P&T committee that the agreed-upon scope of use will be maintained so that KENGREAL may continue to be an important antiplatelet option available to our physicians and for our patients. ■

*KENGREAL is not included in the existing 2014 AHA/ACC Guidelines. KENGREAL was approved by the FDA in 2015.

Brief Summary

KENGREAL® (cangrelor) for injection, for intravenous use

Brief Summary of Prescribing Information

SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

KENGREAL is a $P2Y_{12}$ platelet inhibitor indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

CONTRAINDICATIONS

Significant Active Bleeding: KENGREAL is contraindicated in patients with significant active bleeding [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)].

Hypersensitivity: KENGREAL is contraindicated in patients with known hypersensitivity (e.g., anaphylaxis) to KENGREAL or any component of the product [see Adverse Reactions (6.1)].

WARNINGS AND PRECAUTIONS

Bleeding: Drugs that inhibit platelet $P2Y_{12}$ function, including KENGREAL, increase the risk of bleeding.

In CHAMPION PHOENIX, bleeding events of all severities were more common with KENGREAL than with clopidogrel [see Adverse Reactions (6.1)]. Bleeding complications with KENGREAL were consistent across a variety of clinically important subgroups [see Figure 1 in Clinical Trials Experience (6.1)].

Once KENGREAL is discontinued, there is no antiplatelet effect after an hour [see Clinical Pharmacology (12.3)].

ADVERSE REACTIONS

The following adverse reactions are also discussed elsewhere in the labeling: Bleeding [see Warnings and Precautions (5.1)].

Clinical Trials Experience:

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of KENGREAL has been evaluated in 13,301 subjects in controlled trials, in whom, 5,529 were in the CHAMPION PHOENIX trial.

Bleeding

There was a greater incidence of bleeding with KENGREAL than with clopidogrel. No baseline demographic factor altered the relative risk of bleeding with KENGREAL [see Table 1 and Figure 1 in Clinical Trials Experience (6.1)].

Table 1. Major Bleeding Results in the CHAMPION PHOENIX Study (Non-CABG related bleeding)[a]

CHAMPION PHOENIX	KENGREAL (N=5529)	CLOPIDOGREL (N=5527)
Any GUSTO bleeding, n (%)	857 (15.5)	602 (10.9)
Severe/life-threatening[b]	11 (0.2)	6 (0.1)
Moderate[c]	21 (0.4)	14 (0.3)
Mild[d]	825 (14.9)	582 (10.5)
Any TIMI bleeding, n (%)	45 (0.8)	17 (0.3)
Major[e]	12 (0.2)	6 (0.1)
Minor[f]	33 (0.6)	11 (0.2)

Abbreviations: GUSTO: Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries; TIMI: Thrombolysis in Myocardial Infarction

[a]Safety population is all randomized subjects who received at least one dose of study drug

[b]intracranial hemorrhage or bleeding resulting in substantial hemodynamic compromise requiring treatment

[c]requiring blood transfusion but not resulting in hemodynamic compromise

[d]all other bleeding not included in severe or moderate

[e]any intracranial hemorrhage, or any overt bleeding associated with a reduction in hemoglobin of ≥5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit ≥15%)

[f]any overt sign of bleeding (including observation by imaging techniques) that is associated with a reduction in hemoglobin of ≥3 g/dL and <5 g/dL (or, when hemoglobin is not available, an absolute reduction in hematocrit of ≥9% and <15%)

Drug Discontinuation

In CHAMPION PHOENIX, the rate of discontinuation for bleeding events was 0.3% for KENGREAL and 0.1% for clopidogrel. Discontinuation for non-bleeding adverse events was low and similar for KENGREAL (0.6%) and for clopidogrel (0.4%). Coronary artery dissection, coronary artery perforation, and dyspnea were the most frequent events leading to discontinuation in patients treated with KENGREAL.

Non-Bleeding Adverse Reactions

Hypersensitivity - Serious cases of hypersensitivity were more frequent with KENGREAL (7/13301) than with control (2/12861). These included anaphylactic reactions, anaphylactic shock, bronchospasm, angioedema, and stridor.

Decreased renal function - Worsening renal function was reported in 3.2% of KENGREAL patients with severe renal impairment (creatinine clearance <30 mL/min) compared to 1.4% of clopidogrel patients with severe renal impairment.

Dyspnea - Dyspnea was reported more frequently in patients treated with KENGREAL (1.3%) than with control (0.4%).

DRUG INTERACTIONS

Thienopyridines: Clopidogrel or prasugrel administered during KENGREAL infusion will have no antiplatelet effect until the next dose is administered. Therefore, administer clopidogrel or prasugrel after KENGREAL infusion is discontinued [see Dosage and Administration (2.2) and Clinical Pharmacology (12.3)].

(cont'd on next page)

Brief Summary for KENGREAL® (cangrelor) for injection, for intravenous use (cont'd)

USE IN SPECIFIC POPULATIONS

Pregnancy:

Risk Summary

There are no available data on cangrelor use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Untreated myocardial infarction can be fatal to the pregnant women and fetus [see Clinical Considerations (8.1)].

In animal reproduction studies, continuous infusion of cangrelor in pregnant rats and rabbits throughout organogenesis at dose approximately 2-times the maximum recommended human dose (MRHD) did not result in fetal malformations [see Data (8.1)].

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Myocardial infarction is a medical emergency in pregnancy which can be fatal to the pregnant woman and fetus if left untreated. Life-sustaining therapy for the pregnant woman should not be withheld due to potential concerns regarding the effects of cangrelor on the fetus.

Labor or delivery

Cangrelor use during labor and delivery may increase the risk for maternal bleeding and hemorrhage. Performance of neuraxial blockade procedures is not advised during cangrelor use due to potential risk of spinal hematoma. When possible, discontinue cangrelor 1 hour prior to labor, delivery, or neuraxial blockade [see Clinical Pharmacology (12.2)].

Data

Animal Data

A prenatal and postnatal development study in female rats demonstrated a slight increase in the incidence of maternal mortality in dams treated at doses up to 30 mcg/kg/min (approximately 7.5 times the MRHD) cangrelor continuous infusion from Day 6 of gestation up to Day 23 post-partum. Pregnancy rates, gestation index, length of gestation, numbers of live, dead and malformed pups, sex ratio, live birth index, and lactation of the maternal animals were unaffected.

Cangrelor administered at dose levels of ≥3 mcg/kg/min in pregnant rats from Day 6 to 17 post-coitum resulted in dose-related fetal growth retardation characterized by increased incidences of incomplete ossification and unossified hind limb metatarsals.

An embryo-fetal development study in rabbits administered 4, 12, or 36 mcg/kg/min cangrelor continuous IV infusion from Day 6 to Day 19 post-coitum resulted in increased incidences of abortion and intrauterine losses at ≥12 mcg/kg/min (3 times the MRHD). Fetal growth retardation occurred at 36 mcg/kg/min (9 times the MRHD) and was characterized by decreased fetal weights, slight reduction in ossification, and a slight increase in skeletal variants. Cangrelor did not produce malformations in either the rat or rabbit embryo-fetal development studies and is not considered to be a teratogen.

Lactation:

Risk Summary

There are no data on the presence of cangrelor in human milk or animal milk, the effects on the breastfed infant, or the effects on milk production. However, due to its short half-life, cangrelor exposure is expected to be very low in the breastfed infant.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In CHAMPION PHOENIX, 18% of patients were ≥75 years. No overall differences in safety or effectiveness were observed between these patients and those patients <75 years [see Clinical Studies (14.1)].

Renal Impairment: No dosage adjustment is required for patients with mild, moderate, or severe renal impairment [see Clinical Pharmacology (12.3)].

Hepatic Impairment: KENGREAL has not been studied in patients with hepatic impairment. However, the metabolism of KENGREAL is not dependent on hepatic function, so that dosage adjustment is not required for patients with hepatic impairment [see Clinical Pharmacology (12.3)].

OVERDOSAGE

There is no specific treatment to reverse the antiplatelet effect of KENGREAL but the effect is gone within one hour after the drug is discontinued.

In clinical trials, 36 patients received an overdose of KENGREAL, ranging from 36 to 300 mcg/kg (bolus dose) or 4.8 to 13.7 mcg/kg/min (infusion dose). The maximum overdose received was 10 times the PCI bolus dose or 3.5 times the PCI infusion dose in 4 patients. No clinical sequela were noted as a result of overdose following completion of KENGREAL therapy.

Please see Full Prescribing Information at www.KENGREAL.com.

References: 1. KENGREAL® (cangrelor) Prescribing Information. 2020. **2.** Data on file. Chiesi USA, Inc. **3.** Akers WS, Oh JJ, Oestreich JH, Ferraris S, Wethington M, Steinhubl SR. Pharmacokinetics and pharmacodynamics of a bolus and infusion of cangrelor: a direct, parenteral $P2Y_{12}$ receptor antagonist. *J Clin Pharmacol*. 2010;50(1):27-35. **4.** Levine GN, Bates ER, Blankenship JC, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines for the Society for Cardiovascular Angiography and Interventions. *J Am Coll Cardiol*. 2011;58(24):e44-e122. **5.** Bhatt DL, Stone GW, Mahaffey KW, et al; CHAMPION PHOENIX Investigators. Effect of platelet inhibition with cangrelor during PCI on ischemic events. *N Engl J Med*. 2013;368(14):1303-1313.

03/21 PP-K-0657 V1.0

Chiesi

KENGREAL®
(cangrelor) for injection

recommended only if the results will change clinical management.

The Pharmacist's Role

Pharmacists are essential for combating infectious disease and providing support throughout each influenza season and the current COVID-19 pandemic. Consistently rated the most accessible healthcare professionals, pharmacists have a significant presence in the community, with more than 88,000 community pharmacies across the United States.[14] Therefore, pharmacists are well positioned to assist the population by providing fact-based education, infectious-disease testing, and vaccine distribution throughout each influenza season as well as the current pandemic.

Education Centers: The COVID-19 pandemic has been a significant target for misinformation, with everything from household cleaners to vitamin C being suggested as cures.[15] However, even prior to the pandemic misinformation was common, and various home remedies, such as elderberry syrup and essential oils, have been touted as cures for influenza. Fact-based education can be readily supplied by pharmacists, who serve as an information resource accessible to most patients, as more than 90% of people live within 5 miles of a pharmacy.[16]

Answering patients' questions will continue to be a major role of the everyday pharmacist, and that is especially true this influenza season. Pharmacists must be prepared to answer any questions that patients may pose. Some common questions and answers include the following:

Patient: Can I get the flu vaccine and the COVID-19 vaccine at the same time?
Pharmacist: Yes. Current CDC recommendations allow the COVID-19 vaccine to be administered regardless of other recent immunizations. It is recommended that the vaccines be given in opposite arms, as more muscle pain may occur if the same arm is used for both.[17]

Patient: If the flu was nonexistent last year, is it necessary to get the flu vaccine this year?
Pharmacist: Yes. Influenza will circulate again this year, and it may also increase complications of COVID-19.[17]

Patient: Will medications such as Tamiflu work for COVID-19?
Pharmacist: No. Oseltamivir (Tamiflu) inhibits a compound used specifically by influenza and other viruses to release the newly formed virus from an infected cell so it can spread throughout the body. COVID-19 does not use the same compound for its release.[18]

Point-of-Care Testing: Point-of-care testing (POCT) gives pharmacists the ability to actively engage with patients and promote the direct-patient-care aspect of pharmacy.[19] Pharmacies offering POCT must obtain a clinical laboratory improvements amendment (CLIA) waiver from the Centers for Medicare & Medicaid Services (CMS).[20] Although pharmacists cannot bill CMS for time or services as a heathcare provider, a CLIA waiver allows them to bill CMS for their time and service in administering specific tests, such as that for COVID-19.[20,21] Several products are available for rapid detection of COVID-19 and/or influenza A and B viruses via POCT. In 2019, only 12,157 pharmacies were eligible to administer POCT; in August 2021, the number nearly doubled (23,689 pharmacies).[22] POCT services will remain critically important throughout the current and future influenza seasons.

POCT services may also open the door to increased protocol-based, prescriptive authority for pharmacists.[19] Depending on specific state regulations, it may be possible for pharmacists to test patients for influenza and, if positive, to prescribe oseltamivir based on a protocol. Certain states already allow pharmacists to participate in collaboration agreements and to prescribe medications such as HIV preexposure prophylaxis provided that the patient has a negative HIV test, with POCT eliminating the need for a separate laboratory visit.

Vaccine Distribution: Pharmacists are trusted healthcare professionals with specific training enabling them to counsel and administer immunizations. Pharmacists have been performing immunizations for nearly three decades; the first formal immunization training took place in 1994.[23] During the 2020–2021 influenza season, more than 48 million influenza vaccines were administered in pharmacies.[24] On February 11, 2020, the U.S. government tapped pharmacists' accessibility and experience by initiating the federal community-pharmacy program for COVID-19 vaccination with the purpose of provid-

ing access to COVID-19 vaccines.[25] Following the CDC's recommendation for a booster dose in high-risks persons, community pharmacists administered more than 400,000 booster doses over the course of one weekend.[26] The program has proved successful, with more than 162.8 million COVID-19 doses administered by community pharmacies as of November 9, 2021.[25]

Conclusion

Each year, influenza puts significant strain on the healthcare system and causes thousands of deaths. However, given the impact of the current COVID-19 global pandemic and increased infection-control measures, the 2020–2021 influenza season was nearly eliminated. Therefore, it is essential that all healthcare professionals prepare for the increased burden that cocirculation of influenza and SARS-CoV-2 may cause. It is important for pharmacists to promote trust in science and to provide fact-based information in order to encourage immunization and help protect patients from the damage influenza may cause in this new COVID-19 world.

The content contained in this article is for informational purposes only. The content is not intended to be a substitute for professional advice. Reliance on any information provided in this article is solely at your own risk.

REFERENCES

1. Potter CW. A history of influenza. *J Appl Microbiol.* 2001;91(4):572-579.
2. CDC. History of 1918 flu pandemic. www.cdc.gov/flu/pandemic-resources/1918-commemoration/1918-pandemic-history.htm?web=1&wdLOR=cCA07C6BA-7D2A-404B-8A44-B17501ED95F4. Accessed September 20, 2021.
3. CDC. Disease burden of flu. www.cdc.gov/flu/about/burden/index.html. Accessed September 20, 2021.
4. World Health Organization. WHO Director-General's opening remarks at the media briefing on COVID-19—11 March 2020. www.who.int/director-general/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020. Accessed September 25, 2021.
5. World Health Organization. WHO coronavirus (COVID-19) dashboard. https://covid19.who.int. Accessed November 1, 2021.
6. CDC. 2020-2021 flu season summary. www.cdc.gov/flu/season/faq-flu-season-2020-2021.htm#anchor_1627000324276. Accessed September 20, 2021.
7. CDC. Influenza Hospitalization Surveillance Network (FluSurv-NET). www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm. Accessed September 21, 2021.
8. CDC. Historical reference of seasonal influenza vaccine doses distributed. www.cdc.gov/flu/prevent/vaccine-supply-historical.htm?web=1&wdLOR=cFBD27FBD-6D5F-BD45-841E-3F4931E-6AEA7. Accessed September 23, 2021.
9. Bai L, Zhao Y, Dong J, et al. Coinfection with influenza A virus enhances SARS-CoV-2 infectivity. *Cell Res*. 2021;31(4):395-403.
10. Zhang AJ, Lee AC, Chan JF, et al. Coinfection by severe acute respiratory syndrome coronavirus 2 and influenza A(H1N1)pdm09 virus enhances the severity of pneumonia in golden Syrian hamsters. *Clin Inf Dis*. 2021;72(12):e978-e992.
11. Yue H, Zhang M, Xing L, et al. The epidemiology and clinical characteristics of co-infection of SARS-CoV-2 and influenza viruses in patients during COVID-19 outbreak. *J Med Virol.* 2020;92(11):2870-2873.
12. National Institutes of Health. COVID-19 treatment guidelines: what's new in the guidelines. www.covid19treatmentguidelines.nih.gov/about-the-guidelines/whats-new/. Accessed September 21, 2021.
13. CDC. Testing guidance for clinicians when SARS-CoV-2 and influenza viruses are co-circulating. www.cdc.gov/flu/professionals/diagnosis/testing-guidance-for-clinicians.htm. Accessed September 30, 2021.
14. IQVIA. U.S. national pharmacy market summary. www.onekey-data.com/downloads/reports/IQVIA_Report_US_Pharmacy_Market_Report_2019.pdf. Accessed November 15, 2021.
15. Erku DA, Belachew SA, Abrha S, et al. When fear and misinformation go viral: pharmacists' role in deterring medication misinformation during the 'infodemic' surrounding COVID-19. *Res Social Adm Pharm*. 2021;17(1):1954-1963.
16. CDC. Get to know your pharmacist. www.cdc.gov/heartdisease/pharmacist.htm. Accessed September 25, 2021.
17. CDC. COVID-19 ACIP vaccine recommendations. www.cdc.gov/vaccines/hcp/acip-recs/vacc-specific/covid-19.html. Accessed September 25, 2021.
18. Tamiflu (oseltamivir) package insert. South San Francisco, CA: Genentech, Inc; August 2019.
19. Klepser NS, Klepser DG, Adams JL, et al. Impact of COVID-19 on prevalence of community pharmacies as CLIA-waived facilities. *Res Social Adm Pharm*. 2021;17(9):1574-1578.
20. CDC. Waived tests. www.cdc.gov/labquality/waived-tests.html. Accessed September 30, 2021.
21. American Society of Health-System Pharmacists. Provider status. www.ashp.org/advocacy-and-issues/provider-status?loginreturnUrl=SSOCheckOnly. Accessed September 30, 2021.
22. Division of Clinical Laboratory Improvement and Quality, Centers for Medicare & Medicaid Services. Laboratories by type of activity. www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/factype.pdf. Accessed September 30, 2021.
23. Hogue MD, Grabenstein JD, Foster SL, Rothholz MC. Pharmacist involvement with immunizations: a decade of professional advancement. *J Am Pharm Assoc (2003)*. 2006;46(2):168-179.
24. CDC. Influenza vaccinations administered in pharmacies and physician medical offices, United States. www.cdc.gov/flu/fluvaxview/dashboard/vaccination-administered.html. Accessed September 25, 2021.
25. CDC. The Federal Retail Pharmacy Program for COVID-19 vaccination. www.cdc.gov/vaccines/covid-19/retail-pharmacy-program/index.html. Accessed November 1, 2021.
26. White House. Press briefing by White House COVID-19 response team and public health officials. www.whitehouse.gov/briefing-room/press-briefings/2021/09/28/press-briefing-by-white-house-covid-19-response-team-and-public-health-officials-58/. Accessed September 30, 2021.
27. Dou D, Revol R, Östbye H, et al. Influenza A virus cell entry, replication, virion assembly and movement. *Front Immunol.* 2018;9:1581.
28. Huang Y, Yang C, Xu XF, et al. Structural and functional properties of SARS-CoV-2 spike protein: potential antivirus drug development for COVID-19. *Acta Pharmacol Sin*. 2020;41(9):1141-1149.
29. Scudellari M. How the coronavirus infects cells—and why Delta is so dangerous. *Nature*. 2021;595(7869):640-644.
30. Solomon DA, Sherman AC, Kanjilal S. Influenza in the COVID-19 era. *JAMA*. 2020;324(13):1342-1343.
31. Flerlage T, Boyd DF, Meliopoulos V, et al. Influenza virus and SARS-CoV-2: pathogenesis and host responses in the respiratory tract. *Nat Rev Microbiol.* 2021;19(7):425-441.
32. Piroth L, Cottenet J, Mariet AS, et al. Comparison of the characteristics, morbidity, and mortality of COVID-19 and seasonal influenza: a nationwide, population-based retrospective cohort study. *Lancet Respir Med*. 2021;9(3):251-259.
33. CDC. Flu symptoms & complications. www.cdc.gov/flu/symptoms/symptoms.htm. Accessed September 30, 2021.
34. CDC. Symptoms of COVID-19. www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. Accessed September 27, 2021.
35. CDC. Different COVID-19 vaccines. www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html. Accessed September 30, 2021.
36. CDC. Selected adverse events reported after COVID-19 vaccination. www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html. Accessed September 30, 2021.

Different. Bold.

BREXAFEMME®
Ibrexafungerp, 150 mg per tablet

A first-in-class, oral fungicidal treatment for vulvovaginal candidiasis (VVC), also known as vaginal yeast infection

BREXAFEMME, a non-azole,
works by inhibiting glucan synthase

1 day: 2 pills, 2 times

Proven to completely resolve the signs and
symptoms of VVC in most patients

Broad spectrum* antifungal activity against
all *Candida* species that cause VVC

*Based on *in vitro* studies. Clinical significance is unknown.

Indication

BREXAFEMME® is a triterpenoid antifungal indicated for the treatment of adult and postmenarchal pediatric females with vulvovaginal candidiasis (VVC).

Important Safety Information

- BREXAFEMME is contraindicated during pregnancy and in patients with a history of hypersensitivity to ibrexafungerp
- BREXAFEMME administration during pregnancy may cause fetal harm based on animal studies. Prior to initiating treatment, verify pregnancy status in females of reproductive potential and advise them to use effective contraception during treatment
- When administering BREXAFEMME with strong CYP3A inhibitors, the dose of BREXAFEMME should be reduced to 150 mg twice a day for one day. Administration of BREXAFEMME with strong CYP3A inducers should be avoided

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†For Terms and Conditions, visit BREXAFEMMEHCP.com/SAVINGS.
‡Message and data rates may apply. 1 message per request. Reply "HELP" for help and "STOP" to stop.

For questions with processing, call 1-800-433-4893.

Important Safety Information (continued)

- Most common adverse reactions observed in clinical trials (incidence ≥2%) were diarrhea, nausea, abdominal pain, dizziness, and vomiting

To report SUSPECTED ADVERSE REACTIONS, contact SCYNEXIS, Inc. at 1-888-982-SCYX (1-888-982-7299) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Learn more at BREXAFEMMEHCP.com

Please see accompanying Brief Summary of full Prescribing Information on the following page.

Reference: BREXAFEMME. Prescribing information. SCYNEXIS, Inc; 2021.

Printed in the USA. US-BREX-2100083 September 2021.

SCYNEXIS

BREXAFEMME® (ibrexafungerp tablets), for oral use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all information needed to use BREXAFEMME safely and effectively. Please visit www.BREXAFEMMEHCP.com for full prescribing information (PI).

INDICATIONS AND USAGE

BREXAFEMME® is indicated for the treatment of adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).

Usage

If specimens for fungal culture are obtained prior to therapy, antifungal therapy may be instituted before the results of the cultures are known. However, once these results become available, antifungal therapy should be adjusted accordingly.

DOSAGE AND ADMINISTRATION

Recommended Dosage

The recommended dosage of BREXAFEMME is 300 mg (two 150 mg tablets) administered approximately 12 hours apart (e.g., in the morning and in the evening) for one day, for a total daily dosage of 600 mg (four 150 mg tablets).

BREXAFEMME may be taken with or without food.

Dosage Modifications in Patients due to Concomitant Use of a Strong Inhibitor of Cytochrome P450 Isoenzymes (CYP) 3A

With concomitant use of a strong CYP3A inhibitor, administer BREXAFEMME 150 mg approximately 12 hours apart (i.e., in the morning and in the evening) for one day. No dosage adjustment is warranted in patients with concomitant use of a weak or moderate CYP3A inhibitor.

Pregnancy Evaluation Prior to Initiating Treatment

Verify the pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME.

CONTRAINDICATIONS

BREXAFEMME is contraindicated in pregnancy and in patients with hypersensitivity to ibrexafungerp.

WARNINGS AND PRECAUTIONS

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In animal reproduction studies, ibrexafungerp administered orally to pregnant rabbits during organogenesis was associated with fetal malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the recommended human dose (RHD).

Prior to initiating treatment with BREXAFEMME, verify the pregnancy status in females of reproductive potential. Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

ADVERSE REACTIONS

The most frequent adverse reactions (≥ 2%) reported with BREXAFEMME in clinical trials of vulvovaginal candidiasis treatment were diarrhea (16.7%), nausea (11.9%), abdominal pain (11.4%), dizziness (3.3%), and vomiting (2.0%).

There were no serious adverse reactions and 2 out of 545 (0.4%) patients discontinued treatment with BREXAFEMME due to vomiting (1) and dizziness (1).

The following adverse reactions occurred in < 2% of patients receiving BREXAFEMME: dysmenorrhea, flatulence, back pain, elevated transaminases, vaginal bleeding, rash/hypersensitivity reaction.

DRUG INTERACTIONS

Ibrexafungerp is a substrate of CYP3A4. Drugs that inhibit or induce CYP3A may alter the plasma concentrations of ibrexafungerp and affect the safety and efficacy of BREXAFEMME. Avoid concomitant administration of BREXAFEMME with strong and moderate CYP3A inducers and reduce the BREXAFEMME dosage with strong CYP3A inhibitors (see Dosage and Administration above).

USE IN SPECIFIC POPULATIONS

Pregnancy

Based on findings from animal studies, BREXAFEMME use is contraindicated in pregnancy because it may cause fetal harm. In pregnant rabbits, oral ibrexafungerp administered during organogenesis was associated with rare malformations including absent forelimb(s), absent hindpaw, absent ear pinna, and thoracogastroschisis at dose exposures greater or equal to approximately 5 times the human exposure at the RHD. Oral ibrexafungerp administered to pregnant rats during organogenesis was not associated with fetal toxicity or increased fetal malformations at a dose exposure approximately 5 times the human exposure at the RHD. Available data on BREXAFEMME use in pregnant women are insufficient to draw conclusions about any drug-associated risks of major birth defects, miscarriage, or other adverse maternal or fetal outcomes.

There is a pregnancy safety study for BREXAFEMME. If BREXAFEMME is inadvertently administered during pregnancy or if pregnancy is detected within 4 days after a patient receives BREXAFEMME, pregnant women exposed to BREXAFEMME and healthcare providers should report pregnancies to SCYNEXIS, Inc. at 1-888-982-SCYX (7299).

Lactation

There are no data on the presence of ibrexafungerp in either human or animal milk, the effects on the breast-fed infant, or the effects on milk production.

Females and Males of Reproductive Potential

Based on animal data, BREXAFEMME may cause fetal harm when administered to a pregnant female. Verify the pregnancy status in females of reproductive potential prior to initiating treatment with BREXAFEMME. Advise females of reproductive potential to use effective contraception during treatment with BREXAFEMME and for 4 days after the last dose.

Pediatric Use

The safety and effectiveness of BREXAFEMME for treatment of VVC have been established in post-menarchal pediatric females. Use of BREXAFEMME in post-menarchal pediatric patients is supported by evidence from adequate and well-controlled studies of BREXAFEMME in adult non-pregnant women with additional safety data from post-menarchal pediatric females.

The safety and effectiveness of BREXAFEMME have not been established in pre-menarchal pediatric females.

Geriatric Use

Clinical studies with ibrexafungerp did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. No clinically meaningful differences in the pharmacokinetics of ibrexafungerp were observed in geriatric patients compared to younger adults.

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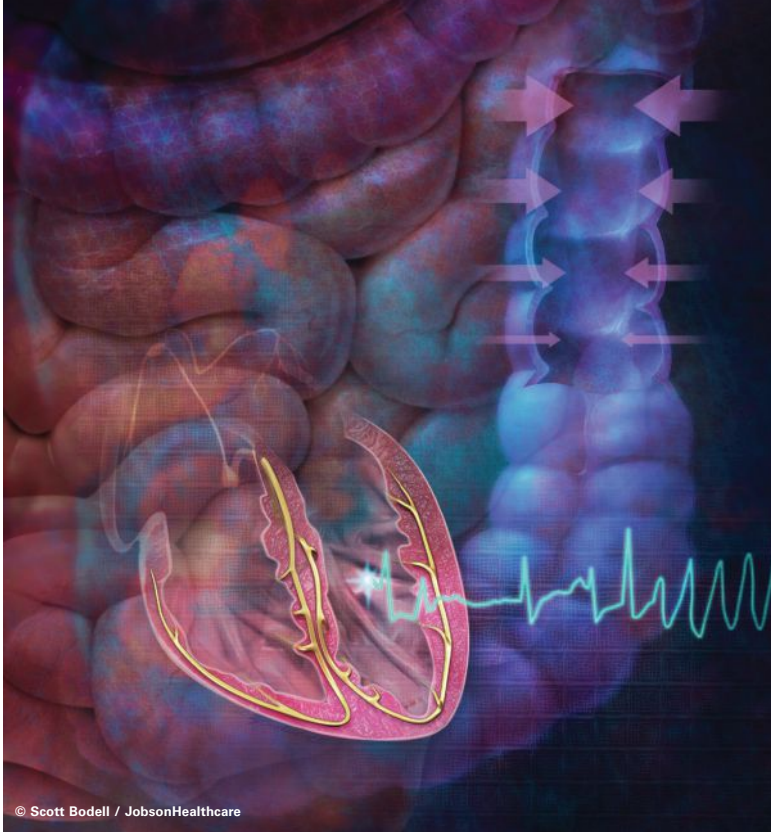
Pharmacist Review of Loperamide Abuse



ABSTRACT: Loperamide is a common OTC antidiarrheal medication, also known as Imodium, that has been targeted as a drug of abuse by those seeking to relieve opioid withdrawal symptoms or achieve a euphoric high. Loperamide is a synthetic opioid agonist that lacks central nervous system effects when taken as directed. When taken at supratherapeutic doses, however, loperamide can cross the blood-brain barrier and lead to a variety of adverse effects, including cardiovascular-related complications. A concerning rise in overdose cases and fatalities associated with loperamide overdose has prompted the FDA to limit the amount of loperamide available in OTC packages. Pharmacists should be aware of the patterns of loperamide abuse and diversion and understand how to implement effective measures to prevent patient harm within their practice setting.

Loperamide is a well-known, easily accessible, and effective nonprescription antidiarrheal agent that is sold under the brand name Imodium. Loperamide was first manufactured by Janssen Pharmaceuticals in 1969 and then marketed in 1977.[1] Over the years, it has consistently been included on the World Health Organization's list of Essential Medicines due to its safety and effectiveness.[1] Most cases of acute, nonspecific diarrhea are self-limiting, but the use of OTC antidiarrheal products such as loperamide may be necessary to help alleviate symptoms. In addition to controlling the symptomatic relief of acute nonspecific diarrhea in patients, it is also indicated in adults for chronic diarrhea associated with irritable bowel syndrome and for reducing the volume of discharge from ileostomies.[2] Loperamide is not recommended for all types of diarrhea, however, and may lead to worsened outcomes in patients with invasive bacterial diarrhea caused by enteroinvasive *Escherichia coli, Salmonella, Shigella, Campylobacter jejuni*, or antibiotic-associated diarrhea, such as *Clostridium difficile*.[3]

Loperamide has historically been viewed as safe, and most consumers abide by the labeled instructions and

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GOAL: *To provide pharmacists with comprehensive knowledge about loperamide, loperamide abuse, and how to address the rising cases of loperamide toxicity in the midst of the opioid crisis.*

OBJECTIVES: *After completing this activity, the participant should be able to:*

1. ***Recognize*** *the prevalence and risk factors associated with loperamide abuse.*
2. ***Describe*** *the clinical presentation of a loperamide overdose and associated cardiotoxicity.*
3. ***Summarize*** *how to screen patients for loperamide abuse.*
4. ***Review*** *the pharmacist's role and potential interventions to mitigate abuse.*

recommended dosing range.[3] Recent data, however, denote that there has been a rise in loperamide abuse. Like prescription and illegal drugs, OTC medications can also be abused. In the past, the two most commonly abused OTC medications included dextromethorphan and pseudoephedrine, which could produce psychoactive effects and a high when taken at higher than recommended doses.[4] Readily available and found online and on the shelves of most grocery stores, loperamide has been anecdotally touted as the "poor man's methadone," as it has allowed users to self-treat opioid-withdrawal symptoms or produce euphoria at supratherapeutic doses.[5] With a recommended maximum daily dosage of 8 mg for OTC use, cases of loperamide overdoses have detailed incidents of patients ingesting daily doses ranging from 70 mg up to 1,600 mg, which would involve the ingestion of up to 800 2-mg loperamide tablets in one day.[2,6]

Overdose deaths continue to be a serious national crisis that has yet to be controlled. In 2019, nearly 50,000 people in the United States died of an opioid overdose.[7] That number skyrocketed the next year with more than 81,000 drug overdose deaths in 2020, accounting for the highest number of overdose deaths ever recorded in a 12-month period.[1,7] As the opioid epidemic continues to take a devastating toll on our nation and as access to prescription pain products becomes more regulated, more individuals appear to be searching for readily accessible alternatives, such as OTC loperamide.

Pharmacological Properties of Loperamide

Loperamide, a phenylpiperidine derivative, is classified as an antimotility agent that acts as a peripheral mu-opioid receptor agonist to provide symptomatic relief of acute, nonspecific diarrhea (**TABLE 1**).[2] The synthetic opioid agonist produces its antidiarrheal effect by stimulating peripheral mu-opioid receptors on the intestinal circular muscles of the myenteric plexus to slow intestinal motility, allowing absorption of electrolytes and water.[3,8] Additionally, loperamide inhibits the release of acetylcholine and prostaglandins, which results in reduced propulsive peristalsis and increased intestinal transit time.[2,8] Loperamide also has antisecretory effects, possibly mediated via gastrointestinal (GI) micro opioid–receptor stimulation, calmodulin inhibition, and voltage-dependent calcium-channel inhibition.[3] Loperamide comes in oral tablet, oral capsule, oral liquid, oral solution, and oral suspension formulations (**TABLE 2**).[2] After the intake of loperamide 2 mg, plasma concentrations of unchanged drugs remain under 2 ng/mL.[2] Plasma concentration of the drug is highest 5 hours after administration of the oral capsule and 2.5 hours after administration of the oral liquid.[2] Loperamide has high protein binding at about 95%, and the elimination half-life is approximately 10.8 hours, with a range of 9.1 to 14.4 hours.[2]

Although loperamide displays agonist activity 50 times more potent than morphine on peripheral mu-opioid receptors, there are several biologic factors that limit its ability to produce the common central nervous system (CNS) effects associated with opioid analgesics.[9] The lack of CNS effects when administered at therapeutic dosages (up to 16 mg/day for prescription use) is attributed to loperamide's poor oral bioavailability (<2%), extensive first-pass metabolism by cytochrome P450 (e.g., CYP450 3A4 and 2C8) enzymes to inactive metabolites, and low blood-brain barrier (BBB) penetration due to the P-glycoprotein (P-gp) efflux transporter, which prevents it from entering the CNS.[10,11] The P-gp system is part of the adenosine triphosphate (ATP)-binding cassette transporter superfamily, which relies on ATP to actively pump substrates across cell membranes.[12-14] The P-gp transporter can be found in the luminal membrane of the small intestine and BBB.[12-14] The P-gp expression in the BBB plays a vital role in preventing drugs from crossing into the CNS.[12-14] The primary in-vivo metabolites are *N*-desmethylloperamide and *N*-hydroxymethyl-mono-desmethylloperamide, which have a potency that is two to three times less than that of loperamide.[15] As a result, loperamide does not have any clinically significant analgesic activity at therapeutic dosages.[10] Due to these factors, loperamide has historically been viewed as a safe drug associated with minimal side effects and a low potential for abuse.[10]

Prevalence of Loperamide Misuse and Abuse

When loperamide was introduced in 1977, the FDA initially placed it in the Schedule V list of controlled medications, basing their decision on animal data that suggested loperamide had produced opioid-like effects.[11,16,17] Loperamide was later removed from the Schedule V list and became a nonprescription product by 1988 due to several volunteer studies and epidemiological data that demonstrated a low risk of physical dependence and abuse.[16-19] Although safety was established through its low abuse potential, doses exceeding the recommended prescription daily dose of 16 mg demonstrated a variety of adverse effects.[1,20]

Throughout the past decade, a concerning number of published case reports and state poison control cen-

Table 1

Loperamide Indications and Dosages

Medication	Indication (OTC)	Dosage Form	OTC Adult Dosages (Maximum Daily Dose)	OTC Pediatric Dosages (not recommended for children aged <6 years except under medical supervision)	Duration of Use
Loperamide	Acute diarrhea	Caplets (2 mg)	4 mg initially, followed by 2 mg after each loose stool (8 mg/day)	• 6-8 years (48-59 lb [22-27 kg]): 2 mg initially, followed by 1 mg after each loose stool (4 mg/day) • 9-11 years (60-95 lb [27-43 kg]): 2 mg initially, followed by 1 mg after each loose stool (6 mg/day)	48 hours
Loperamide	Acute diarrhea	Liquid (1 mg/7.5 mL)	4 mg (30 mL) initially, followed by 2 mg (15 mL) after each loose stool (8 mg/day [60 mL/day])	• 6-8 years (48-59 lb [22-27 kg]): 2 mg (15 mL) initially, followed by 1 mg (7.5 mL) after each loose stool (4 mg [30 mL]/day) • 9-11 years (60-95 lb [27-43 kg]): 2 mg (15 mL) initially, followed by 1 mg (7.5 mL) after each loose stool (6 mg [45 mL]/day)	48 hours

Source: References 2, 3.

Table 2

Common Loperamide Formulations

Brand Name	Ingredients
Imodium A-D Caplets/Imodium EZ Chews (tablets)	Loperamide HCl 2 mg
Imodium Advanced Caplets/Chewable Tablets	Loperamide HCl 2 mg; simethicone 125 mg
Imodium A-D Liquid	Loperamide 1 mg/7.5 mL

Source: References 2, 3.

ter calls related to loperamide misuse/abuse have been documented. Epidemiologic trends were reviewed by the National Poison Data System from January 1, 2010 to December 31, 2015, assessing the intentional misuse, abuse, and suspected suicide due to loperamide exposure.[21] It found that in the span of 5 years, there was a 91% increase in loperamide exposure, with one-third of cases occurring in teens and young adults.[10,21] During this study period, there were 1,736 intentional loperamide exposures.[21] Overall reasons for the intentional exposure included intentional abuse (13.1%), intentional misuse (32.8%), suspected suicide (48.8%), and other (5.2%).[21] These exposures increased at approximately 38 cases per year and included 15 deaths.[21]

Alongside the growing number of case reports and poison control center calls, researchers have also observed a rise in online discussion revolving around loperamide. The first post on loperamide's misuse appeared in 2005, followed by a pronounced rise in discussions around 2010-2011.[22] Borron (2017) utilized online tools such as Google Trends to detect a trend in loperamide's digital mentions.[10] Google Trends, a tool that measures Google search popularity, allowed the researchers to assess Internet interest in the search terms "loperamide," "loperamide withdrawal," and "loperamide high."[10] The researchers noted a sudden rise in search volume starting in 2011, demonstrating an increased online interest in the drug.[10] Bluelight is an online drug forum where people can discuss individual experiences with illicit drugs and ask questions. One member posted, "I was addicted to lope [loperamide]for about 4 years taken daily. At the apex of my usage, my dose was ~400 mg [1 bottle of 200 2-mg pills a day], but I've done even more at times and to get off

it I slowly went down 10 mg per day. I think it almost killed me a couple times with crazy pressure in my head and loud pops that felt like someone dropping a piano inside my head. I had to do enemas daily to keep my bowels somewhat normal. It became a pain."[23]

There are many posts similar to this one in which users describe taking extremely large doses of loperamide to treat a variety of conditions from heroin to methadone withdrawal. Several posts even go into the pharmacology of using cimetidine or grapefruit juice to help with CYP3A4 inhibition, thus increasing plasma concentrations and the ability of loperamide to cross the BBB.[23] Although not without their limitations, studies using Internet tools and online forum communities have highlighted the potential of the Internet as a resource to identify emerging drug-abuse patterns and gain valuable insight on the hard-to-reach population of illicit drug users.

Pathophysiology of Loperamide Misuse and Abuse

At its recommended dosages, loperamide's effects are limited peripherally to the gut with minimal BBB penetration due to several factors previously mentioned.[11] However, with the discovery of loperamide's ability to produce CNS effects at supratherapeutic doses, a concerning number of people have turned to the historically safe drug in an attempt to self-treat their opioid withdrawal symptoms or seek euphoria.[11] In addition to using high doses of loperamide, some individuals are also taking other prescription medications to enhance the CNS-related effects of loperamide. This method of pharmacokinetic manipulation has been employed by users in an attempt to increase loperamide's systemic absorption and enhance its ability to penetrate the CNS to exert the desired opioid-like effects.[11,24] Since loperamide is a known substrate for the efflux protein P-gp, the use of P-gp inhibitors may assist with loperamide's access to the BBB, thus producing similar effects seen with opioid analgesics.[11] Some of the P-gp inhibitors include ketoconazole, fluoxetine, citalopram, omeprazole, quinine, quinidine, and verapamil (**TABLE 3**).[25-27] Drugs listed as P-gp inhibitors have been shown in clinical studies to increase the AUC of a sensitive substrate >25% or decrease the clearance of a sensitive substrate >20%, as well as increase the plasma concentration by twofold to threefold.[14,28,29]

Furthermore, adding a CYP450 inhibitor may further increase plasma concentration and the duration of effect by decreasing the metabolism of loperamide. CYP450 inhibitors include grapefruit juice, clarithromycin, ketoconazole, quinidine, ritonavir, and omeprazole and may increase the plasma concentration of loperamide by two- to threefold.[25,26,28] One user on a discussion thread of Bluelight stated that she could remain "high" for 12 hours by ingesting 60 mg of loperamide along with cimetidine, grapefruit juice, and an energy drink containing quercetin and quinine.[17] Famotidine is an OTC histamine-2 receptor antagonist, similar to cimetidine, that is commonly used to treat gastroesophageal reflux disease and other conditions that cause excess stomach acid. It is possible that at supratherapeutic doses, famotidine and cimetidine can inhibit CYP3A4, resulting in an increase in loperamide serum levels. A case report highlighted this combination of products in a 32-year-old male who presented with severe palpitations and syncope.[30] He admitted to taking up to 200 mg of loperamide and up to 500 mg of famotidine daily for 10 consecutive days. The patient had a prior history of alcohol, opiate, and methamphetamine abuse. After 5 days of treatment for QT prolongation and ventricular tachycardia, the patient recovered and was discharged home with a normal ECG reading. Many cases, however, do not always result in patient recovery and subsequent discharge.[30]

Loperamide-Induced Toxicity

The misuse of loperamide in supratherapeutic doses has been associated with a significant increase in morbidity and mortality.[31] Case reports have shown CNS depression, respiratory depression, and cardiotoxicity complications, including QT prolongation, torsades de pointes (TdP), QRS prolongation, ventricular dysrhythmias, syncope, cardiac arrest, and death.[11,32-34] The CNS and respiratory depression associated with loperamide overdose present similarly to overdoses typically seen with opioid analgesics, which include the hallmark characteristics of pinpoint pupils, unresponsiveness, and hypoventilation.[2] Swank (2017) conducted a study that utilized the FDA Adverse Event Reporting System (FAERS) database to search for postmarketing reports of serious cardiac adverse events associated with loperamide use from 1976 to 2015.[6] The researchers noted 48 cases of serious loperamide-induced cardiac adverse events, which resulted in 10 fatalities.[6] In the 22 cases that were characterized as drug abuse, the median daily dose was 250 mg, with a range from 70 mg to 1,600 mg, which would involve the ingestion of 35 to 800 2-mg loperamide tablets per day.[6] A majority of the cases reviewed exhibited ECG abnormalities of a widened QRS interval (up to 200 ms) and a prolonged QT interval (up to 704 ms), and

Table 3

Substrates (x), Inhibitors (+), and Strong Inhibitors (++) of P-gp

Drug	Substrate	Inhibitor
Antiarrhythmic agents		
Amiodarone		++
Digoxin	x	
Felodipine		+
Quinidine	x	++
Verapamil	x	++
Anticoagulants		
Apixaban	x	
Dabigatran	x	
Rivaroxaban	x	
Edoxaban	x	
Warfarin	x	
Antihypertensives		
Captopril		+
Carvedilol		++
Diltiazem	x	+
Losartan	x	+
Nifedipine		+
Propranolol	x	+
Antiplatelets		
Clopidogrel	x	
Ticagrelor	x	+
Statins		
Atorvastatin	x	++
Lovastatin	x	
Gastrointestinal agents		
Cimetidine	x	+
Loperamide	x	
Omeprazole		+
Ondansetron	x	

Continued >>

all developed ventricular dysrhythmias, including monomorphic or polymorphic ventricular tachycardia (TdP).[11] These cardiotoxic effects (e.g., cardiac arrest, syncope, and respiratory depression) were also prevalent in postmarketing cases for children younger than age 2 years, making it contraindicated in this patient population (TABLE 4).[2]

The exact mechanism of loperamide-induced dysrhythmia has not yet been determined, but loperamide has been observed to inhibit potassium and sodium channels in cardiocytes at excessive dosages.[35] These aforementioned cardiac channels are not blocked at standard doses but only in the setting of deliberate loperamide overdose, especially with concomitant P-gp or CYP3A4 inhibition.[11] QRS complex widening has been associated with inhibition of cardiac sodium channels, and excessively prolonged QTc intervals are associated with drugs that block voltage-dependent cardiac potassium channels, namely the *human ether-a-go-go–*related gene (*hERG*) K+ channel that underlies the delayed rectifier current, which is crucial for repolarization of cardiac action potentials.[36,37] In addition, the *N*-desmethyl metabolite of loperamide can contribute secondarily to the cardiotoxicity.[38]

Kang (2016) explored loperamide's ability to inhibit cardiac ion channels and found that loperamide exhibited high-affinity dose-dependent inhibition of the cardiac sodium channel, Nav1.5, and even higher inhibition of the cardiac hERG potassium channel, potentially resulting in the QRS and QTc interval prolongations observed with overdose.[36] These findings support the hypothesis that loperamide-induced cardiac transmembrane ion channel inhibition is the underlying cause of cardiotoxicity following excessive ingestion.[36]

As mentioned previously, the elimination half-life of loperamide is 10.8 hours, with a range of 9.1 to 14.4 hours.[2] There have been rare reports of half-lives extending to 40.9 hours with 16-mg dosages in healthy volunteers. Given the standard half-life, most poison control centers estimate 4 to 5 days before cardiac stabilization; however, one case report described a patient who remained symptomatic for 11 days postingestion with recurrent TdP and ventricular arrhythmias.[39]

Screening

Loperamide-induced cardiotoxicity is an under-recognized clinical presentation that has only started appearing more frequently throughout the past decade. Since its transition from prescription drug to OTC status, loperamide had not been suspected to be a drug of abuse. A challenge that healthcare establishments may

Table 3

Substrates (x), Inhibitors (+), and Strong Inhibitors (++) of P-gp (Cont.)

Drug	Substrate	Inhibitor
Psychotropic agents		
Amitriptyline		+
Citalopram	x	+
Disulfiram		+
Doxepin		+
Fluoxetine	x	+
Fluphenazine		+
Haloperidol		+
Sertraline		+
Varenicline		+
Antimicrobial agents		
Azithromycin		+
Clarithromycin		++
Erythromycin	x	+
Itraconazole		++
Ketoconazole		++
Rifampin	x	+
Miscellaneous		
Fexofenadine	x	
Grapefruit juice		+
Orange juice		+
Progesterone		+
Testosterone		+

P-gp: P-glycoprotein. Source: References 6, 14, 27.

face is lack of awareness surrounding loperamide abuse and its life-threatening complications by both providers and patients. Loperamide is not detected in routine drug screens, and concentrations must be specifically tested for through special laboratories. Tests, therefore, would only be ordered if there is a reasonable suspicion of abuse.[40] Patients may also not be forthcoming regarding their medication history, which adds to the challenge of proper diagnosis. For example, Ahmed et al describe a patient case in which a 23-year-old woman was referred for evaluation of wide complex tachycardia.[41] The care team did not initially suspect loperamide toxicity until the patient's mother informed the nursing staff that "hundreds" of empty Imodium boxes were found in her daughter's car.[41] The patient did not consider this discovery to be clinically relevant enough to mention, repeatedly answering "no" when asked if she took any nonprescription or OTC medications.[41] This case demonstrates the need for greater awareness of the potentially life-threatening toxicity associated with loperamide so that proper diagnosis, management, and patient education can be provided in a timely manner.

According to the National Poison Data System, male subjects were more likely to intentionally abuse loperamide, whereas female subjects more often used it in reported suicidal attempts.[21] Even though single-agent exposure is more frequent than polysubstance exposures, providers should still be mindful that both patterns contribute to increasing exposure rates. Single-agent loperamide exposures showed an increase of 24.7 exposures per year (95% CI 21.3-28.0; P <.001), whereas polysubstance loperamide exposures increased at a rate of 13.1 exposures per year (95% CI 10.7-15.4; P <.001).[21] Polysubstance exposure can also put patients at a higher risk for medical complications. Approximately one-third of polysubstance exposure patients were admitted to a critical care unit compared with 14.1% of patients with single-agent exposures. Common coingestions included antihistamines (13.7%), sedatives, hypnotics, antipsychotics (12.0%), antidepressants (11.1%), alcohol (7.5%), opioids (6.9%), and cough or cold medications (7.1%).[21]

Due to the lack of guideline-directed therapy for loperamide overdose, clinicians need to be aware of signs and symptoms associated with loperamide toxicity and should be cognizant of when to refer the patient to a psychiatrist or cardiac electrophysiologist.[42] These signs might include GI complications, such as nausea, vomiting, constipation, and a paralyzed intestine.[42] Loperamide overdose should be considered in the differential diagnosis of patients with a history of opioid abuse or recent ingestion of unknown drugs presenting with unexplained cardiotoxicity and/or signs of opioid overdose.[40] Even though a patient may be asymptomatic, physicians should consider obtaining a consultation with a medical toxicologist and order an ECG, given the high incidence for loperamide-related cardiotoxicity.[28] An extensive medication history, including both prescription and nonprescription drugs, should be obtained, either through the patient or their family and friends, so that any offending agents can be identi-

Table 4

Loperamide Contraindications

Pediatric patients younger than age 2 years due to the risks of respiratory depression and serious cardiac adverse reactions
Patients with a known hypersensitivity to loperamide hydrochloride or to any of the excipients
Patients with abdominal pain in the absence of diarrhea
Patients with acute dysentery, which is characterized by blood in stools and high fever
Patients with acute ulcerative colitis
Patients with bacterial enterocolitis caused by invasive organisms, including *Salmonella, Shigella,* and *Campylobacter*
Patients with pseudomembranous colitis (e.g., *Clostridium difficile*) associated with the use of broad-spectrum antibiotics

Source: References 2, 3.

fied.[40] For example, when patients are being treated for opioid withdrawal, common treatment options include clonidine and methadone, which both have the potential to worsen cardiac conduction and should be used with caution.[12] Many common psychotropic medications are also known to worsen QT prolongation, which could potentially worsen outcomes.[43]

Acute Treatment of Loperamide Overdose

Management of a loperamide overdose can be quite challenging due to the unclear understanding of loperamide's mechanism of action and the resulting effect on the cardiovascular system. The majority of cardiac adverse events were reported in patients who intentionally misused and abused supratherapeutic doses of loperamide to achieve euphoria or analgesia and to attempt to self-treat opioid withdrawal symptoms that resulted from the discontinuation of chronic opioid therapy.[6] While there is information throughout the medical literature on clinical presentation and treatment options of loperamide overdose, current data are mostly limited to case reports.[11] There is currently no guideline-directed therapy for the treatment of loperamide overdose.[30]

Upon diagnosis of loperamide-induced toxicity, any offending agents should be discontinued, and supportive care should be initiated.[30] Selection of supportive-care treatment options is determined by individual patient factors and can include electrolyte replacement, heart rate support with isoproterenol or temporary overdrive pacing, avoidance of QT-prolonging agents, and defibrillation.[30] Presentation during the early stages of ingestion can be treated similarly to other ingestions with the use of activated charcoal for patients presenting within 2 to 4 hours after ingestion.[11,44,45] Activated charcoal is an adsorbent that is widely used to treat overdoses of a variety of medications and may reduce absorption in acute loperamide overdoses by up to ninefold.[11,30] Activated charcoal is typically administered as a single dose, and it possesses a large surface area that allows the molecule to bind many drugs and toxins in the GI lumen, with the goal of decreasing their absorption into the systemic circulation.[46] When used to treat overdoses of other toxic compounds, activated charcoal is effective within 1 hour post ingestion, but the extended administration window of 2 to 4 hours post ingestion is justified with loperamide due to its ability to reduce peristalsis.[11,47]

If respiratory depression is observed during a loperamide overdose, then administration of naloxone is recommended, given loperamide's opioid-related effects in the CNS and naloxone's competitive inhibitor action on mu-opioid receptors in the CNS.[30,33] However, it is important to note that naloxone administration will not affect the cardiotoxicity effects since they are mediated by alterations in the cardiac ion channel activity.[11,30,44,45] Naloxone administration can be repeated at 2- to 3-minute intervals if the patient's overdose status does not improve.[2] Because naloxone has a shorter serum half-life (approximately 60 minutes) compared with loperamide (approximately 10.8 hours), vital signs for patients receiving naloxone to treat loperamide overdose should be closely monitored, and if signs and symptoms of opioid toxicity reappear, naloxone should be readministered.[2,48]

Standard advanced cardiovascular life support measures have been employed by clinicians to treat cardiac arrest and dysrhythmias secondary to loperamide overdose.[24] It has been recommended that synchronized cardioversion should be performed for patients presenting with ventricular tachycardia and hemodynamic instability.[24] Synchronized cardioversion involves the delivery of a low-energy shock, which is timed or synchronized to be delivered at a specific point in the QRS complex.[49] For patients who are pulseless and experiencing ventricular fibrillation or ventricular tachycardia, asynchronous cardioversion (defibrillation) should be used.[24] Patients experiencing TdP or polymorphic ventricular tachycardia without spontaneous resolution

of their dysrhythmia should also be treated with asynchronous cardioversion.[24] Once there is a perfusable rhythm established, IV magnesium should be considered.[24] Amiodarone or transvenous pacing are options for patients with recurrent dysrhythmias.[24]

To prevent further QT prolongation, electrolyte abnormalities including potassium, calcium, and magnesium should be identified and corrected.[24] QRS-interval widening associated with sodium channel blockade can be addressed by using a trial of IV sodium bicarbonate, although the efficacy of this treatment option has not yet been established.[11] If using sodium bicarbonate, there should be close monitoring of serum potassium, sodium, and pH due to sodium bicarbonate's ability to induce hypokalemia, which can further prolong the QT interval.[24]

Another option to treat sodium channel blockade is with the Class 1B antiarrhythmics, notably lidocaine, which have rapid binding and dissociation properties compared with other drugs.[50] Several case reports have used IV isoproterenol if the patient is experiencing significant QT prolongation associated with hemodynamic instability.[11,44,45] For more severe cases of loperamide-induced cardiotoxicity, IV lipid emulsion therapy, molecular adsorbent recirculating system, and venoarterial extracorporeal membrane oxygenation have been used in a few published cases after traditional methods have been exhausted, although their uses have not been frequently documented throughout the clinical literature.[11]

A study reviewed 48 cases of serious adverse events associated with loperamide use, using the FAERS database.[6] The most frequently reported cardiac adverse events were syncope (n = 24), cardiac arrest (n = 13), electrocardiographic QT-interval prolongation (n = 13), ventricular tachycardia (n = 10), and TdP (n = 7).[6] Of the 48 cases, the most commonly reported reasons for use can be characterized as drug abuse (n = 22) and diarrhea treatment (n = 17).[6] Medical intervention was reported in 16 of the 22 drug abuse cases and consisted of one or more medications or procedures: sodium bicarbonate (n = 6), IV magnesium (n = 6), placement of an implantable cardioverter-defibrillator or pacemaker (n = 5), cardioversion (n = 4), IV potassium (n = 4), amiodarone (n = 3), isoproterenol (n = 3), lipid emulsion (n = 3), and lidocaine (n = 2).[6]

Long-Term Treatment of Loperamide Abuse

Postacute care and follow-up evaluation are critical in this patient population, as some case reports have detailed instances where patients were successfully treated but readmitted to the hospital following complications of recurrent loperamide abuse.[51] Since many users have reported ingesting loperamide in large amounts to ameliorate opioid-withdrawal effects, it is possible that there could be an underlying opioid-use disorder (OUD), which should be screened for and addressed prior to discharge to prevent another overdose event.[11] Referral to substance-use disorder treatment programs may be warranted in patients with OUD, and patient education should be provided with the goal of cessation.[28]

A long-term treatment option that is being explored for loperamide-abuse postdischarge is buprenorphine, either as monotherapy or coformulated with naloxone as buprenorphine/naloxone (BUP/NAL). Buprenorphine and BUP/NAL are FDA-approved drugs used to treat OUD, in addition to methadone.[52] The medication-assisted treatment (MAT) strategy for OUD often combines these drugs with behavioral therapy and psychosocial support.[52] Although MAT is typically reserved for treating OUD associated with narcotics, there have been promising reports of successful treatment using MAT in patients who were previously hospitalized for loperamide abuse, although the data are still limited. Varghese (2019) described a case of a 40-year-old female with a history of OUD who reported that she had been taking 200 mg (100 2-mg tablets/day) of loperamide every day for 6 months due to reduced effectiveness of hydrocodone (TABLE 5).[53] After assessment, the patient was initiated on BUP 2 mg/NAL 0.5 mg, and the dose was gradually titrated up during follow-up visits to BUP 16 mg/NAL 4 mg daily.[53] In the following 6 months, she remained abstinent from both loperamide and hydrocodone.[53] Similarly, Brar (2020) describes a case series where three patients with loperamide-associated OUD were successfully treated with on-going buprenorphine treatment.[54]

Proposed Changes

The FDA has taken several steps to help decrease the misuse and abuse of loperamide. In June 2016, the FDA released a Drug Safety Communication stating that loperamide was causing serious and fatal cardiac events (e.g., QT-interval prolongation, TdP, syncope, and cardiac arrest).[55] Patients were also warned not to exceed prescribed or OTC doses, as doing so could lead to severe heart rhythm complications or death.[56] Additionally, the FDA Center for Drug Evaluation and Research approved a safety-related drug labeling change in November 2016.[55] A black box warning was added to Imodium's package insert stating that "Cases

Table 5

Summary of Case Reports of Patients With Loperamide Overdose

Patient Characteristics and Presentation	Diagnostic Workup	Diagnosis and Treatment	Result
• Male aged 42 y • Found unconscious in cardiac arrest; emergency medical personnel restored normal sinus rhythm • Family reported complaints of abdominal pain and that the patient "went through a lot" of loperamide	• In emergency department, the patient exhibited symptoms consistent with an opioid overdose • ECG: revealed a prolonged QTc interval which progressed to TdP	• Diagnosis: loperamide overdose • Treatment: naloxone	• Mental status improved after administration of naloxone • Patient eventually died from hypoxic brain injury • Loperamide and desmethylloperamide (loperamide metabolite) were detected in blood sample • Cause of death was ruled loperamide toxicity
• Female aged 40 y • PMH: opioid-use disorder, anxiety, ADHD, and migraine • Medications: alprazolam, amphetamine, and hydrocodone	• Patient admitted to excessive use of loperamide (200 mg for the past 6 months) due to limited access to hydrocodone • After abstaining from loperamide for 4 days and hydrocodone for 10 days, patient's COWS = 9 (rhinorrhea, mild pupillary dilation, irritability, and restlessness)	• Diagnosis: loperamide withdrawal • Treatment (initial): buprenorphine 2 mg/naloxone 0.5 mg • Treatment (maintenance): buprenorphine 16 mg/naloxone 4 mg	• After initial dose, the COWS score dropped to 4 and then to 1 with a second dose • For maintenance, buprenorphine/naloxone was gradually up-titrated during follow-up visits • In the subsequent 6 months, she remained abstinent from both loperamide and hydrocodone
• Female aged 38 y • PMH: polysubstance abuse • Presented after an outside-hospital cardiac arrest that was documented as ventricular fibrillation • Her family reported daily use of two boxes of loperamide (144 tabs, 288 mg) daily for an indefinite period to control heroin withdrawal • Formerly used codeine and Suboxone for opioid-withdrawal symptom control but no longer had access to these treatments	• Patient resuscitated in the field as per ACLS protocol with defibrillation and intubation • ECG: wide complex undetermined atrial rhythm at a rate of 58 bpm with prolonged QT/ QTc interval (666/653 ms) • Urine toxicology screen was negative	• Diagnosis: loperamide overdose • Treatment: sodium bicarbonate and lipid infusions. IV electrolytes maintained within normal limits • Isoproterenol drip for bradycardia. Later developed ventricular tachycardia and treated with amiodarone push and lidocaine infusion • Day 5: continued to experience ventricular fibrillation and restarted on isoproterenol • Day 11: continued to have TdP, received an ICD	• ICD placed to prevent ventricular fibrillation cardiac arrest given recurrent TdP • Repeated ECG showed progressive shortening of the QT/ QTc intervals, followed as outpatient • Patient denied any further use of loperamide, and device interrogation demonstrated normal sensing and pacing pacemaker • Patient enrolled in remote device monitoring every 3 months and had no detected device shocks

Continued >>

Table 5

Summary of Case Reports of Patients With Loperamide Overdose (Cont.)

Patient Characteristics and Presentation	Diagnostic Workup	Diagnosis and Treatment	Result
• Male aged 32 y • PMH: alcohol, opiate, and methamphetamine abuse • Presented with severe palpitations and syncope • Patient admitted to taking, over the prior 10 days, up to 200 mg daily of loperamide and multiple doses of famotidine (~500 mg daily)	• Vitals: BP (121/76 mm Hg), pulse (62 bpm), temperature 98°F, O^2 sat 97% • Patient appeared disheveled, but otherwise no abnormal physical exam findings • ECG: ventricular tachycardia and QT interval prolongation	• Diagnosis: loperamide-induced QT prolongation resulting in incessant ventricular tachycardia • Treatment: loperamide was discontinued • IV magnesium, supportive care, and monitoring	• After 5 days, his PR interval, QRS duration, and QT interval normalized, and VT resolved. Patient discharged • Naranjo assessment score of 8 obtained, indicated a probable relationship between QT prolongation and his loperamide use • 6-month follow-up visit—maintained abstinence from loperamide, ECG WNL
• Female aged mid-20s • PMH: hypertension, obsessive-compulsive disorder, chronic back pain, and narcolepsy • Medication history: fluvoxamine, lisdexamfetamine, lorazepam • Presented with syncopal episodes • Methadone treatment for low back for 3 years before admission • After methadone was d/c, she began using 200-400 mg of loperamide per day to treat withdrawal symptoms	• ECG: broadening QRS complex and QTC interval prolongation (>640 ms) • TdP x2 with syncope • Guarded, irritable, depressed, and anxious • Opioid withdrawal symptoms present; abdominal pain, myalgia, mydriasis, piloerection, yawning, and rhinorrhea	• Diagnosis: Fluvoxamine and lisdexamfetamine held • Treatment (initial): magnesium sulfate and lidocaine to treat TdP • Psychiatric consultation ordered for anxiety and opioid use disorder • Treatment (outpatient): start baclofen 20 mg QID for opiate-withdrawal symptoms • Resume fluvoxamine • Gabapentin to treat anxiety	• Her opiate withdrawal symptoms progressively improved during her 5-day hospitalization • After discussion with patient and her family, she was referred to outpatient substance abuse treatment

ACLS: advanced cardiac life support; ADHD: attention-deficit/hyperactivity disorder; BP: blood pressure; COWS: clinical opiate withdrawal scale; d/c: discontinued; ICD: implantable cardioverter defibrillator; PMH: personal medical history; QTC: QT corrected for heart rate; TdP: torsades de pointes; WNL: within functional limits. Source: References 12, 30, 32, 39, 53.

of Torsades de Pointes, cardiac arrest, and death have been reported with the use of a higher than recommended dosages of IMODIUM."[55] It also prompted loperamide consumers to notify their healthcare provider about all the medications they are taking, especially if they are taking Class 1A or Class III antiarrhythmics, antipsychotics, antibiotics, or any drugs known to prolong the QT interval to reduce the likelihood of known drug-drug interactions that could predispose individuals to a potentially fatal overdose.[55] This black box warning was based on 48 case reports the FDA received over the course of 39 years, involving 31 required hospitalizations and 10 deaths.[21,57,58] In January 2018, the FDA issued an updated Drug Safety Communication reporting that it was working with manufacturers to develop abuse-resistant packaging with fewer doses.[21,57,58]

In September 2019, the FDA approved new packaging for brand-name OTC loperamide intended to increase the safe use of loperamide products without limiting OTC access for consumers who use loperamide for its approved indication.[59] The packaging changes

were applied to Imodium A-D tablets (Janssen), Imodium Multi-Symptom Relief tablets (Janssen), and Be Health Loperamide HCl capsules (Bionpharma).[59] The changes limit each package to no more than 48 mg of loperamide, in addition to requiring unit-dose blister packaging.[59] Liquid formulations will continue to be sold in 4-ounce and 8-ounce containers, with no more than 32 mg of loperamide in 8 fluid ounces.[59] The FDA continues to work with other loperamide manufacturers and online distributors to support the safe use of loperamide.[59]

The federal government previously took steps to limit another OTC product, pseudoephedrine, which is used to make illicit methamphetamine. Congress passed the Combat Methamphetamine Epidemic Act (CMEA) in 2005, which requires pharmacies and other retail stores to keep logs of pseudoephedrine purchases and limit the amount that an individual can purchase in one day.[60] The CMEA limited daily sales of pseudoephedrine to 3.6 grams, and sales within a 30-day period were limited to 9 grams.[61] Pseudoephedrine-containing products are now located behind the pharmacy counter, and patients must present valid photo identification prior to purchase, which allows pharmacies to track whether or not a pseudoephedrine sale would be over the patient's allotted limit.[61] These restrictions dramatically reduced domestic production of the drug, dropping domestic methamphetamine laboratory incidents over 80% from 15,256 in 2010 to 3,036 in 2017.[60]

Although the FDA has limited the amount of loperamide available in packages, there is currently no policy in place to deter abusers from purchasing an unlimited number of packages. A major reason contributing to loperamide's abusive capability is its accessibility as an OTC product that can be purchased in large volumes throughout multiple channels outside of a pharmacy, such as online retailers and convenience stores. One individual reported that they were able to purchase 2,400 capsules of loperamide from Amazon, an amount equal to 100 fatal doses.[62] Despite FDA limitations, individuals can still purchase large quantities/in bulk from online retailers without pharmacovigilance or any regulatory barriers. Unfortunately, ease of accessibility still remains a significant limitation towards reducing the chances of loperamide misuse and abuse.

It will be up to the FDA if they wish to make loperamide a prescription product, which would give the tightest control over availability and ensure that all prescribers are aware of its use. Regulation of loperamide sales in a manner similar to that of pseudoephedrine and dextromethorphan could prove to be an effective measure to reduce further loperamide overdoses, but careful consideration must be taken so that patients who use loperamide as indicated are not inadvertently limited.

Pharmacist's Role

Prevention in the outpatient setting is key to reducing unnecessary harm and death associated with loperamide abuse. Greater awareness regarding this issue among pharmacists is warranted to minimize further adverse events. Pharmacists can implement risk-stratification strategies and should provide effective patient and community education to ensure that individuals are being properly informed.[63] In addition, through community outreach about appropriate pain management and medication use, pharmacists can play an active role in addressing the opioid crisis.[63] However, how pharmacists do this is pivotal. Pharmacists need to ask the right questions and choose their words carefully when discussing proper loperamide use.[42] When counseling a patient, pharmacists should be cautious with which words they use and what information they share to avoid inadvertently informing a patient that loperamide can be used to achieve euphoria or manage withdrawal.[42] Examples of questions to ask include "Have you been taking loperamide?, "How often do you take loperamide and how much?," "What do you take loperamide for?," and "Are you aware of the risks associated with taking too much loperamide?"

By being cognizant of the signs and symptoms of loperamide misuse and abuse, pharmacists can be vigilant and identify patterns of diversion among consumers. Since routine drug tests do not look for the presence of loperamide and because there are no established treatment guidelines for loperamide overdose, pharmacists need to be especially mindful of identifying patients at risk.[64] Oftentimes, the first point of contact between patients and the healthcare system, pharmacists are in a position to play a crucial role in combating loperamide abuse by identifying patients at risk of this atypical OUD, providing education on the dangers of nonmedical loperamide use to both clinicians and patients, and referring patients to an appropriate source of treatment for substance-use disorder.

In a national assessment of pharmacists' awareness of loperamide abuse and their ability to restrict sales if abuse is suspected, 72% of 153 pharmacies reported that they were aware of how loperamide abuse occurred and felt that they could decrease the quantity purchased or deny the sale if abuse was suspected.[65] However, only 3.2% of pharmacists had taken measures by placing loperamide behind the counter.[65] With this in mind, there is substantial room for pharmacists to make inter-

ventions. As loperamide abuse has been growing over the years, it is vital that measures are taken to avert misuse. Multiple studies have provided significant evidence that pharmacists can make an impact in the opioid crisis by providing opioid overdose–prevention training, medication reviews, and counseling.[63] With the rising cases of loperamide abuse, steps need to be taken to address this issue. Every member of the healthcare team has a role to play, whether it is providing appropriate pain management, providing education, or making changes at the state level. To prevent patient harm, the healthcare team needs to work quickly and effectively to circumvent this rising concern.

It is important to note that many of the numbers reported by the poison centers may not be a true representation of ongoing incidents. Much of the loperamide overdose data we rely on has limitations since reporting to poison centers is voluntary and symptom driven, relying on the validity of the information provided by the caller.[10] Experienced physicians who are comfortable handling loperamide overdose cases on their own may not refer out to a poison control center for consultation, which could decrease the number of actual cases. Given the widespread availability of loperamide and its low cost, the number of individuals misusing and abusing loperamide may be far greater than we predict.[10] Further research and education for healthcare providers and patients should continue to reduce the trends for loperamide abuse and misuse.[22] Patients will unfortunately continue to get their loperamide information from online forums, but pharmacists can provide up-to-date education on the dangers of loperamide abuse.

The Consumer Healthcare Products Association has launched a Loperamide Safety education campaign to increase healthcare provider awareness of loperamide abuse, providing fact sheets, resources, and peer-reviewed studies for members of the healthcare team who may encounter this throughout their profession, including pharmacists.[66] The education campaign materials can be accessed at www.loperamidesafety.org.[66]

Conclusion

The number of loperamide-induced overdose cases have risen, seemingly coinciding with the restrictions placed on prescription opioids, throughout the past decade. Healthcare providers should be aware of the abuse potential of loperamide, an easily accessible OTC medication that allows users to self-treat opioid withdrawal or experience euphoric opioid effects at large doses. Patients with loperamide overdose typically present with signs and symptoms similar to an opioid overdose in addition to cardiac rhythm disturbances. There are currently no guideline-directed therapies for loperamide overdose. Management of loperamide overdose is supportive therapy, which can include naloxone, advanced cardiovascular life support, and correction of electrolyte imbalances. Close follow-up and monitoring are warranted in patients with an underlying substance-use disorder due to a likelihood of recurrence, and referral to a rehabilitation center should be considered. The FDA has recognized loperamide's abuse potential and has taken steps to minimize misuse by limiting the amount of loperamide per package as well as requiring unit-dose blister packaging. Pharmacists play a critical role in prevention of further overdoses by identifying patterns of abuse and diversion, providing education on the dangers of loperamide overdose, and referring at-risk patients to substance-use treatment.

References available online at www.uspharmacist.com.

Disclosure Statements:
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Pharmacist Review of Loperamide Abuse

1. Loperamide is indicated for which of the following?
A. Acute nonspecific diarrhea
B. Travelers' diarrhea
C. Chronic diarrhea associated with irritable bowel syndrome
D. All of the above

2. At recommended doses, how does loperamide exert its antidiarrheal effects on the gastrointestinal (GI) tract?
A. Loperamide stimulates mu-opioid receptors in the myeteric plexus in the GI tract and stimulates acetylcholine receptors resulting in increased propulsive peristalsis
B. Loperamide stimulates mu-opioid receptors in the myenteric plexus in the GI tract and reduces water and electrolyte loss through the bowel
C. Loperamide inhibits the action of pepsin and increases the secretion of mucus. Additionally, it has a salicylate component that exerts anti-inflammatory and antisecretory actions
D. Loperamide crosses the blood-brain barrier to send signals to the myenteric plexus in the GI tract to inhibit water and electrolyte reabsorption

3. Which of the following is the primary reason that loperamide does not cross the blood-brain barrier when taken at therapeutic doses?
A. Loperamide freely crosses the blood-brain barrier even at therapeutic doses
B. Loperamide is rapidly converted to inactive metabolites by cytochrome P450 1A2
C. Loperamide has a very short elimination half-life of .5 to 1 hour
D. The presence of permeability glycoprotein in the blood-brain barrier

4. In 2016, the FDA issued a black box warning for loperamide. What was this warning for?
A. Consumption of high doses of loperamide can cause internal bleeding
B. Consumption of high doses of loperamide can have significant health consequences, including torsades de pointes and death
C. Consumption of high doses of loperamide can cause Stevens-Johnson syndrome and toxic epidermal necrolysis
D. Consumption of high doses of loperamide can cause increased risk of suicidal thinking and behavior in pediatric patients

5. Which of the following treatment options may be beneficial for a patient experiencing QT prolongation secondary to a loperamide overdose?
A. Isoproterenol
B. Naloxone
C. Magnesium infusion
D. Amiodarone

6. Which of the following treatment options may be beneficial for a patient experiencing respiratory depression secondary to a loperamide overdose?
A. Isoproterenol
B. Naloxone
C. Lidocaine
D. Metoprolol

7. What is one of the main reasons loperamide is contraindicated in patients younger than age 2 years?
A. Bowel impaction, which may require surgical intervention
B. Paradoxical reaction in toddlers that may lead to profuse diarrhea
C. Risk of respiratory depression and cardiac adverse effects
D. Severe abdominal pain

8. Which of the following medication interactions would increase the plasma concentration of loperamide and the likelihood that it crosses the blood-brain barrier?
A. Use with P-glycoprotein inducers
B. Use with CYP3A4 inducers
C. Use with CYP2D6 inhibitors
D. Use with P-glycoprotein inhibitors

9. Which of the following statements is true regarding the OTC use of loperamide (caplets)?
A. The maximum daily dose is 8 mg/day for adults
B. The starting dose is 2 mg, followed by 4 mg after each loose stool for adults
C. The maximum daily dose is 6 mg/day for children aged 4 to 6 years
D. OTC use for pediatrics is not recommended for children younger than age 8 years

10. In 2018, the FDA issued new packaging requirements limiting the amount of loperamide in one carton to contain no more than ____.
A. 55 mg
B. 37 mg
C. 75 mg
D. 48 mg

Examination Answer Sheet

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Pharmacist Review of Loperamide Abuse

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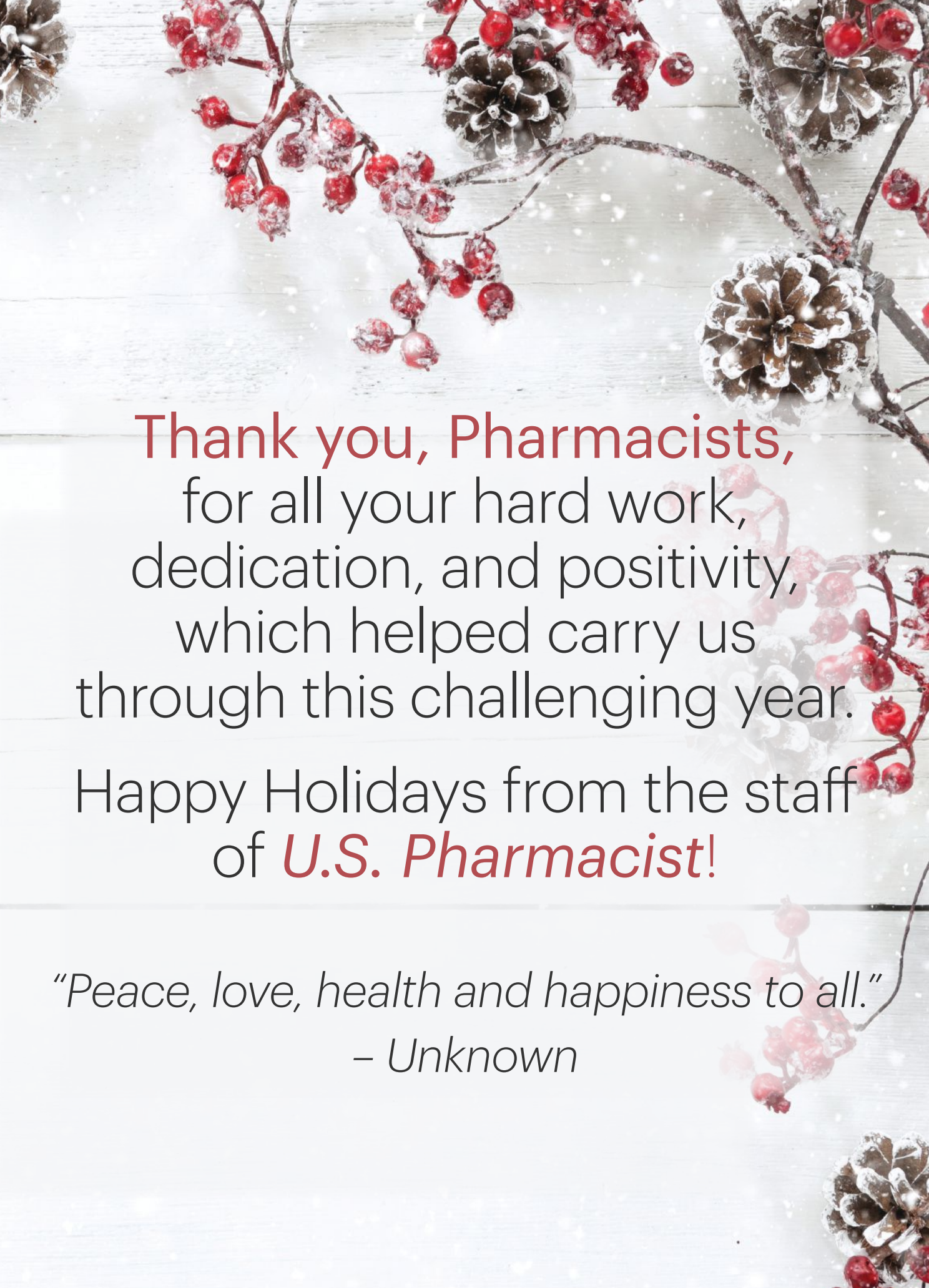
Thank you, Pharmacists,
for all your hard work,
dedication, and positivity,
which helped carry us
through this challenging year.
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"Peace, love, health and happiness to all."
– Unknown

5-Aminosalicylic Acid 1.2 g and 2.5 g Enemas

This preparation provides a sulfite-free formulation with variable concentrations for different patients.

FORMULA

5-Aminosalicylic Acid 1.2 g and 2.5 g Enemas

Rx (for 60 mL):	Ingredient		Quantity	
	5-Aminosalicylic acid		1.2 g	2.5 g
	Ascorbic acid		100 mg	100 mg
	Methylcellulose 2% gel		30 mL	30 mL
	Xanthan gum		100 mg	100 mg
	Purified water, preserved	qs	60 mL	60 mL

Method of Preparation: Calculate the required quantity of each ingredient for the total amount to be prepared. Accurately weigh or measure each ingredient. Place the 5-aminosalicylic acid (5-ASA) in a glass mortar. Add the ascorbic acid and xanthan gum, and triturate well. In divided portions, add the methylcellulose gel to form a smooth, lump-free dispersion. Add sufficient preserved purified water to final volume in divided portions, and mix until uniform. Package in enema-administration containers and label.

Use: Mesalamine is an anti-inflammatory agent that is used in the treatment of certain gastrointestinal disorders.

Packaging: Package in tight, light-resistant containers.

Labeling: Keep out of reach of children. Discard after ____ [time period]. For rectal use.

Stability: A beyond-use date of up to 30 days may be used for this preparation.[1]

Quality Control: Quality-control assessment can include weight/volume, pH, specific gravity, active drug assay, color, rheologic properties/pourability, physical observation, physical stability (discoloration, foreign materials, gas formation, mold growth), and preservative-effectiveness test.[2,3]

Discussion: This preparation provides a sulfite-free formulation with variable concentrations for different patients.

5-ASA (mesalamine, Rowasa, Asacol, Canasa, Pentasa, $C_7H_7NO_3$, MW 153.14) occurs as light tan to pink-colored, needle-shaped crystals. The color may deepen upon exposure to air. 5-ASA is odorless or may have a slight characteristic odor. 5-ASA is soluble in dilute hydrochloric acid and dilute alkali hydroxides, and it is slightly soluble in water.[1]

Ascorbic acid (L-ascorbic acid, vitamin C, $C_6H_8O_6$, MW 176.12) occurs as white or slightly yellow crystals or an odorless powder. When exposed to light, it will gradually darken. Ascorbic acid is reasonably stable in air when dry, but in solution it rapidly oxidizes. It is freely soluble in water (1:3) and sparingly soluble in alcohol (1:40). Ascorbic acid should be stored in airtight, nonmetallic containers and protected from light. A 5% aqueous solution has a pH in the range of 2.1 to 2.6. Ascorbic acid solutions deteriorate rapidly in air.[4]

Methylcellulose (Methocel) is a practically odorless and tasteless, white to yellowish-white granule or powder that is widely used in both oral and topical formulations. It is available in different viscosity grades; the low viscosity grades are used to emulsify oils and as suspending and thickening agents for oral liquids, and the higher viscosity grades are used to thicken topically applied products such as creams and gels. The pH of a 1% solution is in the range of 5.5 to 8. Methylcellulose is practically insoluble

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in acetone, ethanol, and hot water; in cold water, it swells and disperses to form a viscous, colloidal dispersion. Its solutions are stable between pH values of 3 and 11, and the viscosity is decreased outside this pH range.[5]

Xanthan gum (corn sugar gum) is a high-molecular-weight polysaccharide gum containing, in each repeating unit, five sugar residues (two of D-glucose, two of D-mannose, and one of D-glucuronic acid). It has a molecular weight of approximately 2×10^6. Xanthan gum occurs as a cream-colored or white-colored, odorless, free-flowing, fine powder. It is soluble in cold or warm water but is practically insoluble in ethanol and ether. Xanthan gum is used as a stabilizing agent and as a viscosity-increasing agent in suspensions. It is nontoxic, is compatible with most other excipients, and has good stability (in the presence of enzymes, salts, acids, and bases) and viscosity properties over a wide range (pH 3-12). Xanthan gum solutions can tolerate up to about 60% water-miscible organic solvents, such as ethanol. The pH of a 1% w/v aqueous solution is in the range of 6 to 8.[6]

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REFERENCES

1. *U.S. Pharmacopeia/National Formulary* [current revision]. Rockville, MD: U.S. Pharmacopeial Convention, Inc; November 2021.
2. Allen LV Jr. Summary of quality-control testing for sterile and nonsterile compounded preparations, part 1: physical and chemical testing. *IJPC*. 2019;23(3):211-216.
3. Allen LV Jr. Summary of quality-control testing for sterile and nonsterile compounded preparations, part 2: microbiological testing. *IJPC*. 2019;23(4):299-303.
4. Kibbe AH. Ascorbic acid. In: Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ, eds. *Handbook of Pharmaceutical Excipients*. 9th ed. London, England: Pharmaceutical Press; 2020:116-119.
5. Allen LV Jr. Methylcellulose. In: Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ, eds. *Handbook of Pharmaceutical Excipients*. 9th ed. London, England: Pharmaceutical Press; 2020:665-669.
6. Shah HC, Singh KK. Xanthan gum. In: Sheskey PJ, Hancock BC, Moss GP, Goldfarb DJ eds. *Handbook of Pharmaceutical Excipients*. 9th ed. London, England: Pharmaceutical Press; 2020:1129-1133.

BRIEF SUMMARY

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

SHINGRIX is a vaccine indicated for prevention of herpes zoster (HZ) (shingles) in adults aged 50 years and older.

Limitations of Use:

- SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

2 DOSAGE AND ADMINISTRATION

2.2 Administration Instructions

For intramuscular injection only.

After reconstitution, administer SHINGRIX immediately or store refrigerated between 2° and 8°C (36° and 46°F) and use within 6 hours. Discard reconstituted vaccine if not used within 6 hours.

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule:

- A first dose at Month 0 followed by a second dose administered 2 to 6 months later.

4 CONTRAINDICATIONS

Do not administer SHINGRIX to anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX *[see Description (11) of full prescribing information]*.

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

Prior to administration, the healthcare provider should review the immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX.

5.2 Guillain-Barré Syndrome (GBS)

In a postmarketing observational study, an increased risk of GBS was observed during the 42 days following vaccination with SHINGRIX *[see Adverse Reactions (6.2)]*.

5.3 Syncope

Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Syncope can be accompanied by transient neurological signs such as visual disturbance, paresthesia, and tonic-clonic limb movements. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a vaccine cannot be directly compared with rates in the clinical trials of another vaccine and may not reflect the rates observed in practice. There is the possibility that broad use of SHINGRIX could reveal adverse reactions not observed in clinical trials.

Adults Aged 50 Years and Older

Overall, 17,041 adults aged 50 years and older received at least 1 dose of SHINGRIX in 17 clinical studies.

The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (25%) subjects were aged 50 to 59 years, 4,488 (15%) subjects were aged 60 to 69 years, and 17,531 (60%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were White (74%), followed by Asian (18%), Black (1.4%), and other racial/ethnic groups (6%); 58% were female.

Solicited Adverse Reactions: In Studies 1 and 2, data on solicited local and general adverse reactions were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local and general adverse reaction following administration of SHINGRIX (both doses combined) were pain (78%), redness (38%), and swelling (26%); and myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%).

The reported frequencies of specific solicited local adverse reactions and general adverse reactions (overall per subject), by age group, from the 2 studies are presented in Table 1.

Table 1. Percentage of Subjects with Solicited Local and General Adverse Reactions within 7 Days[a] of Vaccination in Adults Aged 50 to 59 Years, 60 to 69 Years, and 70 Years and Older[b] (Total Vaccinated Cohort with 7-Day Diary Card)

Adverse Reactions	Aged 50-59 Years		Aged 60-69 Years		Aged ≥70 Years	
	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]	SHINGRIX	Placebo[c]
Local Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,311 %**	**n=1,305 %**	**n=2,258 %**	**n=2,263 %**
Pain	88	14	83	11	69	9
Pain, Grade 3[d]	10	1	7	1	4	0.2
Redness	39	1	38	2	38	1
Redness, >100 mm	3	0	3	0	3	0
Swelling	31	1	27	1	23	1
Swelling, >100 mm	1	0	1	0	1	0
General Adverse Reactions	**n=1,315 %**	**n=1,312 %**	**n=1,309 %**	**n=1,305 %**	**n=2,252 %**	**n=2,264 %**
Myalgia	57	15	49	11	35	10
Myalgia, Grade 3[e]	9	1	5	1	3	0.4
Fatigue	57	20	46	17	37	14
Fatigue, Grade 3[e]	9	2	5	1	4	1
Headache	51	22	40	16	29	12
Headache, Grade 3[e]	6	2	4	0.2	2	0.4
Shivering	36	7	30	6	20	5
Shivering, Grade 3[e]	7	0.2	5	0.3	2	0.3
Fever	28	3	24	3	14	3
Fever, Grade 3[f]	0.4	0.2	1	0.2	0.1	0.1
GI[g]	24	11	17	9	14	8
GI, Grade 3[e]	2	1	1	1	1	0.4

Total vaccinated cohort for safety included all subjects with at least 1 documented dose (n).

[a] 7 days included day of vaccination and the subsequent 6 days.

[b] Data for subjects aged 50 to 59 years and 60 to 69 years are based on Study 1. Data for subjects 70 years and older are based on pooled data from Study 1: NCT01165177 and Study 2: NCT01165229.

[c] Placebo was a saline solution.

[d] Grade 3 pain: Defined as significant pain at rest; prevents normal everyday activities.

[e] Grade 3 myalgia, fatigue, headache, shivering, and GI: Defined as preventing normal activity.

[f] Fever defined as ≥37.5°C/99.5°F for oral, axillary, or tympanic route, or ≥38°C/100.4°F for rectal route; Grade 3 fever defined as >39.0°C/102.2°F.

[g] GI = Gastrointestinal symptoms including nausea, vomiting, diarrhea, and/or abdominal pain.

The incidence of solicited local and general reactions was lower in subjects aged 70 years and older compared with those aged 50 to 69 years.

The local and general adverse reactions seen with SHINGRIX had a median duration of 2 to 3 days.

(continued on next page)

There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28% and 21%, respectively) compared with Dose 1 (24% and 14%, respectively). Grade 3 solicited general adverse reactions (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3%, 4%, and 4%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events: Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 51% and 32% of subjects who received SHINGRIX (n = 14,645) or placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in ≥1% of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (4% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

Gout (including gouty arthritis) was reported by 0.18% (n = 27) versus 0.05% (n = 8) of subjects who received SHINGRIX or placebo, respectively, within 30 days of vaccination; available information is insufficient to determine a causal relationship with SHINGRIX.

Serious Adverse Events (SAEs): In the 2 studies, SAEs were reported at similar rates in subjects who received SHINGRIX (2.3%) or placebo (2.2%) from the first administered dose up to 30 days post-last vaccination. SAEs were reported for 10.1% of subjects who received SHINGRIX and for 10.4% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. One subject (<0.01%) reported lymphadenitis and 1 subject (<0.01%) reported fever greater than 39°C; there was a basis for a causal relationship with SHINGRIX.

Optic ischemic neuropathy was reported in 3 subjects (0.02%) who received SHINGRIX (all within 50 days after vaccination) and 0 subjects who received placebo; available information is insufficient to determine a causal relationship with SHINGRIX.

Deaths: From the first administered dose up to 30 days post-last vaccination, deaths were reported for 0.04% of subjects who received SHINGRIX and 0.05% of subjects who received placebo in the 2 studies. From the first administered dose up to 1 year post-last vaccination, deaths were reported for 0.8% of subjects who received SHINGRIX and for 0.9% of subjects who received placebo. Causes of death among subjects were consistent with those generally reported in adult and elderly populations.

Potential Immune-Mediated Diseases: In the 2 studies, new onset potential immune-mediated diseases (pIMDs) or exacerbation of existing pIMDs were reported for 0.6% of subjects who received SHINGRIX and 0.7% of subjects who received placebo from the first administered dose up to 1 year post-last vaccination. The most frequently reported pIMDs occurred with comparable frequencies in the group receiving SHINGRIX and the placebo group.

Dosing Schedule: In an open-label clinical study, 238 subjects 50 years and older received SHINGRIX as a 0- and 2-month or 0- and 6-month schedule. The safety profile of SHINGRIX was similar when administered according to a 0- and 2-month or 0- and 6-month schedule and was consistent with that observed in Studies 1 and 2.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SHINGRIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to the vaccine.

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.

Immune System Disorders

Hypersensitivity reactions, including angioedema, rash, and urticaria.

Nervous System Disorders

Guillain-Barré syndrome.

Postmarketing Observational Study of the Risk of Guillain-Barré Syndrome following Vaccination with SHINGRIX

The association between vaccination with SHINGRIX and GBS was evaluated among Medicare beneficiaries aged 65 years or older. Using Medicare claims data, from October 2017 through February 2020, vaccinations with SHINGRIX among beneficiaries were identified through National Drug Codes, and potential cases of hospitalized GBS among recipients of SHINGRIX were identified through International Classification of Diseases codes.

The risk of GBS following vaccination with SHINGRIX was assessed in self-controlled case series analyses using a risk window of 1 to 42 days post-vaccination and a control window of 43 to 183 days post-vaccination. The primary analysis (claims-based, all doses) found an increased risk of GBS during the 42 days following vaccination with SHINGRIX, with an estimated 3 excess cases of GBS per million doses administered to adults aged 65 years or older. In secondary analyses, an increased risk of GBS was observed during the 42 days following the first dose of SHINGRIX, with an estimated 6 excess cases of GBS per million doses administered to adults aged 65 years or older, and no increased risk of GBS was observed following the second dose of SHINGRIX. These analyses of GBS diagnoses in claims data were supported by analyses of GBS cases confirmed by medical record review. While the results of this observational study suggest a causal association of GBS with SHINGRIX, available evidence is insufficient to establish a causal relationship.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women *[see Use in Specific Populations (8.1) of full prescribing information]*.

8.2 Lactation

Risk Summary

It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion *[see Use in Specific Populations (8.2) of full prescribing information]*.

8.5 Geriatric Use

Adults Aged 60 Years and Older

Of the total number of subjects who received at least 1 dose of SHINGRIX in Studies 1 and 2 (n = 14,645), 2,243 (15%) were aged 60 to 69 years, 6,837 (47%) were aged 70 to 79 years, and 1,921 (13%) were 80 years and older. There were no clinically meaningful differences in efficacy across the age groups *[see Clinical Studies (14.1, 14.2, 14.3) of full prescribing information]*.

The frequencies of solicited local and general adverse reactions in subjects aged 70 years and older were lower than in younger adults (aged 50 through 69 years). *[See Adverse Reactions (6.1).]*

17 PATIENT COUNSELING INFORMATION

- Inform patients of the potential benefits and risks of immunization with SHINGRIX and of the importance of completing the 2-dose immunization series according to the schedule.
- Inform patients about the potential for adverse reactions that have been temporally associated with administration of SHINGRIX.
- Provide the Vaccine Information Statements, which are available free of charge at the Centers for Disease Control and Prevention (CDC) website (www.cdc.gov/vaccines).

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Research Triangle Park, NC 27709

SHINGRIX + EFFICACY = CONVERSATION STARTER

SHINGRIX DELIVERED >90% EFFICACY AGAINST SHINGLES IN PATIENTS 50 YEARS AND OLDER[1,*]

SHINGRIX
(ZOSTER VACCINE RECOMBINANT, ADJUVANTED)

>90% EFFICACY[1,*]

As people age, immunity declines—and they're at an increased risk of getting shingles.[2-4] So, as you're vaccinating patients in your pharmacy, consider this: **SHINGRIX delivered >90% efficacy against shingles regardless of age in those ≥50 years old.[1,*]** With these kinds of results, you can be confident recommending SHINGRIX for your at-risk patients.

The most common side effects observed in the pivotal clinical trials were: pain, redness, and swelling at the injection site, myalgia, fatigue, headache, shivering, fever, and gastrointestinal symptoms.[1]

To review the study results in detail, visit us at SHINGRIXefficacy.com

*Data from the phase 3 ZOE-50 (≥50 years of age) trial and pooled data in individuals ≥70 years of age from the phase 3 ZOE-50 and ZOE-70 trials in subjects who received 2 doses of SHINGRIX (N=7344 and 8250, respectively) or placebo (N=7415 and 8346, respectively) and did not develop a confirmed case of herpes zoster within 1 month after the second dose.[1]

Indication

SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older.

SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

Important Safety Information

- SHINGRIX is contraindicated in anyone with a history of a severe allergic reaction (eg, anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX
- Review immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX
- In a postmarketing observational study, an increased risk of Guillain-Barré syndrome was observed during the 42 days following vaccination with SHINGRIX
- Syncope (fainting) can be associated with the administration of injectable vaccines, including SHINGRIX. Procedures should be in place to avoid falling injury and to restore cerebral perfusion following syncope
- Solicited local adverse reactions reported in individuals aged 50 years and older were pain (78%), redness (38%), and swelling (26%)

Important Safety Information (cont'd)

- Solicited general adverse reactions reported in individuals aged 50 years and older were myalgia (45%), fatigue (45%), headache (38%), shivering (27%), fever (21%), and gastrointestinal symptoms (17%)
- The data are insufficient to establish if there is vaccine-associated risk with SHINGRIX in pregnant women
- It is not known whether SHINGRIX is excreted in human milk. Data are not available to assess the effects of SHINGRIX on the breastfed infant or on milk production/excretion
- Vaccination with SHINGRIX may not result in protection of all vaccine recipients

Please see Brief Summary of Prescribing Information for SHINGRIX on the previous pages.

References: 1. Prescribing Information for SHINGRIX. **2.** Centers for Disease Control and Prevention. Prevention of herpes zoster: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2008;57(RR-5):1-30. **3.** Kilgore PE, Kruszon-Moran D, Seward JF, et al. Varicella in Americans from NHANES III: implications for control through routine immunization. *J Med Virol*. 2003;70(suppl 1):S111-S118. **4.** Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open*. 2014;4(6):e004833. doi:10.1136/bmjopen-2014-004833

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