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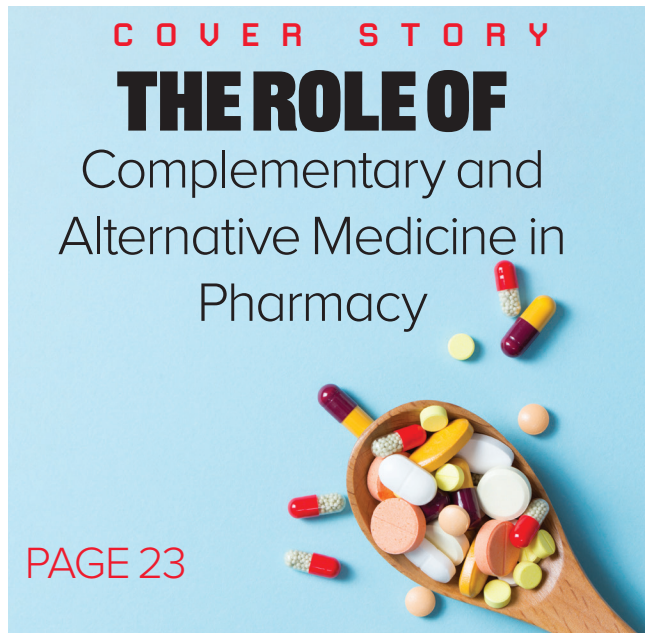

Drug Topics® (ISSN# 0012-6616) is published monthly except July/August and November/December and Drug Topics Digital Edition (ISSN# 1937-8157) is issued every week by MultiMedia Healthcare LLC, 2 Clarke Drive, Suite 100 Cranbury, NJ 08512. One-year subscription rates: $61 in the United States & Possessions; $109 in Canada and Mexico; all other countries, $109. Single copies (prepaid only) $10 in the United States; $10 in Canada and Mexico; all other countries, $15. Include $6 per copy for U.S. postage and handling. **Periodicals postage paid** at Trenton, NJ 08650 and additional mailing offices. POSTMASTER: Please send address changes to Drug Topics®, PO Box 457, Cranbury, NJ 08512-0457. Canadian G.S.T. number: R-124213133RT001. Publications Mail Agreement Number 40612608. Return undeliverable Canadian addresses to: IMEX Global Solutions PO Box 25542 London, ON N6C 6B2 CANADA. Printed in the U.S.A.

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Pharmacists Can Help Us Manage Pain

Each year, Pain Awareness Month is observed in September with the goal of raising awareness about chronic pain and its impact on both individuals and society. Pharmacists can play an important part during this month by educating patients and the public around pain management, promoting safe and effective strategies for pain relief, and offering support to patients living with chronic pain.

To achieve these goals, pharmacists should be knowledgeable about different types of pain. Understanding both the underlying cause and the mechanism of pain can help pharmacists provide the most appropriate recommendations and counsel. Understanding the concept of multimodal pain management means that pharmacists can encourage individuals to address pain from multiple angles, including OTC products, reducing potential reliance on opioid medications.

Unfortunately, the opioid crisis remains an ongoing problem in the United States. Pharmacists can do their part to ensure that patients are educated about the risks and benefits of opioid medications, as well as on proper use, adverse effects, storage, and disposal.

Earlier this year, survey results published by the Harvard T.H. Chan School of Public Health revealed that 3 in 10 adults in the United States know someone who has been directly affected by opioid addiction; more than half of respondents in that group said they know someone who died due to opioid use.[1] In this month's issue, we take a closer look at opioid use disorder in pregnancy: Although opioid use, opioid use disorder, and overdose in pregnancy and the postpartum period are leading causes of pregnancy-associated deaths, patients living with opioid use disorder while pregnant are frequently stigmatized and neither seek nor receive the compassionate, nonjudgmental care that they deserve—representing yet another area where pharmacists can make a difference for the patients in the communities that they serve.

As always, thank you for reading.
Mike Hennessy Jr
President and CEO, MJH Life Sciences

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SAP Spotlight

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In this special CPhT CONNECT episode in partnership with Drug Topics, host Mike Johnston sits down with Meredith Ayers, an experienced CPhT-Adv, to discuss her journey in the field and the unique role of technicians in independent pharmacies.
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***RPhCast*, Episode 4: "Finding Satisfaction in a Pharmacy Career"**
Host Kevin Walker is joined by Thea Blystone, PharmD, to talk about finding fulfilment and satisfaction in the pharmacy world, plus how to find balance between serving others and having time for yourself.
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From Stagnation to Success: Traits That Set Successful Pharmacy Technicians Apart
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Wellbeing Checkup: Avoiding Burnout and Thriving at Conferences
Cedric "Jamie" Rutland, MD, shares how he avoids burnout in an interview with HCPLive after presenting multiple data sets and various talks at ATS 2023.
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Monthly Poll How do you counsel patients about the importance of skin protection during the summer months?

25% Ask patients about their sunscreen habits when they pick up their medications

25% Create a dedicated display with sun protection products in the pharmacy's front end

25% Provide handouts with facts about skin cancer and the importance of SPF

25% Don't regularly counsel patients on this topic

0% Remind patients to conduct a monthly skin self-exam

Featured Podcast

Over the Counter — A podcast from Drug Topics

Reaching the APEX: American Pharmacies Annual Meeting Showcases the Importance of Community
Chuck Waters, vice president of marketing, communications, and data strategy at American Pharmacies, shares why collaboration is so important for the company's annual APEX event.

LISTEN: https://bit.ly/3KRWy7Q

Gluten in Medications: Why Labeling Matters for Patients With Celiac Disease

Despite pleas from celiac disease advocates, the FDA still does not require drug manufacturers to note on the label whether a medication contains gluten. By Killian Meara

Celiac disease is an autoimmune disorder that causes a reaction to gluten—a protein naturally occurring in certain cereal grains—in genetically predisposed individuals. The condition is lifelong and the only treatment currently recommended is total adherence to a gluten-free diet. When left undiagnosed and untreated, celiac disease results in nutritional malabsorption that can lead to anemia, bone disease, growth faltering, and other negative health consequences.[1]

The incidence of celiac disease has increased over the past several decades, likely due to various factors. Aside from having better testing and recognition, the increased incidence may also be attributed to environmental factors that could promote loss of tolerance to gluten.[2] The pooled global prevalence of celiac disease was found to be 1.4% based on blood tests, according to a 2018 meta-analysis.[3]

Patients with celiac disease also often have several comorbidities that need to be treated with medications, including psoriasis, alopecia areata, and rheumatoid arthritis.[4] Because the only treatment for celiac disease is a gluten-free diet and exposure to gluten can result in potentially severe reactions, whether medications contain gluten is an important issue for patients with the autoimmune disorder.

"Although sensitive patients tend to strictly adhere to a gluten-free diet, there is a possibility of unintentional intake via medicines since these may contain gluten in the formulation itself or as a result of the manufacturing process," wrote Lizano-Díez et al in a scoping review of gluten content in pharmaceutical products.[5] "This amount, which should not be ignored by physicians, pharmacists and patients, could reactivate the small-bowel immune response of a sensitive patient."

"Although medical treatment and medically necessitated diet options have grown and the incidence of celiac disease has increased, awareness of the gluten content of medications and a standardized, reliable approach to assess for gluten in medications are lacking."

—Georgina Rubal-Peace, PharmD, and Caroline Sepp, PharmD

Gluten in medication comes primarily from a single source: excipient or filler ingredients used to help medications reach a certain dosage. These filler ingredients form the bulk of the product and also serve a few other purposes, such as to absorb water, act as lubricant for powders, and add color. Starch has widely been used as an excipient in the pharmaceutical industry and is often derived from wheat, rye, or barley, which can leave trace amounts of gluten even if largely extracted from the starch itself.[6]

According to the FDA, most oral medications either "contain no gluten or virtually no gluten."[7] However, the federal public health agency does not require manufacturers to put on the label whether a medication contains gluten. In response to calls for some sort of labeling from celiac disease advocates, the FDA issued draft guidance in 2017 that provides recommendations on how oral drug products should be labeled regarding gluten. Although the labeling is voluntary, Alice Bast, CEO of patient advocacy organization Beyond Celiac, said at the time of the announcement that "it is definitely a step in the right direction."[8]

In a 2018 letter to the FDA,[8] Bast,

along with 2 other leading advocates, asserted that simply adding a voluntary label was not nearly enough to protect the health of people with celiac disease.[9] They added that if something akin to the 2014 FDA gluten-free labeling rule—which requires that food labels claiming to have no gluten meet certain set standards—was not possible, a mandatory label that reads "contains gluten" would be a huge improvement over the current guidance.

"Whereas testing procedures exist to determine the amount of gluten in packaged food products, we are aware that there are no such testing processes in place specifically developed to determine the quantity of gluten in medications," Bast and colleagues wrote in their letter.[8] "Nonetheless, the more that labeling of gluten in medications resembles the labeling of packaged food, the easier it will be for patients to determine if a specific medication will be safe for them."

Despite the pleas and demands from celiac disease advocates, the FDA still doesn't require that manufacturers include a gluten label on any medications.

Although several online resources for patients with celiac disease list any potential gluten allergens in medications, experts recommend that patients get in touch with their pharmacist. Pharmacists can play a vital role in helping a patient determine whether there is a gluten allergen in their medicine by calling the manufacturer and requesting information. And due to the often-complicated way that certain ingredients are named, a pharmacist will also be able to identify a potential allergen on a label more easily.[10]

However, a pharmacist may still not be able to fully determine whether a medication has any gluten allergens in it. That's why experts maintain that it is crucial that the FDA regulate gluten-free labeling in medications. The authors of a commentary who sought to address barriers for patients with celiac disease when assessing for gluten in medications noted that explicit "gluten-free labeling requirements by the FDA are imperative to allow patients with celiac disease to safely take medications."[11]

"Although medical treatment and medically necessitated diet options have grown and the incidence of celiac disease has increased, awareness of the gluten content of medications and a standardized, reliable approach to assess for gluten in medications are lacking," wrote Rubal-Peace et al.[11] "Explicit assessment for gluten in medications is a clinical necessity to prevent immediate and long-term adverse reactions for patients with celiac disease who may require a medication that contains gluten."▪

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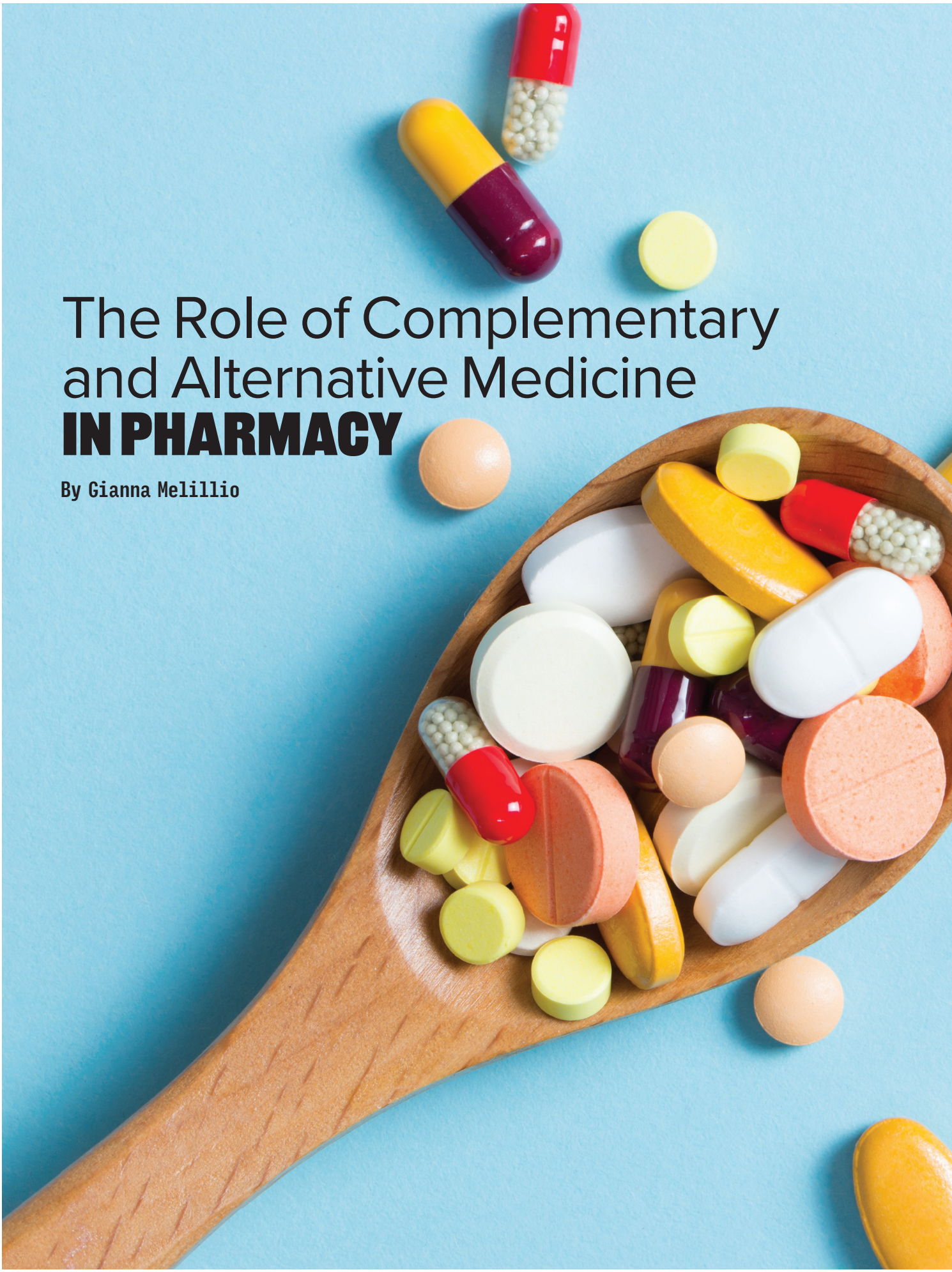

The Role of Complementary and Alternative Medicine **IN PHARMACY**

By Gianna Melillio

It's crucial to be open-minded about these approaches, and to convey accurate information to patients in a nonjudgmental manner.

Pharmacists are often the most accessible health care professionals, and for many Americans, their expertise can be particularly valuable when it comes to counseling on complementary and alternative medicines (CAM).

CAM is an umbrella term encompassing a wide variety of treatments and practices that can range from supplements to vitamins to herbal products. Thanks in part to the COVID-19 pandemic, the popularity of these products has risen dramatically in recent years.

According to the *Nutrition Business Journal*,[1] the supplement market added $4.15 billion in sales in 2021 and came in more than $5 billion higher than pre–COVID-19 projections. Despite CAM's commercial growth, more can be done to better inform pharmacists about this field, which will, in turn, help patients achieve their own individual health goals, experts say.

"We certainly in pharmacy education in general could do much better with teaching these treatment modalities," said Alice Scaletta, PharmD, an associate professor of clinical pharmacy at Philadelphia College of Pharmacy at St Joseph's University in Pennsylvania. She noted that this lack of education creates a domino effect: "My professors were never trained in it, [so] then they aren't going to be able to teach us, and then it just keeps going," she said.

In her role, Scaletta offers an elective course on herbal products, natural medicines, and dietary supplements to all professional-year pharmacy students—a crucial elective, given that a 2020 study of national consumer survey data show that individuals want pharmacists to have a better understanding of these medicines.[2]

That 2020 study also found that respondents had a positive perception of these medicines vs Western medicines.[2] Based on this finding, researchers concluded, "It is important for pharmacists to be more prepared to provide consultation to patients using CAM about proper use, [adverse] effects, and interactions with other remedies."

When it comes to furthering pharmacists' and patients' education on these treatments, keep several things in mind. For one, it's important to be mindful of how the terms are defined. For example, substituting *alternative medicines* with *integrative medicines* can be a more accurate and inclusive way of discussing treatment with supplements, herbal products, and other medicines.

According to Scaletta, most of the time patients aren't using just conventional or nonconventional medicines; they're using both. Therefore, *complementary* refers to patients using conventional and nonconventional approaches at the same time—sometimes without the knowledge of all their health care providers—whereas "integrative medicine is when there's actually a coordination of care between all their treatment modalities, including conventional and nonconventional," she said.

What's more, using the term CAM can imply these treatments are "second tier to traditional allopathic approaches," said Lara Zakaria, PharmD, CNS, IFMCP, an integrative pharmacist and a nutritionist in New York, New York. Zakaria typically uses the term *nutraceutical* to describe these types of therapies.

Moving away from the alternative label can also enable pharmacists to discuss the medicines in a more granular way, with a focus on basic biochemistry and metabolic function. "Pharmacy has the opportunity to step in [and be] the patient's chemistry expert and be on their clinical team," said Kathy Campbell, PharmD, a clinical community pharmacist in Owasso, Oklahoma. "What pharmacists have to realize is, it's all basically chemistry—and pharmacists are the chemistry experts in medicine. Nobody gets trained to the depth of chemical interactions at the cellular level like a pharmacist does. We have a very curated point of view when it comes to medicines and metabolic function."

Being open-minded about these medicines and conveying accurate information to the patient in a nonjudgmental manner is also crucial, especially when the treatments may be doing more harm than good. Campbell noted that, at the end of the day, "what I know doesn't matter. It's what the patient knows and what the patient can do every day that actually create outcomes."

What's more, patients may hesitate to ask pharmacists about these medicines because they fear judgment or worry that they will be immediately shut down, Scaletta said. "For us to have a patient actually open up to us about these things is actually a huge privilege [because] they're opening up this door and an opportunity for us to educate them. So it's really important to recognize that and to approach them in a nonjudgmental way no matter what your

"Pharmacy has the opportunity to step in [and be] the patient's chemistry expert and be on their clinical team. What pharmacists have to realize is, it's all basically chemistry—and pharmacists are the chemistry experts in medicine. Nobody gets trained to the depth of chemical interactions at the cellular level like a pharmacist does. We have a very curated point of view when it comes to medicines and metabolic function."

–KATHY CAMPBELL, PHARMD

"It's not about choosing sides. It's about recognizing that our patients are using both sides. And if I am going to be the most helpful to them, I need to be a trusted, nonjudgmental source of education for them—and not an adversary—for the approach that they're choosing for their lives."

—ALICE SCALETTA, PHARMD

viewpoints are."

It's estimated less than 40% of patients who use herbal supplements disclose it to their health care providers.[3] Creating a trusted environment where patients feel comfortable consulting with their pharmacists about their use of these medicines can also help prevent negative herb-drug interactions. For example, using St John's Wort with a selective serotonin reuptake inhibitor could lead to a potentially life-threatening interaction, according to the National Center for Complementary and Integrative Health.[4]

"As that person [who's] responsible for checking for medication interactions or appropriateness of therapy, it's really important that pharmacists are educated in this realm," Zakaria said.

When it comes to regulation, supplements fall under the food branch of the FDA, receiving far less scrutiny and oversight than pharmaceuticals. This can pose a problem when proprietary blends are marketed with labels that don't disclose every ingredient in the product. Supplements also do not need to be proven safe or effective before being brought to market.

One source that pharmacists can turn to for information is NatMed Pro, a subscription-based service complete with a drug interaction and effectiveness checker—all backed by scientific evidence.

Providing counsel to patients that is evidence based as opposed to opinion can help foster that trusted relationship. Dispelling misconceptions that these treatments have no proven use is also important. "You don't [want to make a] blanket statement saying things like, 'If it's an herbal product, if it's not conventional, then you shouldn't take it,'" Scaletta said.

Drug-induced nutrient depletions are just 1 instance in which supplements can be beneficial to the patient. "Every day, pharmacists would not dispense a thiazide diuretic without a potassium supplement," Campbell noted. Some patients could also be deficient in certain vitamins or minerals due to an underlying disease or injury.

"It's not about choosing sides. It's about recognizing that our patients are using *both* sides," Scaletta said. "And if I am going to be the most helpful to them, I need to be a trusted, nonjudgmental source of education for them—and not an adversary—for the approach that they're choosing for their lives."

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Professional CGM Use May Improve HbA_{1c} in Type 2 Diabetes

Most patients with type 2 diabetes self-monitor their blood glucose levels, but professional continuous glucose monitors can help patients reach their HbA_{1c} goals. By Lauren Biscaldi, MS

Use of professional continuous glucose monitoring (CGM) systems in adults with type 2 diabetes (T2D) using noninsulin therapies may improve glycemic control, according to research results published in *Clinical Diabetes*.[1]

After individuals with T2D begin insulin therapy, most patients begin to self-monitor their blood glucose levels with a blood glucose meter and test strips. However, this self-monitored method has been demonstrated to be "less helpful for reaching glycemic goals, unless the data are being used to make lifestyle changes or manage medications through active, shared decision-making," the researchers noted. For these patients, CGM systems can be an effective and useful tool to achieve these goals.

Personal CGM systems—those owned by the individual patients—present several cost- and access-related limitations. Professional CGM systems—devices owned by clinics and loaned to patients for short-term use—can increase access for patients who otherwise would not be able to afford a CGM system. These professional CGM systems continuously collect glycemic data and transmit that data to the health care provider, who can then use glycemic patterns to recommend modifications to a patient's treatment regimens and lifestyle.

According to investigators, previous studies of professional CGM have demonstrated some evidence of improved glycemic control in individuals with T2D. The goal of the current study, a retrospective, observational database study, was to examine the real-world potential value of professional CGM for those with T2D and poor glycemic control while using 2 or more noninsulin antidiabetic therapies.

The primary study outcome was the change in hemoglobin A_{1c} (HbA_{1c}) determined using the average of available HbA_{1c} values during the baseline and follow-up periods. Secondary outcomes included the change in the number of medications by class, insulin use during the follow-up period, and the change in HbA_{1c} for patients who did and did not start insulin during the follow-up period.

The study cohort included 15,481 patients with T2D (14,774 non-CGM users). Among the 707 patients using professional CGM, endocrinologists prescribed the CGM in 39.9% of cases; in 21.2% of cases, the CGM was prescribed by an internal medicine or family medicine physician or a nurse practitioner.

Overall, the patients using professional CGM reduced their HbA_{1c} by a mean of 0.83% (8.70%-7.87%); non-CGM users had a reduction of 0.32% (8.56%-8.23%). The difference-in-differences estimate was a –0.51% change in HbA_{1c}, which was statistically significant.

A total of 19.8% professional CGM users began using insulin during the follow-up period (15.8% basal insulin), compared with 10% of nonusers. HbA_{1c} change among insulin users in the professional CGM group was –0.57%, compared with the slight increase of 0.13% seen in the nonuser group. Difference-in-differences estimate for HbA_{1c} change was –0.71%, which was statistically significant.

"The findings from this study suggest that there is a glycemic benefit of [professional] CGM use for adults with type 2 diabetes who are not on insulin therapy and are taking multiple [oral antidiabetic drugs] and/or noninsulin injectable medications with poor glycemic control," the researchers wrote.

Study limitations included the relatively small number of professional CGM users vs nonusers, a lack of information about participants' soci-

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oeconomic status or participation in diabetes health coaching programs, and the use of only 3 professional CGM systems (Dexcom G4/G6 Pro, FreeStyle Libre Pro, and Medtronic iPro2). "Differences among these brands may influence users' experience and adherence to wearing the devices," the researchers said.

"Our findings suggest that [professional] CGM use in adults on noninsulin therapies is associated with improved glycemic control and thus may be a tool...to help patients reach their glycemic goals."

"Although randomized controlled trials are considered the gold standard for demonstrating the effects of therapeutic interventions, results from retrospective, observational studies of large health data systems can inform clinicians and regulatory agencies about the real-world efficacy of treatment interventions," the researchers concluded. "Our findings suggest that [professional] CGM use in adults on noninsulin therapies is associated with improved glycemic control and thus may be a tool [health care providers] can use to help patients reach their glycemic goals."

Disclosures: The authors of this study are employees of Dexcom. For a full list of disclosures, please see the full text of the study.■

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Moderna, Novavax Update Vaccines as COVID-19 Variants Cause Rise in Cases

The CDC and the World Health Organization are tracking variants that are driving the majority of new cases around the world. By Killian Meara

Although the Biden administration officially ended the COVID-19 public health national emergency in May, case counts are trending up, as several mutations of the virus continue to circulate. The CDC is tracking multiple different variants, but 2 in particular—EG.5 and FL.1.5.1—account for the majority of new infections in the United States.

According to the latest data from the CDC, 20.6% and 13.3% of new cases were caused by the EG.5 and FL.1.5.1 variants, respectively.[1] These were followed by several different strains of the XBB variant, with the XBB.1.16 variant responsible for 10.7% of total new cases.

The CDC and the World Health Organization (WHO) are also tracking another new strain that is raising concerns. The BA.2.86 variant has 36 mutations from the XBB.1.5 variant and has been detected in the United States, Denmark, and Israel. According to Jesse Bloom, PhD, a virologist at the Fred Hutchinson Cancer Center, mutational scanning indicates that the BA.2.86 variant "will have equal or greater escape than XBB.1.5 from antibodies elicited by pre-Omicron and first-generation Omicron variants."[2]

Although hospitalizations remain well below peaks seen during the pandemic, they have been increasing over the past few weeks. From August 6 to August 12, there were 12,613 hospital admissions due to COVID-19—a 21.6% increase from the previous week.[3]

However, experts are not too concerned as we head into the fall and winter season, when cases are likely to increase further. Mandy Cohen, MD, MPH, director of the CDC, told NBC News that we are in a different place compared to the past few years of the pandemic.[4] This is partly due to widespread immunity, as well as updated booster shots that are set to be available this fall.

On Tuesday, Novavax announced in a release that its updated protein-based vaccine candidate (NVX-CoV2373) induced neutralizing antibody responses to both the EG.5.1 and XBB.1.16.6 variants in small animal and non-human primate studies.[5] Nonclinical data also showed that the vaccine induced functional immune responses to the XBB.1.5, XBB.1.16, and XBB.2.3 variants. The vaccine is currently approved under an emergency use authorization for individuals 12 years of age and older.

"Our data have shown that Novavax's protein based COVID vaccine induces broadly neutralizing responses against XBB subvariants, including EG.5.1 and XBB.1.16.6," Filip Dubovsky, president of research and development at Novavax, said in a release. "We have a lot of confidence in our updated COVID vaccine and are working diligently with global regulatory bodies to ensure our protein-based vaccine is available this fall."

Moderna also recently announced positive data for its updated COVID-19 vaccine (mRNA-1273). The company said that preliminary data showed its vaccine provided a boost in neutralizing antibodies against the EG.5 and FL.1.5.1 variants.[6] Moderna said that it has submitted data to the FDA and hopes it will be ready for the fall.

"These new results show that our updated COVID-19 vaccine generates a robust immune response against the rapidly spreading EG.5 and FL 1.5.1 strains and reflects our updated vaccine's ability to address emerging COVID-19 threats," Stephen Hoge, MD, president of Moderna, said in a release. "Moderna is committed to leveraging our mRNA technology to provide health security around the world."

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Comparing Safety, Efficacy of COVID-19 mRNA Vaccines in Older Adults

Moderna's mRNA-1273 vaccine was associated with a lower risk of diagnosed COVID-19 when compared to Pfizer's BNT162b2. By Killian Meara

Moderna's COVID-19 mRNA vaccine (mRNA-1273) is associated with a lower risk of pulmonary embolism and other adverse events in older adults compared with Pfizer's COVID-19 vaccine (Comirnaty), according to recent data published in *JAMA Network Open*.[1]

Although the mRNA vaccines from both manufacturers have proven to be safe and effective, there are a lack of data about potential differences in older adults. There have been few studies comparing both vaccines, but some have shown that meaningful differences in the risk of adverse events that can vary by age may exist.

The current study, conducted by a team of researchers from Brown University, aimed to address the gap in data between the general population and older adults.

"Immunization with either mRNA vaccine is substantially better and safer than not being vaccinated at all," Daniel Harris, PhD, an epidemiologist and research scientist the Brown University School of Public Health, said in a news release.[2] "But in an ideal world where we can have a choice between which vaccine product is used, we wanted to see whether one vaccine was associated with better performance for older adults and those with increased frailty."

Investigators conducted a retrospective cohort study to compare the risk of adverse events between Moderna and Pfizer's mRNA vaccines for COVID-19 overall, by frailty level, and by prior history of certain adverse events. Data was gathered from a database of community pharmacy and Medicare claims.

The study cohort included 6,388,196 participants who received either the Moderna or Pfizer vaccine. Of those, 59.4% were women and 86.5% were White with a mean age of 76.3 years. A total of 38.1% of participants were categorized as prefrail and 6% as frail.

Primary study outcomes were 12 serious adverse events, including acute myocardial infarction, facial nerve palsy, deep vein thrombosis, Guillain-Barre syndrome, disseminated intravascular coagulation, hemorrhagic stroke, and myocarditis or pericarditis. The risk of diagnosed COVID-19 was assessed as a secondary outcome.

Investigators found that the risk for adverse events was low in both vaccine groups. However, the Moderna vaccine was associated with a lower risk of pulmonary embolism and other adverse events, such as thrombocytopenia purpura. Additionally, the Moderna vaccine was associated with a lower risk of diagnosed COVID-19, which was attenuated by frailty level.

Study limitations include rare outcomes that are hard to examine with precision, residual confounding, nonrandom selection or administration due to early perceptions in differences of vaccine performance, a possibility of incomplete outcome ascertainment, and challenges in determining the timing of adverse events.

"You can imagine regularly updating these types of analyses as new vaccines are developed," said Harris. "Depending on which one comes out on top, even on a very small scale, that may have big implications at the population level and render a preference for that particular vaccine."

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Assessing and Treating Opioid Use Disorder in Pregnancy

Opioid use disorder during pregnancy is stigmatized, but these patients deserve compassionate, nonjudgmental care. Leah Habersham, MD, MBA, MS; and Mishka Terplan, MD, MPH

This article originally appeared in the August issue of Contemporary Ob/Gyn® *and has been lightly edited.*

Opioid use and opioid use disorder (OUD) have profoundly impacted the United States over the past 2 decades. The opioid crisis began with the overprescribing of prescription opioids and has had distinct subsequent waves, first with heroin and more recently with synthetic opioids, including illicitly manufactured fentanyl.[1-3] Overdose rates have continued to rise, with more than 100,000 individuals dying from overdose in 2022.[4]

The ages associated with the highest prevalence of substance use and development of use disorder overlap, especially during the earlier years of pregnancy potential. Hence, opioid use, OUD, and overdose in pregnancy and postpartum have increased in parallel with the opioid crisis, making overdose a leading cause of pregnancy-associated deaths.[2]

Most adults in the United States have used substances; however, only a minority of people develop a use disorder.[5] Risk factors for development of substance use disorder include a younger age of first use, substance availability in both the household and the neighborhood, preexisting mental illness, and—especially for women—gender-based violence, including childhood sexual abuse, that leads to trauma.[6,7]

Health care providers are well positioned to assess, diagnose, and initiate treatment for OUD in pregnancy and through the postpartum period.

Although medications for OUD (MOUDs) have been available for more than 50 years, most pregnant women with OUD receive no treatment because of inadequate access, ambivalence, and fear of stigma and discrimination.[8-10] By integrating OUD assessment and treatment into prenatal and postpartum care, health care providers can directly address the opioid crisis and interrupt the generational cycle of addiction.[11]

STIGMA AND LANGUAGE

Stigma is the process by which people are "marked" by a perceived differentness of deviation from social norms.[12] Stigma is often expressed in language and experienced by people as discrimination. A large body of evidence documents how common stigmatizing beliefs are among health care providers and how the experience of health care discrimination negatively impacts care.[13-17] Pregnant women who use drugs experience compounded stigmas (of substance use, pregnancy, treatment) and consequentially may be legitimately fearful to disclose their use despite desiring treatment.

Responsibility of ensuring patient safety rests upon the provider. It is important to that providers interact with patients in a nonjudgmental way and provide support to patients who are at a variety of entry points of change (**Table 1**).[18,19] Harm reduction should be explored, including naloxone and syringe services and safer injection practices if appropriate.[20]

ASSESSMENT

Screening is the primary means by which substance use is identified clinically, whether the patient is pregnant or not.[21] Screening should be distinguished from testing. Screening is characterized by a series of questions or use of a validated tool, such as a questionnaire.[21] See **Box 1** for examples of validated screening tools.[22] Testing is the examination of a biological specimen (such as urine) for the presence of drug metabolites or parent compounds. Although universal screening is recommended for all pregnant women by the American College of Obstetricians and Gynecologists, drug testing is not.[23]

"Presumptive tests" utilize ELISA technology and are the most common testing used. Although they render results rapidly, providers should be aware that the information quality obtained from a presumptive test is poor because of a high rate of both false-positive and false-negative results. Definitive tests use the technology of liquid or gas chromatography–mass spectrometry and provide quantified results and exact substance identification.[24] Definitive tests are more expensive and take days to report. In addition, the window of detection varies by substances and for many is typically fewer than 3 days.[25] The primary symptoms of addiction are behaviors, and a positive drug test cannot identify a substance use disorder, much less parenting competence, even when a positive result is confirmed.[21] Finally, professional society recommendations are unanimous: Drug testing, if done, requires informed written patient consent.

Assessment for substance use should be performed via validated screening instrument. A positive screen should be followed by diagnostic assessment. The *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)* diagnostic criteria should be used to diagnose OUD (**Table 2**).[26] To meet criteria for OUD, 2 or more affirmative responses to the criteria are required.[27]

TABLE 1. **NONSTIGMATIZING, CLINICALLY ACCURATE LANGUAGE AND TERMINOLOGY**[18,19]

TERMS TO AVOID	PREFERRED TERMINOLOGY
Addict, abuser, alcoholic, crack head, dope fiend, junkie	Use people-first language and name the substance used, eg, person with an opioid use disorder
Abuse	Use
Addicted baby	Baby experiencing substance withdrawal
Dirty versus clean urine	Positive or negative; detected or not detected
High, drunk, strung out	Intoxicated
Relapse	Return to use, recurrence of use

TREATMENT

After confirmation of OUD, treatment should be offered. The standard of care for OUD rests on medications. Methadone and buprenorphine are the safest and most effective MOUDs in pregnancy; there are less data for naltrexone in pregnancy. These 3 medications differ in pharmacology: Methadone is a full opioid receptor agonist, buprenorphine is a partial agonist, and naltrexone is an opioid antagonist (**Figure**).[28] The μ-opioid receptor is the primary site of action and is responsible for many of the favorable aspects of opioids, namely euphoria, analgesia, and stress coping. However, MOUD also exerts activity on both δ- and κ-opioid receptors, which are important to understand in terms of potential medication adverse effects. δ-Receptor activation leads to anxiolysis and positive affect, whereas κ activation is associated with dysphoria, stress, and negative affect.[29] Methadone is a full

Box 1.

Validated Screening Tools[22]

DAST-10
10-item general substance use screening questionnaire
sensitivity, 47%; specificity, 82%

SURP-P
3-item substance use screening questionnaire
marijuana sensitivity, 68%; specificity, 86%

4P's Plus
4-item questionnaire in pregnancy
sensitivity, 87%; specificity, 76%

NIDA Quick Screen
4-item questionnaire assessing frequency of use

DAST-10, Drug Abuse Screening Test; NIDA, National Institute on Drug Abuse; SURP-P, Substance Use Risk Profile–Pregnancy.
[a]Not yet validated in pregnant population.

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TABLE 2. ***DSM-5*** **SUMMARY OF DIAGNOSTIC CRITERIA FOR OPIOID USE DISORDER**[26]

CATEGORY	CRITERIA
Impaired control	• Using opioids in greater quantities or longer periods than intended
Social impairment	• Failing to meet obligations at home, school, or work due to continued use of opioids • Extensive social or interpersonal problems that are exacerbated by opioids or continued use of opioids despite such problems • Limiting important social, recreational, or occupational activities due to opioid use
Risky use	• Use of opioids leading to physically hazardous situations • Continued use of opioids despite subsequent physical and psychological problems that result from use
Pharmacological effects	• Tolerance leading to a need for increasing the amount of opioid use to achieve the desired effect and/or decreased effect if the same amount is used • Withdrawal symptoms experienced when opioids are decreased or discontinued; the use of opioids relieves symptoms of withdrawal

Mild: 2-3 criteria
Moderate: 4-5 criteria
Severe: ≥6 criteria

DSM-5, Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

agonist at the μ, δ, and κ receptors; buprenorphine is a partial μ agonist and a δ and κ antagonist; and naltrexone is an antagonist at the μ, δ, and κ receptors.[30]

Opioids are addictive, in part because they are both positively and negatively reinforcing. These dual characteristics lead to neuroadaptations that follow chronic use, causing a patient to develop tolerance, experience withdrawal when the substance is not used, and experience cravings. MOUD works first by treating opioid withdrawal and then by controlling drug cravings, which interrupts negative reinforcement. MOUD also works by establishing an "opioid blockade" (blocking the effect of other opioids if used), which interrupts positive reinforcement and establishes a cross-tolerance. Collectively, these features are associated with decreased mortality and reduced substance use.[31]

Behavioral therapy can be an important dimension of recovery for many people. However, the overall literature on OUD treatment demonstrates little to no additional benefit of behavioral therapies such as group counseling vs medication. Therefore, providers should support behavioral therapy but not insist upon it—and certainly not withhold medication for counseling nonadherence. Some patients may be reluctant or resistant to initiate MOUD because of prior negative experiences with medication or because of mistrust or family/peer pressure. Engagement in prenatal care, even in the context of continued substance use, improves birth outcomes, and providers should utilize a harm reduction framework, in which the provider not only "meets the patient where they are," but also "helps them get where they want to go."[32]

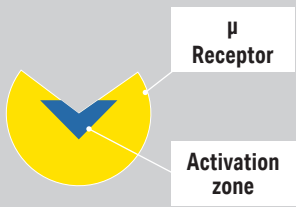
MOUDS

Methadone is among the most federally regulated medications in the United States; it cannot be prescribed for OUD but can be administered directly to patients in the outpatient setting from a federally licensed opioid treatment program (OTP). Methadone can also be initiated or continued in a hospital. Methadone does not require withdrawal for initiation.[33] Because of its differential metabolism between individuals, initiation is often slower than for buprenorphine. However, pregnancy is a rapid metabolic state, and more rapid protocols have been suggested.[34]

Buprenorphine is less regulated and, hence, more easily integrated into prenatal care settings. The Drug Enforcement Administration X-waiver, which had previously limited who could prescribe buprenorphine, was recently removed. Buprenorphine can now be prescribed by any provider with prescribing authority.[35] This regulatory change should increase access to buprenorphine both for medication initiation and continuation.

Buprenorphine is a partial agonist: The patient needs to be withdrawn before medication initiation. If not, buprenorphine can precipitate withdrawal.[33] Although there is concern that fentanyl might lead to a greater likelihood of precipitated withdrawal, population health data

FIGURE. **PHARMACOLOGY OF MOUD OPTIONS**[28]



MOUD, medication for opioid use disorder.

Antagonist: Receptor is occupied while activation zone is blocked.
Example: **Naltrexone**

Agonist: Receptor is occupied while activation zone is activated.
Example: **Methadone**

Partial agonist: Receptor is partially occupied while activation zone is partially activated.
Example: **Buprenorphine**

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Box 2. Resources

- University of California, San Francisco National Clinician Consultation Center Substance Use Warmline offers free and confidential clinician-to-clinician telephone consultation at 855-300-3595. Visit https://nccc.ucsf.edu/clinical-resources/substance-use-resources/ for more information
- Lifeline for Moms: Warmline for Perinatal Mental Health: 508-856-8455, LifelineforMoms@umassmed.edu
- CABridge medication protocols for addiction medicine: https://cabridge.org/
- The Academy of Perinatal Harm Reduction's Pregnancy and Substance Use: A Harm Reduction Toolkit: https://www.perinatalharmreduction.org/toolkit-pregnancy-substance-use
- Substance Abuse and Mental Health Services Administration's "Clinical Guidance for Treating Pregnant and Parenting Women with Opioid Use Disorder and Their Infants": https://store.samhsa.gov/sites/default/files/d7/priv/sma18-5054.pdf

to support this are lacking, and the likelihood of precipitated withdrawal can be lessened with microdosing or cross-tapering protocols (**Box 2**). Buprenorphine is available in 2 formulations: sublingual films or tablets and a monthly extended release.[33] Although the initial literature recommended the use of the buprenorphine monoproduct in pregnancy, subsequent research has concluded that the combination product of buprenorphine plus naloxone is as safe and effective.[36]

Naltrexone is an opioid receptor antagonist and requires a week of opioid abstinence prior to initiation to avoid precipitated withdrawal. Naltrexone can be prescribed by anyone with prescribing authority and comes in both oral and extended-release formulations.[33] The existing literature on naltrexone in pregnancy is limited to case series. There are less data on the safety and effectiveness of naltrexone compared with buprenorphine or meth-

TABLE 3. **COMPARISON OF FDA–APPROVED MEDICATION FOR THE TREATMENT OF OPIOID USE DISORDERS**[37]

MEDICATION	MECHANISM OFACTION ATM-OPIOID RECEPTOR	FORMULATIONS	CAUTION/AES	AVAILABILITY	INPREGNANCY
Methadone	Agonist	Oral	Sedation and respiratory depression, particularly in combination with other sedatives; QTc interval prolongation; torsade de pointes AEs: nausea, constipation, weight gain, decreased libido, hypothalamic-pituitary-adrenal axis suppression	Federally regulated opioid treatment programs	First line
Buprenorphine	Partial agonist	Sublingual, buccal	Respiratory depression and sedation; hepatotoxicity AEs: Similar effects to full agonist, but they may be milder.	Office-based treatment	First line; monoproduct is standard; buprenorphine-naloxone increasingly accepted
Naltrexone	Antagonist	Oral, intramuscular	Increased vulnerability to opioid overdose once discontinued; hepatotoxicity; cautioned use in patients with hepatic impairment or bleeding disorders AEs: insomnia, anxiety, nausea/vomiting, transaminitis, headache, injection-site pain, nasopharyngitis	Office-based treatment	Insufficient data

AEs, adverse events; QTc, corrected QT interval.

adone, so its use is not recommended.[24] See **Table 3** for a comparison of medications.[37]

OPIOID WITHDRAWAL AND BUPRENORPHINE INITIATION

Withdrawal is the inverse of dependence and occurs following cessation of opioid use or administration of either a partial or a full opioid antagonist. Chronic opioid use leads to dependence on sympathetic and parasympathetic control by the exogenous opioid, and withdrawal, consequentially, leads to noradrenergic imbalance seen in the increase of norepinephrine from the locus coeruleus, which leads to the typical symptoms of withdrawal: irritability, abdominal cramps, nausea/vomiting, diarrhea, increased blood pressure and pulse rate, lacrimation, rhinorrhea, yawning, and pupil dilation.[34] Withdrawal can be clinically measured using the Clinical Opiate Withdrawal Scale and should be assessed at every visit, especially early in treatment and in pregnancy.

Because buprenorphine is a partial agonist, withdrawal may be precipitated if the medication is initiated too early. Standard buprenorphine initiation protocols begin medication administration when the Clinical Opiate Withdrawal Scale score is at least 8.[38] However, microdosing or cross-tapering protocols can be started before the patient has experienced withdrawal.[39] These protocols begin with low-dose buprenorphine administration (typically 0.5 mg), below the threshold of precipitated withdrawal (**Box 2**). **Table 4** describes a standard buprenorphine initiation protocol.[40]

MOUD CARE CONTINUITY

Following stabilization on MOUD, patients should be assessed for withdrawal, cravings, and other substance use. Both metabolic and physiologic changes of pregnancy can lead to more rapid metabolism of both methadone and buprenorphine. Hence, some patients who had previously been stable on

TABLE 4.

BUPRENORPHINE INITIATION[40]

Day 1

- Counsel patient on benefits, alternatives, and risks of buprenorphine use—including precipitated withdrawal.
- Patient should be in at least moderate opioid withdrawal (COWS score > 8).
- Give first dose of buprenorphine, 2-4 mg.
- Monitor for signs of precipitated withdrawal and treat any symptoms that do occur.
- If first dose is tolerated, give an additional 2-4 mg of buprenorphine.
- Dosing can be repeated as needed until the patient is stable.
- Average day 1 dose is 8-16 mg.

Day 2

- Patient should take sum total of day 1 dose and an additional 2-4 mg if withdrawal symptoms are not adequately relieved, up to 24 mg.
- Average dose is 16-24 mg.
- Prescribe total day 2 dose as a recurrent daily dose until the patient is next scheduled to return to the clinic.

Maintenance

- Check in with the patient within 1 week to determine whether adjustment is needed for daily buprenorphine dose. Range of dose may vary for stabilization; effective dose may reach up to 32 mg.
- At clinical visits, assess withdrawal, cravings, and return to use.
- Once patient is stabilized on a dose, determine frequency of visits and urine toxicology testing. Assess whether and when patient attends counseling and support groups, and check PDMP regularly. Keep in mind that each of these variables may need to be reassessed at any point in the future.

COWS, Clinical Opiate Withdrawal Scale; PDMP, prescription drug monitoring program.

a medication dose may present with increased drug cravings or even withdrawal symptoms. In this circumstance, providers should consider split dosing (twice, 3 times, or even 4 times daily) before dose increases, especially if the symptoms occur hours after medication administration. Split dosing increases the pharmacokinetic area under the curve by minimizing peaks and troughs and encourages a more optimal steady state. For methadone, split dosing provided by the OTP in the form of take-home bottles should be considered and fully discussed with the patient.[24]

THE IMPORTANCE OF NALOXONE

Naloxone is a short-acting opioid antagonist with high affinity for the μ-opioid receptor. It is highly effective in reversing an overdose through the displacement of other opioids at the μ receptor. Anyone who uses opioids (prescribed, MOUD, or untreated OUD) and anyone who may witness an overdose (such as friends and families of people who use opioids) should receive naloxone and know how to use it.[41] This is particularly important postpartum because overdose is a leading cause of maternal death in the United States and timely administration of naloxone saves lives.[2]

Naloxone can be prescribed, distributed directly often through local public health agencies, or obtained from a pharmacy under a regional standing order. The FDA recently approved naloxone for OTC sale. Naloxone has a short half-life, and its effect begins to wear off within 10 minutes. People can be reversed with naloxone and then slip back into overdose again. Therefore, multiple doses are often needed, and patients and families should be advised to call 911 following an overdose event.

CONCLUSION

Health care providers are well positioned to assess, diagnose, and initiate treatment for OUD in pregnancy and through the postpartum period. Methadone and buprenorphine are the safest and most effective medications for OUD in pregnancy. Utilizing the key fundamental principles of OUD management, providers will be better prepared to confidently introduce this life-saving treatment into their practice repertoire.

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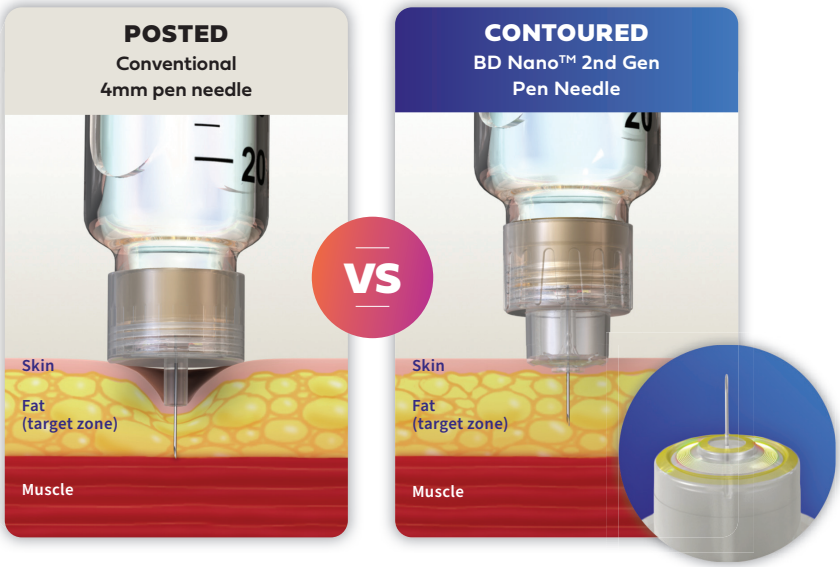

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RSV Vaccine Is Now Available in Some US Pharmacies: Here's What You Need to Know

A Q&A with Marc Ost, co-owner of Eric's RX Shoppe, which was one of the first community pharmacies to receive the new vaccine. By Killian Meara

On May 3, 2023, the FDA announced its approval of Arexvy, GSK's respiratory syncytial virus (RSV) vaccine, adjuvanted, marking the first global approval of a vaccine to prevent lower respiratory tract disease caused by RSV in adults aged 60 and older. The approval, which was based on the landmark phase 3 AReSVi-006 clinical trial (NCT04886596), allows older adults to be protected from the virus for the first time.

"Today marks a turning point in our effort to reduce the significant burden of RSV," Tony Wood, chief scientific officer at GSK, said in a news release at the time of the approval.[1] "Arexvy is the first approved RSV vaccine for older adults, expanding GSK's industry-leading vaccine portfolio, which protects millions of people from infectious diseases each year. Our focus now is to ensure eligible older adults in the US can access the vaccine as quickly as possible and to progress regulatory review in other countries."

Drug Topics spoke with Marc Ost, co-owner of Eric's RX Shoppe, about the new RSV vaccine. The community pharmacy, located in Horsham, Pennsylvania, was one of the first in the country to receive and administer the vaccine.

***Drug Topics*: Can you discuss the significance of this vaccine being the first approved by the FDA to prevent lower respiratory tract disease caused by RSV in older adults?**

Marc Ost: I think the biggest thing this vaccine does is provide a solution for people who are at risk for RSV. Right now, it's just for the older population, but our hope eventually is that people will be able to get it while they're pregnant to protect their newborns. It's a [preventive] measure that hopefully enough people will take that will help them treat a disease that really doesn't have much treatment available.

Health care providers are familiar with RSV, but it isn't necessarily as well-known among the public. What should people know about it?

For me personally, I've always associated [RSV] with kids. My son had RSV when he was less than a year old, and it's scary. It's something that there's not really treatment for. In our pharmacy, we deal with a lot of [individuals in] the long-term-care population, where you hear about RSV and it spreads very quickly. It's dangerous how quickly it spreads. For someone [who is] healthy, middle aged… it's a common cold. But for someone who's at risk, or who has comorbidities, it could be a lot more serious. For those who are at risk, we want to do everything we can to help them fight the virus if they contract it.

How much does the RSV vaccine cost, and is it covered by insurance?

The cost is about $300 to $315, including the administration. We're working with GSK [and] the Centers for Medicare & Medicaid Services… to get the vaccine covered. Because it's so new, insurance companies take [some time] to put it on the formulary and add it. It is an ACIP [Advisory Committee on Immunization Practices]–recommended vaccine. Under the Inflation Reduction Act [of 2022], Medicare Part D is mandated to cover it.

Our policy right now is, anybody who has Medicare Part D we're contracted with, we'll give them a vaccine at no cost, then we'll figure out reimbursement once it's covered. We don't know about commercial insurers, whether they will or won't cover it or allow pharmacies to. It's just a wait-and-see process.

Vaccine hesitancy is a big problem. What would you tell a patient who maybe is hesitant about getting the new RSV vaccine?

"I think that what you're going to find, similar to other vaccines, is that pharmacies will probably be the best point [of access] to get this vaccine. It's expensive, and what we're seeing is a lot of providers' offices don't want to stock the vaccine; they don't want money sitting in the fridge."

—MARC OST

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Have a discussion with your health care provider. It's always a risk-or-benefit discussion. You really want to look at who the vaccine is approved for. "Why should I get it?" That's a question that [patients] should ask, and health care providers or pharmacists should have an answer. They should be able to tell [patients], "This is why I recommend you get it."

I think one of the big reasons for vaccine hesitancy that has come up in the last few years has been the COVID-19 vaccine. A lot of people got the COVID-19 vaccine, and then they got COVID-19, not realizing that the vaccine wasn't designed to stop you from testing positive; the vaccine was designed to stop you from going to the hospital or dying. I think having that understanding, and having clear information, makes a big difference [along with] increased trust between the patient, the health care provider, and the technology or vaccine.

Is there anything else important about the RSV vaccine that you want to add?

I think that what you're going to find, similar to other vaccines, is that pharmacies will probably be the best point [of access] to get this vaccine. It's expensive, and what we're seeing is a lot of providers' offices don't want to stock the vaccine; they don't want money sitting in the fridge.

Pharmacies, especially community pharmacies, are very nimble. We will make [the vaccination process] as accommodating to patients as we can. We'll hold clinics at churches, synagogues, businesses. We're also doing a lot of clinics at long-term-care centers. And at community pharmacies, we know our patients. There's a trust factor. For my business partner, Eric, one of the biggest things that we've seen with the COVID-19 vaccine—and even with this vaccine—is [patients asking], "Did you get it? Would you give it to your mom?" And that's a question that they'll always ask him, because he has trust in the community. Because he's been around and has taken care of patients and built those relationships, there's a level of trust. They take what he says seriously, and it means something. It's not just the pharmacist giving it, it's someone they know and trust.

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FDA Approves Pfizer RSV Vaccine for Use During Pregnancy to Protect Infants

The respiratory syncytial virus vaccine Abrysvo is the first maternal RSV vaccine used to help protect infants from the virus. By Killian Meara

The FDA has approved Pfizer's bivalent respiratory syncytial virus (RSV) vaccine (Abrysvo) for use during pregnancy to prevent lower respiratory tract disease (LRTD) and severe lower respiratory tract disease caused by RSV in infants from birth through 6 months, according to a news release.[1] The approval makes Abrysvo the first RSV vaccine for pregnant women.

RSV is a highly contagious virus that causes respiratory infections and can infect people of all ages, but it's especially common in children. It is the leading cause of respiratory-related hospitalizations in infants worldwide and is the main cause of hospitalizations in the first year of life.[2] Although the virus often only causes symptoms similar to a cold, it can lead to pneumonia and bronchiolitis.[1]

"RSV is a common cause of illness in children, and infants are among those at highest risk for severe disease, which can lead to hospitalization," Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research, said in a news release.[1] "This approval provides an option for health care providers and pregnant individuals to protect infants from this potentially life-threatening disease."

The approval of Abrysvo was based on efficacy data from the phase 3 MATISSE clinical trial (NCT04424316).[1] The study included 3682 participants who received the vaccine and 3676 who received a placebo at 24 through 36 weeks' gestation, with 3570 and 3558 infants evaluated, respectively. Abrysvo reduced the risk of severe LRTD by 81.8% within 90 days after birth, and 69.4% within 180 days after birth, the results show.

"This approval provides an option for health care providers and pregnant individuals to protect infants from this potentially life-threatening disease."

–PETER MARKS, MD, PHD

The safety of Abrysvo was evaluated in 2 studies. The first study included 3600 pregnant participants who received a single dose and 3600 pregnant participants who received a placebo. In the second, 100 received Abrysvo and 100 received placebo. The most commonly reported adverse effects included injection site pain, headache, muscle pain, and nausea. Additionally, preeclampsia was reported in 1.8% of participants.[1]

"Newborns and young infants—whose immune systems are still developing and are not yet strong enough to defend against infections—may now be protected from RSV from the moment of birth through maternal immunization," Eric A.F. Simões, MD, clinical professor of pediatrics-infectious diseases at the University of Colorado School of Medicine and Children's Hospital Colorado in Aurora, said in a news release.[3] "The approval of Pfizer's Abrysvo is a major triumph as it helps ensure no delay in potential RSV protection during an infant's most vulnerable first 6 months of life and offers health care providers a new opportunity to help prevent severe RSV."

Abrysvo prescribing information states that "a numerical imbalance in preterm births in Abrysvo recipients (5.7%) occurred" compared with those who received placebo, but "the available data currently are insufficient to establish or exclude a causal relationship," according to the FDA news release.[1] In addition, Pfizer will be required to "conduct postmarketing studies to assess the signal of serious risk of preterm birth and hypertensive disorders of pregnancy, including preeclampsia."[1]■

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Evaluating Underlying Health Conditions of Infants Hospitalized With RSV

Infants younger than 3 months, those born prematurely, and those publicly insured were at a higher risk for intubation, study results show. By Killian Meara

Most infants who were admitted to intensive care units for an infection with the respiratory syncytial virus (RSV) were previously healthy and had no underlying conditions, according to recent data published in *JAMA Network Open*.[1]

RSV is the leading cause of respiratory-related hospitalizations in infants across the world, with 57,000 annually in children younger than 5 in the United States. The virus is the main cause of hospitalizations in the first year of life, and 1 in 5 children hospitalized for RSV are admitted into the intensive care unit (ICU).[1]

Unusual surges in RSV infections during 2021 and 2022 were the result of disrupted circulation patterns caused by the COVID-19 pandemic. In an effort to evaluate infants admitted to the ICU due to RSV during 2022, researchers from the Vanderbilt University Medical Center in Nashville, Tennessee, conducted a study evaluating clinical characteristics and outcomes of critical illness during peak transmission.[1]

Data were gathered from a public health prospective surveillance registry, which included 39 pediatric hospitals across 27 different states. The study cohort included 600 infants who were admitted to an ICU with RSV in one of the hospitals between October 17 and December 16 during the peak of the 2022 RSV season.[1]

Main outcomes included clinical characteristics, signs and symptoms, and clinical outcomes such as receipt of noninvasive respiratory support, invasive mechanical ventilation, and death.

Investigators found that, of the infants admitted to the ICU, the median age was 2.6 months, 60.2% were boys, 28.9% were born prematurely, and 82.1% had no underlying medical conditions. The most common reasons for being admitted to the ICU included lower respiratory tract infection, and apnea or bradycardia.[1]

Additionally, 143 infants received invasive mechanical ventilation and 243 required high-flow nasal cannula. Infants younger than 3 months, those born prematurely, and those who were publicly insured were at higher risk for intubation.[1]

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"Most of the infants in our study receiving ICU-level care were young, healthy, and born at term," Natasha Halasa, MD, MPH, lead author on the study, said in an interview with Vanderbilt University Medical Center.[2] "Although mortality was rare, our findings emphasize the significant illness caused by RSV in young infants."

Study limitations include a limit on the influence of single centers or regions; not including all cases of severe RSV admitted to the ICU during the study period; potential for missed RSV cases due to only including clinician-ordered, laboratory-confirmed RSV cases; and only half of participants having been tested with a respiratory viral panel.[1]

"We hope that our study findings will aid in the design of future RSV prophylactic and maternal RSV vaccine effectiveness and usage studies and recommendations," Halasa said.[2]■

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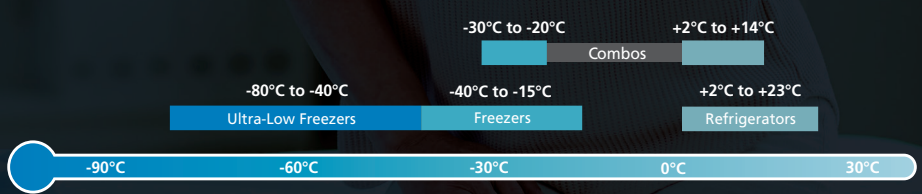

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How AI Can Improve Controlled Substance Security

Artificial intelligence can enhance the surveillance systems used to screen for potential drug diversion. ***By Keith Loria***

Each year, drug diversion is estimated to cost the US health care system an estimated $70 billion. Outside of these costs, drug diversion poses a significant risk to patient safety and patients' communities.

Compared with manual methods of identifying drug diversion, which can be inefficient and slow in uncovering patterns in prescribing and administration, artificial intelligence (AI) can employ predictive analytics to rapidly and accurately identify behavioral patterns that are red flags for the diversion of controlled substances and other drugs.

Machine learning models can also identify patients at risk of drug diversion based on their prescription history and other factors. AI-powered inventory management systems can help maintain accurate counts of controlled substances and flag discrepancies faster, minimizing opportunities for diversion.

Anthony Buzzetta, founder and CEO of G TIER, an AI technology company specializing in the health care and pharmacy spaces, said AI technology can minimize challenges associated with controlled substances by providing real-time monitoring, improving accountability, and enhancing overall security measures. However, pharmacies using AI tools need to think carefully about how best to use technology when managing controlled substances.

Buzzetta said there are numerous uses for AI tools, "from detecting early signs of diversion through predictive analytics models to developing automated workflow processes that help pharmacies regulate inventory levels and automate reports efficiently without causing disruption or compromising quality assurance procedures. If done correctly, implementing intelligent systems will result in improved compliance measures related to controlled substance management. Also, it could provide enhanced patient safety and privacy protections within a pharmacist's day-to-day operations."

An AI model can be trained to identify what "regular" or "normal" usage looks like with any medication, including controlled substances; once trained, the AI platform can then identify deviations from the norm. In the scope of controlled substances, this would identify potential cases of drug diversion if leveraged appropriately. If the data model is appropriately sized, pharmacists could also detect deviations at any stage of diversion to help limit proliferation and impact.

Among the metrics that can be detected are individuals who may be diverting or abusing controlled substances; prescribers or dispensers who are inappropriately prescribing; anomalies in inventory data; and high-risk patients for early intervention.

Crystal Riggs, PharmD, senior vice president of pharmacy services at Curative, an employer-based health insurer based in Texas, noted that AI will be used by independent pharmacies more to assist with modeling and predictive tools to manage controlled substances. "This can aid with a lessening of drug diversion, overprescribing, and better management of controlled substances," she said. "Pharmacies and pharmacists will be better equipped on how to combat the opioid crisis, increased ADHD [attention-deficit/hyperactivity disorder] medication prescribing, benzodiazepine utilization in [older patients], and several other issues stemming from controlled substances. AI will also alleviate constraints on resource allocation, as access will be available for all parties who are involved with the care of the patient. The opioid epidemic affected rural areas drastically, and having access to AI tools will help those involved in the care of those affected."

AI can enhance surveillance systems that monitor prescriptions and flag unusual activities such as rapid increases in prescription quantities or high-risk combinations of drugs. AI can also help pharmacies build profiles of patients based on past prescriptions and behaviors. This could help identify patients at risk of substance abuse or diversion. AI algorithms can optimize management of controlled substances inventory, minimizing the chances of theft or diversion.

Furthermore, AI integration within pharmacy can promote efficiency in controlled substance auditing. For instance, without AI, a controlled substance audit of 5% of controlled substance fills may take several hours; however, AI-backed software systems can provide a complete audit of these administrations in significantly less time. This is because AI systems can provide a significantly quicker analysis of data than humans can.

AI will also provide real-time alerts when a patient's prescription order is unusual, allowing pharmacists to take preventive action before a medication is dispensed. Moreover, AI can be used to track controlled substances throughout the supply chain and detect any discrepancies in order tracking that could indicate theft or diversion..

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Rethinking Pharmacy Education in the Era of Artificial Intelligence

As AI becomes more prevalent, how must the pharmacy world change how it learns? *By Keith Loria*

Despite the huge impact artificial intelligence (AI) is having—including in the pharmacy world—the technology is infrequently covered during pharmacy education, with some exceptions. For instance, at the University of Florida College of Pharmacy in Gainesville, researchers use AI tools to address the nation's health care challenges, from developing new cancer drugs to stemming the opioid epidemic. The university has also beefed up education around AI for students enrolled in the pharmacy program. Similarly, the University of California's pharmacy program has added lessons in AI to its syllabus in recent years.

As AI becomes more prevalent in health care, pharmacy schools will need to introduce it in their curricula to prepare students for effectively utilizing these tools. This could include courses on how AI tools work, interpreting outputs, and ethical considerations.

"Interestingly, the topic of AI doesn't always get the attention it deserves in the curriculum," said Sam Brackett, PharmD, director of operations at long-term care and specialty pharmacy Altruix, and a 2016 graduate of the University of Maryland School of Pharmacy in Baltimore. "This gap is a little concerning as AI has the potential to reshape the pharmacy industry."

Pharmacy schools must address AI in their curriculum to equip students with the necessary knowledge and skills; the curriculum should cover topics such as AI fundamentals, data ethics, privacy regulations, and cybersecurity. During his interactions with students at industry conferences, Brackett often encourages them to pursue knowledge in AI and data analysis alongside their pharmacy studies.

"Embracing this dual skill set, they can make more informed decisions and better understand how AI can enhance patient care, safety, and privacy," Brackett said. "Pharmacy students should be preparing themselves for a future where AI is integrated into their practice by developing an understanding of how this technology works and its potential applications in health care. They should also be familiarizing themselves with the ethical considerations that come with using AI and understanding how to use it responsibly."

Bryan Shaw, PharmD, senior director of pharmacy analytics and informatics for health care service company Vizient, noted that AI is not commonly addressed in pharmacy didactic curricula across the country, although many schools are considering how these concepts best fit within their programs. AI's potential role within future accreditation standards also is under discussion. "Research is ongoing across [the health care industry] to establish where AI is most applicable and effective while maintaining safe and ethical patient-centered care, as its emergence is still quite recent in the field," he said.

In preparation for the continued evolution and integration of AI in health care, students should take the time to understand the basic concepts at play and how they interact with the pharmacy profession.

"Pharmacy students should be preparing themselves for a future where AI is integrated into their practice by developing an understanding of how this technology works and its potential applications in health care."

—Sam Brackett, PharmD

"The most pressing concepts are the ethical and legal consequences of leveraging AI in health care and how it could directly and indirectly impact our patients," Shaw said. "As a profession, pharmacists are lifelong learners, and it would be prudent for us to ensure we understand the implications of something that has the potential to greatly influence the care we deliver patients across the world."

But as with any new technology, challenges exist: There often are knowledge gaps around understanding AI concepts, including machine learning, deep learning, and natural language processing. Additionally, pharmacy students may lack training in data science and programming, which are key to leveraging AI.

Open access to AI technology platforms—such as ChatGPT—is still in the early phases, leading to some pharmacy schools discouraging the use of AI capabilities due to potential negative impact on student learning.

In preparation for utilizing AI, pharmacy students should understand basic concepts and AI's applications in pharmacy and health care. This can be achieved through interdisciplinary courses blending technology and health care. They also need hands-on experience with AI tools, possibly through internships, workshops, or projects. Another key area of study involves ethical considerations and regulations surrounding use of AI in health care, including patient privacy and data security.

Pharmacy schools are where training occurs for emerging cohorts of new pharmacists. These pharmacists must be up-to-date on these trends and equipped to perform evolving job functions, and AI is a key part of that. Pharmacy schools can assist students with their learning by incorporating technology solutions in their curricula, as well as educating students on AI. ■

USP <797> Updated Guidelines

The long-awaited revised *USP* <797> guidelines will become official on November 1, 2023.

By Cassi Prosper, CPhT

Millions of sterile compounds are made each year in the United States to meet the unique needs of patients. Understanding the risks inherent in sterile compounding, and incorporating established standards, are essential for patient safety.

The United States Pharmacopeia (USP) develops standards for preparing compounded sterile medications to ensure the patient's benefit and reduce risks such as contamination, infection, or incorrect dosing. Although it is not a governing body, USP standards and guidelines are often adopted and enforced by state boards of pharmacy.

USP Chapter <797>, enacted in 2008, sets forth standards for sterile compounding. *USP* <797> aims to reduce negative outcomes related to compounded medication.

Following a multiyear effort dating to 2019, the long-awaited revision of *USP* <797> was published on November 1, 2022, and will become official on November 1, 2023. This is the date by which compounders are expected to meet the requirements of the new standards. However, ensuring compliance with the requirements of these standards is the responsibility of the applicable regulatory jurisdiction. Regulatory bodies—including state boards of pharmacy—may have different adaptations, so pharmacists should check with their local state board of pharmacy; USP has no role in enforcement.

The updated version of *USP* <797> includes several changes. These revisions pertain to the beyond-use dates (BUDs) and reflect advances in science and clinical practice. Additionally, the revisions aim to clarify topics that were not consistently understood. The updated version of *USP* <797> also incorporates input from stakeholder engagements and over 1400 comments received during the public comment period of September 2021 to March 2022. This official document can be accessed by subscribing to the *USP Compounding Compendium*.

Some of these updates to *USP* <797> are more than 3 years in the making, and many facilities and state boards of pharmacy have preemptively adopted some of the standards. For example, some facilities have already spent millions of dollars on clean rooms to meet the updated standards. The design of the clean room must consider all essential processes, procedures, and personnel. All furniture and materials that enter the area must be nonpermeable, nonshedding, cleanable, and disinfectant resistant. Ceilings, walls, floors, shelving, fixtures, cabinets, pass-throughs, and counters must also support cleaning, be nonshedding, and remain free of cracks and crevices that hinder sanitation. The clean room must have epoxy paint, clean room–grade (smooth and seamless) ceiling tiles, and seamlessly coved vinyl flooring. In addition, the primary engineering control (or hood) must be an International Standards Organization (ISO) class 5 environment or better. The positive pressure buffer area must be an ISO class 7 environment or better, and positive pressure ante rooms must be an ISO class 8 environment or better.

Although many updates have already been adopted, several changes cannot be implemented until the official chapter release date. Let's briefly discuss some of the major changes.

As outlined in the **Table**, the revised chapter changed the categorization of compounded sterile preparations (CSPs) from microbial contamination risk levels (ie, low-, medium-, and high-risk levels) to category 1 and category 2 CSPs. Category 3 CSPs were added to describe the requirements a compounding facility must meet at all times for assigning BUDs up to a maximum of 180 days. *[Editor's note: To view the table, visit https://bit.ly/3Usal8Q.]*

Personnel who are compounding category 1 and 2 CSPs will have to complete a visual observation of hand hygiene and garbing, gloved fingertip sampling, and media fill testing every 6 months; and every 3 months for category 3 CSPs. Supportive roles that oversee compounding staff but do not compound will have to demonstrate competency every 12 months.

Viable air sampling is required every 6 months for categories 1 and 2 and is now required monthly for category 3 compounders. Surface sampling is now required monthly for categories 1 and 2 CSPs and weekly for category 3 CSPs.

The revised chapter clarifies that docking, a proprietary bag and vial system for immediate use, is *not* considered compounding, whereas docking for future use is considered compounding and must comply with all standards. The BUD on immediate-use compounds has now been extended from 1 to 4 hours if fewer than 3 ingredients exist.

These are just a few of the major changes, and there is no doubt that many of the chapter revisions will create many changes in our practices. Still, we will increase patient safety and have the opportunity for extended BUDs—a win-win in my book!

This article originally appeared on pharmacytechnician.org and was republished as part of a partnership between Drug Topics *and the National Pharmacy Technician Association.*

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MONALEESA-2, statistically significant overall survival and preserved quality of life in 1L postmenopausal patients: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. At a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237). PFS was the primary end point.

1L=first line; HR=hazard ratio; NR=not reached; OS=overall survival; PFS=progression-free survival; TTD=time to deterioration.

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MONALEESA-2 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + letrozole (n=334) vs placebo + letrozole (n=334) in postmenopausal patients with HR+/HER2- mBC who received no prior therapy for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. Quality of life was a secondary end point: at a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237).[2-6]

MONALEESA-7 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + ET (NSAI or tamoxifen) + goserelin vs placebo + ET (NSAI or tamoxifen) + goserelin (ITT) in premenopausal patients with HR+/HER2- mBC who received no prior ET for advanced disease. **KISQALI is not indicated for concomitant use with tamoxifen.** Efficacy results are from a prespecified subgroup analysis of 495 patients who received KISQALI (n=248) or placebo (n=247) with an NSAI + goserelin and were not powered to show statistical significance. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 54 months (exploratory analysis), median OS was 58.7 months with KISQALI + NSAI + goserelin (95% CI: 48.5-NR) vs 47.7 months with NSAI + goserelin (95% CI: 41.2-55.4); HR=0.798 (95% CI: 0.615-1.035). At a median follow-up of 35 months, statistical significance was established for overall survival in the ITT population; HR=0.71 (95% CI: 0.54-0.95); *P*=0.00973. Quality of life was a secondary end point: at a median follow-up of 35 months, median TTD ≥10% was 34.2 months vs 23.3 months; HR=0.69 (95% CI: 0.52-0.91).[2,7-10]

MONALEESA-3 was a randomized, double-blind, placebo-controlled phase III study of KISQALI + fulvestrant (n=484) vs placebo + fulvestrant (n=242) for the treatment of postmenopausal patients with HR+/HER2- mBC who have received no or only 1 line of prior ET for advanced disease. OS was a secondary end point; PFS was the primary end point. At a median follow-up of 71 months (exploratory analysis), in a 1L subgroup analysis, median OS was 67.6 months (95% CI: 59.6-NR) with KISQALI + fulvestrant vs 51.8 months with placebo + fulvestrant (95% CI: 40.4-61.2); HR=0.673 (95% CI: 0.504-0.899). At a median follow-up of 39 months, statistical significance was established for overall survival in the ITT population; HR=0.724 (95% CI: 0.568-0.924); *P*=0.00455. Quality of life was a secondary end point: at a median follow-up of 39 months, median TTD ≥10% was 35.9 months vs 33.1 months; HR=0.81 (95% CI: 0.62-1.06).[2,11-14]

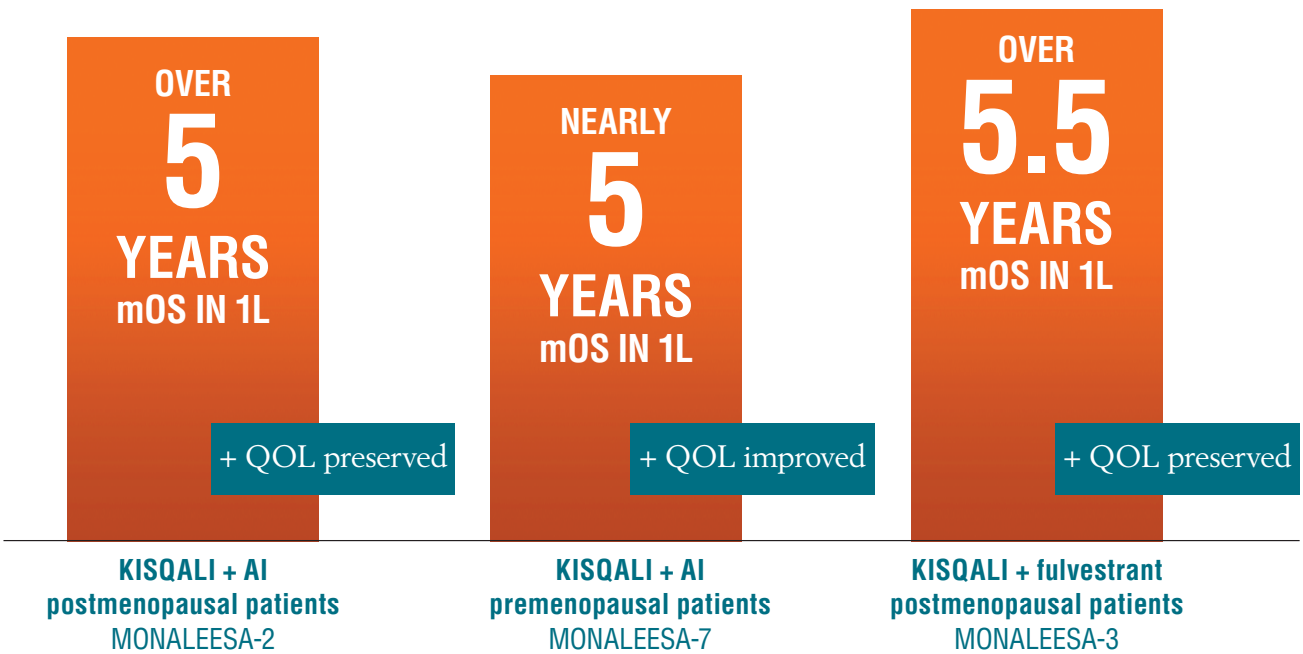
Quality of life was assessed using the EORTC QLQ-C30 questionnaire, a validated tool used worldwide to assess quality of life in patients with cancer. Quality of life was a secondary end point measured by patient-reported outcomes and was assessed at baseline and throughout treatment. Time to deterioration was defined as a decline of at least 10% of the global health status/QOL scale score. There was no prespecified statistical procedure controlling for type 1 error. The EORTC QLQ-C30 incorporates 5 functional scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, pain, and nausea and vomiting), a global health status/QOL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and perceived financial impact of the disease.[10,14-16]

AI=aromatase inhibitor; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; ET=endocrine therapy; ITT=intent to treat; mBC=metastatic breast cancer; mOS=median overall survival; NSAI=nonsteroidal aromatase inhibitor; QOL=quality of life.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

Living longer, living well

Only KISQALI—a proven first-line overall survival benefit, with preserved quality of life, across all 3 phase III trials



1L refers to patients with mBC.

"Overall survival is the hardest end point to achieve in clinical trials. And in many respects, perhaps the most important…we're trying to improve the survival of a patient; not just the progression-free survival or the time where the tumor is controlled, but **how long they live…**"

Dennis Slamon, MD, PhD
University of California, Los Angeles

IMPORTANT SAFETY INFORMATION (continued)

Interstitial lung disease/pneumonitis (continued). Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis, which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt treatment with KISQALI immediately and evaluate the patient. Permanently discontinue treatment with KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis.

KISQALI® ribociclib 200 mg tablets

Isn't it time to start your next first-line patient on KISQALI?

"**[MONALEESA-2] demonstrates that patients with advanced hormone receptor-positive breast cancer can now expect on average to exceed a life expectancy of five years.** And for many of them, much longer than five years. And this is an important development."

Gabriel Hortobagyi, MD

"**Having independence means the world to me—** being able to do things on my own, go places when I feel like going. That's part of quality for life for me, being independent and doing my own thing."

Rose, KISQALI patient

See how KISQALI could help your next first-line patient

MONALEESA-2: At a median follow-up of 80 months, median OS was 63.9 months with KISQALI + letrozole (95% CI: 52.4-71.0) vs 51.4 months with letrozole (95% CI: 47.2-59.7); HR=0.765 (95% CI: 0.628-0.932); *P*=0.004. At a median follow-up of 26 months, median TTD ≥10% was 27.7 months vs 27.6 months; HR=0.944 (95% CI: 0.720-1.237). PFS was the primary end point.[2-6]

IMPORTANT SAFETY INFORMATION (continued)

Severe cutaneous adverse reactions. Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI.

If signs or symptoms of SCARs occur, interrupt KISQALI until the etiology of the reaction has been determined. Consultation with a dermatologist is recommended.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

Important Safety Information (continued)

Severe cutaneous adverse reactions (continued). If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

QT interval prolongation. KISQALI has been shown to prolong the QT interval in a concentration-dependent manner. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction, or discontinuation. Across KISQALI treatment groups, 15 of 1054 patients (1.4%) had >500 ms postbaseline QTcF value, and 61 of 1054 (6%) had a >60 ms increase from baseline in QTcF intervals. These electrocardiogram (ECG) changes were reversible with dose interruption and most occurred within the first 4 weeks of treatment. No cases of torsades de pointes were reported. In MONALEESA-2, on the KISQALI + letrozole treatment arm, there was 1 (0.3%) sudden death in a patient with grade 3 hypokalemia and grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values <450 ms. Repeat ECG at approximately Day 14 of the first cycle, at the beginning of the second cycle, and as clinically indicated. Monitor serum electrolytes (including potassium, calcium, phosphorus, and magnesium) prior to the initiation of treatment, at the beginning of each of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting therapy with KISQALI.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong the QT interval and/or strong CYP3A inhibitors, as this may lead to prolongation of the QTcF interval.

Increased QT prolongation with concomitant use of tamoxifen. KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was ≥10 ms higher in the tamoxifen + placebo subgroup compared with the non-steroidal aromatase inhibitor (NSAI) + placebo subgroup. In the placebo arm, an increase of >60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of >60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI.

Hepatobiliary toxicity. Across KISQALI treatment groups, increases in transaminases were observed. Across all trials, grade 3/4 increases in alanine aminotransferase (ALT) (11% vs 2.1%) and aspartate aminotransferase (AST) (8% vs 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had grade ≥3 ALT/AST elevation, the median time to onset was 92 days and median time to resolution to grade ≤2 was 21 days for the KISQALI treatment groups.

In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than 3 times the upper limit of normal (ULN) and total bilirubin greater than 2 times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation. Recommendations for patients who have elevated AST/ALT grade ≥3 at baseline have not been established.

KISQALI® ribociclib 200 mg tablets

IMPORTANT SAFETY INFORMATION (continued)

Neutropenia. Across KISQALI treatment groups neutropenia was the most frequently reported adverse reaction (AR) (75%), and a grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients in the KISQALI treatment groups. Among the patients who had grade 2, 3, or 4 neutropenia, the median time to grade ≥2 was 17 days. The median time to resolution of grade ≥3 (to normalization or grade <3) was 12 days in the KISQALI treatment groups. Febrile neutropenia was reported in 1.7% of patients in the KISQALI treatment groups. Treatment discontinuation due to neutropenia was 1%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each of the subsequent 4 cycles, and as clinically indicated. Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction, or discontinuation.

Embryo-fetal toxicity. Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of KISQALI to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve. Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose.

Adverse reactions. Most common (incidence ≥20%) adverse reactions include infections, nausea, fatigue, diarrhea, vomiting, headache, constipation, alopecia, cough, rash, and back pain.

Laboratory abnormalities. Across clinical trials of patients with advanced or metastatic breast cancer, the most common laboratory abnormalities reported in the KISQALI arm (all grades, pooled incidence ≥20%) **were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, AST increased, gamma-glutamyl transferase increased, ALT increased, creatinine increased, platelets decreased, and glucose serum decreased**.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.4.2022. © National Comprehensive Cancer Network, Inc. 2022. All rights reserved. Published June 21, 2022. Accessed October 13, 2022. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way. **2.** Kisqali [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp. **3.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Overall survival with ribociclib plus letrozole in advanced breast cancer. *N Engl J Med.* 2022;386(10):942-950. doi:10.1056/NEJMoa2114663 **4.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748. doi:10.1056/NEJMoa1609709 **5.** Data on file. Novartis Pharmaceuticals Corp; 2021. **6.** Data on file. Novartis Pharmaceuticals Corp; 2017. **7.** Tripathy D, Im S-A, Colleoni M, et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. *Lancet Oncol.* 2018;19(7):904-915. doi:10.1016/S1470-2045(18)30292-4 **8.** Data on file. Novartis Pharmaceuticals Corp; 2020. **9.** Im S-A, Lu Y-S, Bardia A, et al. Overall survival with ribociclib plus endocrine therapy in breast cancer. *N Engl J Med.* 2019;381(4):307-316. doi:10.1056/NEJMoa1903765 **10.** Harbeck N, Franke F, Villanueva-Vazquez R, et al. Health-related quality of life in premenopausal women with hormone-receptor-positive, HER2-negative advanced breast cancer treated with ribociclib plus endocrine therapy: results from a phase III randomized clinical trial (MONALEESA-7). *Ther Adv Med Oncol.* 2020;12:1758835920943065. doi:10.1177/1758835920943065 **11.** Slamon DJ, Neven P, Chia S, et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor–positive, human epidermal growth factor receptor 2–negative advanced breast cancer: MONALEESA-3. *J Clin Oncol.* 2018;36(24):2465-2472. doi:10.1200/JCO.2018.78.9909 **12.** Data on file. Novartis Pharmaceuticals Corp; 2022. **13.** Slamon DJ, Neven P, Chia S, et al. Overall survival with ribociclib plus fulvestrant in advanced breast cancer. *N Engl J Med.* 2020;382(6):514-524. doi:10.1056/NEJMoa1911149 **14.** Fasching PA, Beck JT, Chan A, et al. Ribociclib plus fulvestrant for advanced breast cancer: health-related quality-of-life analyses from the MONALEESA-3 study. *Breast.* 2020;54:148-154. doi:10.1016/j.breast.2020.09.008 **15.** Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med.* 2016;375(18):1738-1748;(protocol). doi:10.1056/NEJMoa1609709 **16.** Fayers PM, Aaronson NK, Bjordal K, et al. EORTC QLQ-C30 Scoring Manual (3rd edition). 2001.

Please see additional Important Safety Information throughout and accompanying Brief Summary of Prescribing Information on the following pages.

NOVARTIS

KISQALI® ribociclib 200 mg tablets

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

KISQALI® (ribociclib) tablets, for oral use
Initial U.S. Approval: 2017

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

KISQALI is indicated for the treatment of adult patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer in combination with:

- an aromatase inhibitor as initial endocrine-based therapy; or
- fulvestrant as initial endocrine-based therapy or following disease progression on endocrine therapy in postmenopausal women or in men.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease/Pneumonitis

Severe, life-threatening, or fatal interstitial lung disease (ILD) and/or pneumonitis can occur in patients treated with KISQALI and other CDK4/6 inhibitors.

Across clinical trials (MONALEESA-2, MONALEESA-3, MONALEESA-7), 1.6% of KISQALI-treated patients had ILD/pneumonitis of any grade, 0.4% had Grade 3 or 4, and 0.1% had a fatal outcome. Additional cases of ILD/pneumonitis have been observed in the postmarketing setting, with fatalities reported *[see Adverse Reactions (6.2)]*.

Monitor patients for pulmonary symptoms indicative of ILD/pneumonitis which may include hypoxia, cough, and dyspnea. In patients who have new or worsening respiratory symptoms suspected to be due to ILD or pneumonitis, interrupt KISQALI immediately and evaluate the patient. Permanently discontinue KISQALI in patients with recurrent symptomatic or severe ILD/pneumonitis *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.2 Severe Cutaneous Adverse Reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-induced hypersensitivity syndrome (DiHS)/drug reaction with eosinophilia and systemic symptoms (DRESS) can occur in patients treated with KISQALI *[see Adverse Reactions (6.2)]*.

If signs or symptoms of severe cutaneous reactions occur, interrupt KISQALI until the etiology of the reaction has been determined *[see Dosage and Administration (2.2) in the full prescribing information]*. Early consultation with a dermatologist is recommended to ensure greater diagnostic accuracy and appropriate management.

If SJS, TEN, or DiHS/DRESS is confirmed, permanently discontinue KISQALI. Do not reintroduce KISQALI in patients who have experienced SCARs or other life-threatening cutaneous reactions during KISQALI treatment.

5.3 QT Interval Prolongation

KISQALI has been shown to prolong the QT interval in a concentration-dependent manner *[see Clinical Pharmacology (12.2) in the full prescribing information]*. Based on the observed QT prolongation during treatment, KISQALI may require dose interruption, reduction or discontinuation as described in Table 4 *[see Dosage and Administration (2.2) in the full prescribing information, Drug Interactions (7.4)]*.

Across MONALEESA-2, MONALEESA-7, and MONALEESA-3 in patients with advanced or metastatic breast cancer who received the combination of KISQALI plus an aromatase inhibitor or fulvestrant, 15 out of 1054 patients (1.4%) had a > 500 ms post-baseline QTcF value, and 61 out of 1054 patients (6%) had a > 60 ms increase from baseline in QTcF intervals.

These ECG changes were reversible with dose interruption and the majority occurred within the first four weeks of treatment. There were no reported cases of Torsades de Pointes.

In MONALEESA-2, on the KISQALI plus letrozole treatment arm, there was one (0.3%) sudden death in a patient with Grade 3 hypokalemia and Grade 2 QT prolongation. No cases of sudden death were reported in MONALEESA-7 or MONALEESA-3 *[see Adverse Reactions (6)]*.

Assess ECG prior to initiation of treatment. Initiate treatment with KISQALI only in patients with QTcF values less than 450 ms. Repeat ECG at approximately Day 14 of the first cycle and the beginning of the second cycle, and as clinically indicated.

Monitor serum electrolytes (including potassium, calcium, phosphorous and magnesium) prior to the initiation of treatment, at the beginning of the first 6 cycles, and as clinically indicated. Correct any abnormality before starting KISQALI therapy *[see Dosage and Administration (2.2) in the full prescribing information]*.

Avoid the use of KISQALI in patients who already have or who are at significant risk of developing QT prolongation, including patients with:

- long QT syndrome
- uncontrolled or significant cardiac disease, including recent myocardial infarction, congestive heart failure, unstable angina, and bradyarrhythmias
- electrolyte abnormalities

Avoid using KISQALI with drugs known to prolong QT interval and/or strong CYP3A inhibitors as this may lead to prolongation of the QTcF interval.

5.4 Increased QT Prolongation With Concomitant Use of Tamoxifen

KISQALI is not indicated for concomitant use with tamoxifen. In MONALEESA-7, the observed mean QTcF increase from baseline was > 10 ms higher in the tamoxifen plus placebo subgroup compared with the non-steroidal aromatase inhibitors (NSAIs) plus placebo subgroup. In the placebo arm, an increase of > 60 ms from baseline occurred in 6/90 (7%) of patients receiving tamoxifen, and in no patients receiving an NSAI. An increase of > 60 ms from baseline in the QTcF interval was observed in 14/87 (16%) of patients in the KISQALI and tamoxifen combination and in 18/245 (7%) of patients receiving KISQALI plus an NSAI *[see Clinical Pharmacology (12.2) in the full prescribing information]*.

5.5 Hepatobiliary Toxicity

In MONALEESA-2, MONALEESA-7 and MONALEESA-3, increases in transaminases were observed. Across all studies, Grade 3 or 4 increases in alanine aminotransferase (ALT) (11% vs. 2.1%) and aspartate aminotransferase (AST) (8% vs. 2%) were reported in the KISQALI and placebo arms, respectively.

Among the patients who had Grade ≥ 3 ALT/AST elevation, the median time-to-onset was 92 days for the KISQALI plus aromatase inhibitor or fulvestrant treatment group. The median time to resolution to Grade ≤ 2 was 21 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. In MONALEESA-2 and MONALEESA-3, concurrent elevations in ALT or AST greater than three times the ULN and total bilirubin greater than two times the ULN, with normal alkaline phosphatase, in the absence of cholestasis occurred in 6 (1%) patients and all patients recovered after discontinuation of KISQALI. No cases occurred in MONALEESA-7.

Perform liver function tests (LFTs) before initiating therapy with KISQALI. Monitor LFTs every 2 weeks for first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated *[see Dosage and Administration (2.2) in the full prescribing information]*.

Based on the severity of the transaminase elevations, KISQALI may require dose interruption, reduction, or discontinuation as described in Table 5 (Dose Modification and Management for Hepatobiliary Toxicity) *[see Dosage and Administration (2.2) in the full prescribing information]*. Recommendations for patients who have elevated AST/ALT Grade ≥ 3 at baseline have not been established.

5.6 Neutropenia

In MONALEESA-2, MONALEESA-7, and MONALEESA-3, neutropenia was the most frequently reported adverse reaction (75%), and a Grade 3/4 decrease in neutrophil count (based on laboratory findings) was reported in 62% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Among the patients who had Grade 2, 3, or 4 neutropenia, the median time to Grade ≥ 2 neutropenia was 17 days. The median time to resolution of Grade ≥ 3 (to normalization or Grade < 3) was 12 days in the KISQALI plus aromatase inhibitor or fulvestrant treatment group. Febrile neutropenia was reported in 1.7% of patients receiving KISQALI plus an aromatase inhibitor or fulvestrant. Treatment discontinuation due to neutropenia was 1%.

Perform complete blood count (CBC) before initiating therapy with KISQALI. Monitor CBC every 2 weeks for the first 2 cycles, at the beginning of each subsequent 4 cycles, and as clinically indicated.

Based on the severity of the neutropenia, KISQALI may require dose interruption, reduction or discontinuation as described in Table 6 *[see Dosage and Administration (2.2) in the full prescribing information]*.

5.7 Embryo-Fetal Toxicity

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of ribociclib to pregnant rats and rabbits during organogenesis caused embryo-fetal toxicities at maternal exposures that were 0.6 and 1.5 times the human clinical exposure, respectively, based on area under the curve (AUC). Advise pregnant women of the potential risk to a fetus. Advise women of reproductive potential to use effective contraception during therapy with KISQALI and for at least 3 weeks after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the labeling:

- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.1)]*
- Severe Cutaneous Adverse Reactions *[see Warnings and Precautions (5.2)]*
- QT Interval Prolongation *[see Warnings and Precautions (5.3, 5.4)]*
- Hepatobiliary Toxicity *[see Warnings and Precautions (5.5)]*
- Neutropenia *[see Warnings and Precautions (5.6)]*

6.1 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.

The pooled safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to KISQALI in 1065 patients in MONALEESA-2, MONALEESA-7, and MONALEESA-3. Among these patients who received KISQALI, 76% were exposed for 6 months or longer and 62% were exposed for greater than one year. In this pooled safety population, the most common (≥ 20%) adverse reactions, including laboratory abnormalities, were leukocytes decreased (95%), neutrophils decreased (93%), hemoglobin decreased (68%), lymphocytes decreased (66%), aspartate aminotransferase increased (55%), gamma glutamyl transferase increased (53%), alanine aminotransferase increased (52%), infections (47%), nausea (47%), creatinine increased (42%), fatigue (35%), platelets decreased (34%), diarrhea (33%), vomiting (29%), headache (27%), constipation (25%), alopecia (25%), cough (24%), rash (24%), back pain (24%), and glucose serum decreased (20%).

MONALEESA-2: KISQALI in Combination with Letrozole

Postmenopausal Women with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

The safety of KISQALI was evaluated in MONALEESA-2, a clinical study of 668 postmenopausal women receiving KISQALI plus letrozole or placebo plus letrozole *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure to KISQALI plus letrozole was 13 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 21% of patients who received KISQALI plus letrozole. Serious adverse reactions in ≥1 % of patients receiving KISQALI plus letrozole included abdominal pain (1.5%), vomiting (1.5%), constipation (1.2%), nausea (1.2%), anemia (1.2%), febrile neutropenia (1.2%), dyspnea (1.2%), and alanine aminotransferase increased (1.2%).

Permanent discontinuation of both KISQALI and letrozole due to an adverse reaction occurred in 7% of patients. Permanent discontinuation of KISQALI alone occurred in of 7% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and letrozole in ≥ 2% of patients were alanine aminotransferase increased (5%), aspartate aminotransferase increased (3%), and vomiting (2%).

Dosage interruptions of both KISQALI and letrozole due to an adverse reaction occurred in 71% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (39%), neutrophils decreased (12%), vomiting (6%), nausea (5%), alanine aminotransferase increased (5%), and leukocytes decreased (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 45% of patients receiving KISQALI plus letrozole. Adverse reactions which required dose reductions in ≥ 2% of patients included neutropenia (24%), neutrophils decreased (8%), and alanine aminotransferase increased (3%).

Antiemetics and antidiarrheal medications were used to manage symptoms as clinically indicated.

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were neutrophils decreased, leukocytes decreased, hemoglobin decreased, nausea, lymphocytes decreased, alanine aminotransferase increased, aspartate aminotransferase increased, fatigue, diarrhea, alopecia, vomiting, platelets decreased, constipation, headache, and back pain.

Table 8 summarizes the adverse reactions in MONALEESA-2.

Table 8: Adverse Reactions (≥ 10% and ≥ 2% Higher Than Placebo Arm) in MONALEESA-2

Adverse reaction	KISQALI + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea[1]	52	2.4	29	0.6
Diarrhea[1]	35	1.2	22	0.9
Vomiting[1]	29	3.6	16	0.9
Constipation[1]	25	1.2	19	0
Stomatitis[1]	12	0.3	7	0
Abdominal pain[1]	11	1.2	8	0
General Disorders and administration-site conditions				
Fatigue	37	2.4	30	0.9
Pyrexia[1]	13	0.3	6	0
Edema peripheral[1]	12	0	10	0
Skin and subcutaneous tissue disorders				
Alopecia[1]	33	0	16	0
Rash[1]	17	0.6	8	0
Pruritus[1]	14	0.6	6	0
Nervous system disorders				
Headache[1]	22	0.3	19	0.3
Insomnia[1]	12	0.3	9	0
Musculoskeletal and connective tissue disorders				
Back pain[1]	20	2.1	18	0.3
Metabolism and nutrition disorders				
Decreased appetite[1]	19	1.5	15	0.3
Respiratory, thoracic and mediastinal disorders				
Dyspnea[1]	12	1.2	9	0.6
Infections and infestations				
Urinary tract infections[1]	11	0.6	8	0

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Only includes a Grade 3 adverse reaction.

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-2 receiving KISQALI plus letrozole included interstitial lung disease (0.3%), lung infiltration (0.3%), pneumonitis (0.3%), and pulmonary fibrosis (0.6%). Table 9 summarizes the laboratory abnormalities in MONALEESA-2.

Table 9: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-2 Who Received KISQALI Plus Letrozole

Laboratory abnormality	KISQALI + Letrozole (n = 334)		Placebo + Letrozole (n = 330)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	93	34	29	1.5
Neutrophils decreased	93	60	24	1.2
Hemoglobin decreased	57	1.8	26	1.2
Lymphocytes decreased	51	14	22	3.9
Platelets decreased	29	0.9	6	0.3
Chemistry				
Alanine aminotransferase increased	46	10	36	1.2
Aspartate aminotransferase increased	44	7	32	1.5
Creatinine increased	20	0.6	6	0
Phosphorous decreased	13	5	4	0.6
Potassium decreased	11	1.2	7	1.2

MONALEESA-7: KISQALI in Combination with an Aromatase Inhibitor

Pre/perimenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy

The safety of KISQALI was evaluated in MONALEESA-7, a clinical study of 672 pre/perimenopausal patients with HR-positive, HER2-negative advanced or metastatic breast cancer receiving either KISQALI plus a NSAI or tamoxifen plus goserelin or placebo plus NSAI or tamoxifen plus

goserelin *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure on the KISQALI plus a NSAI arm was 15.2 months with 66% of patients exposed for ≥ 12 months. The safety data reported below are based on 495 pre/perimenopausal patients receiving KISQALI plus NSAI plus goserelin or placebo plus NSAI plus goserelin.

Serious adverse reactions occurred in 17% of patients who received KISQALI plus NSAI plus goserelin. Serious adverse reactions in ≥ 1% of patients receiving KISQALI plus NSAI plus goserelin included drug-induced liver injury (1.6%), abdominal pain (1.2%), dyspnea (1.2%), febrile neutropenia (1.2%), and back pain (1.2%).

Permanent discontinuation of both KISQALI and NSAI due to an adverse reaction occurred in 3% of patients. Permanent discontinuation of KISQALI alone occurred in of 3% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and NSAI in ≥ 2% of patients were alanine aminotransferase increased (2%), and aspartate aminotransferase increased (2%).

Dosage interruptions of KISQALI plus NSAI plus goserelin due to an adverse reaction occurred in 73% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (41%), neutrophils decreased (26%), and leukocytes decreased (6%).

Dose reductions of KISQALI due to an adverse reaction occurred in 33% of patients receiving KISQALI plus NSAI plus goserelin. Adverse reactions which required dose reductions in ≥ 2 % of patients included neutropenia (17%), neutrophils decreased (5%), and alanine aminotransferase increased (2%).

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, hemoglobin decreased, lymphocytes decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, infections, arthralgia, alanine aminotransferase increased, nausea, platelets decreased, and alopecia.

Table 10 summarizes the adverse reactions in MONALEESA-7.

Table 10: Adverse Reactions Occurring in ≥ 10% and ≥ 2% Higher Than Placebo Arm in MONALEESA-7 (NSAI) (All Grades)

Adverse reaction	KISQALI + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Infections and infestations				
Infections[1;2]	36	1.6	24	0.4
Musculoskeletal and connective tissue disorders				
Arthralgia[2]	34	0.8	29	1.2
Gastrointestinal disorders				
Nausea[2]	32	0	20	0
Constipation[2]	16	0	12	0
Stomatitis[2]	10	0	8	0.4
Skin and subcutaneous tissue disorders				
Alopecia[2]	21	0	13	0
Rash[2]	17	0.4	9	0
Pruritus[2]	11	0	4	0
General disorders and administration-Site Conditions				
Pyrexia[2]	17	0.8	7	0
Pain in extremity[2]	10	0	8	1.2
Respiratory, thoracic and mediastinal disorders				
Cough[2]	15	0	10	0

Abbreviation: NSAI, non-steroidal aromatase inhibitor.
Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Infections: urinary tract infections; respiratory tract infections, gastroenteritis, sepsis (< 1%).
[2]Only includes a Grade 3 adverse reactions.

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-7 receiving KISQALI plus NSAI included thrombocytopenia (9%), dry skin (9%), oropharyngeal pain (7%), dyspepsia (5%), lacrimation increased (4%), dry eye (4%), vitiligo (3%), hypocalcemia, (2%), blood bilirubin increased (1%), syncope (0.4%), and pneumonitis (0.4%).

Table 11: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-7 Who Received KISQALI Plus NSAI Plus Goserelin

Laboratory abnormality	KISQALI + NSAI + Goserelin (n = 248)		Placebo + NSAI + Goserelin (n = 247)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	93	36	30	0.8
Neutrophils decreased	92	63	27	2.4
Hemoglobin decreased	84	2.4	51	0.4
Lymphocytes decreased	55	14	18	2.8
Platelets decreased	26	0.4	9	0.4
Chemistry				
Gamma-glutamyl transferase increased	42	7	42	9
Aspartate aminotransferase increased	37	4.8	35	1.6
Alanine aminotransferase increased	33	6	31	1.6
Phosphorous decreased	14	1.6	11	0.8
Potassium decreased	11	1.2	14	1.2
Glucose serum decreased	10	0.4	10	0.4
Creatinine increased	8	0	2	0

MONALEESA-3: KISQALI in Combination with Fulvestrant

Postmenopausal Patients with HR-positive, HER2-negative Advanced or Metastatic Breast Cancer for Initial Endocrine-Based Therapy or After Disease Progression on Endocrine Therapy

The safety of KISQALI was evaluated in MONALEESA-3, a clinical study of 724 postmenopausal women receiving KISQALI plus fulvestrant or placebo plus fulvestrant *[see Clinical Studies (14) in the full prescribing information]*. The median duration of exposure to KISQALI plus fulvestrant was 15.8 months with 58% of patients exposed for ≥ 12 months.

Serious adverse reactions occurred in 29% of patients who received KISQALI plus fulvestrant. Serious adverse reactions in ≥ 1% of patients receiving KISQALI plus fulvestrant included pneumonia (1.9%), nausea (1.4%), vomiting (1.4%), anemia (1.2%), dyspnea (1.2%), neutropenia (1.2%). One case (0.2%) of fatal adverse reaction (pneumonia) occurred in patients who received KISQALI plus fulvestrant.

Permanent discontinuation of both KISQALI and fulvestrant due to an adverse reaction occurred in 8% of patients. Permanent discontinuation of KISQALI alone occurred in of 9% of patients. Adverse reactions which resulted in permanent discontinuation of both KISQALI and fulvestrant in ≥ 2% of patients were alanine aminotransferase increased (5%), and aspartate aminotransferase increased (3%).

Dosage interruptions of KISQALI plus fulvestrant due to an adverse reaction occurred in 72% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients included neutropenia (40%), neutrophils decreased (13%), alanine aminotransferase increased (8%), aspartate aminotransferase increased (8%), and leukocytes decreased (5%).

Dose reductions of KISQALI due to an adverse reaction occurred in 32% of patients receiving KISQALI plus fulvestrant. Adverse reactions which required dose reductions in ≥ 2% of patients included neutropenia (15%), and neutrophils decreased (3%).

The most common (≥ 20% on the KISQALI arm and ≥ 2% higher than placebo) adverse reactions, including laboratory abnormalities, were leukocytes decreased, neutrophils decreased, lymphocytes decreased, creatinine increased, hemoglobin decreased, gamma-glutamyl transferase increased, aspartate aminotransferase increased, nausea, alanine aminotransferase increased, infections, platelets decreased, diarrhea, vomiting, constipation, glucose serum decreased, cough, rash, and pruritus.

Table 12 summarizes the adverse reactions in MONALEESA-3.

Table 12: Adverse Reactions (≥ 10% and ≥ 2% Higher Than Placebo Arm) in MONALEESA-3

Adverse reaction	KISQALI + Fulvestrant (n = 483)		Placebo + Fulvestrant (n = 241)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Gastrointestinal disorders				
Nausea[2]	45	1.4	28	0.8
Diarrhea[2]	29	0.6	20	0.8
Vomiting[2]	27	1.4	13	0
Constipation[2]	25	0.8	12	0
Abdominal pain[2]	17	1.4	13	0.8
Infections and infestations				
Infections[1;2;3]	42	4.6	30	1.7
Skin and subcutaneous tissue disorders				
Rash[2]	23	0.8	8	0
Pruritus[2]	20	0.2	7	0
Alopecia[2]	19	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough[2]	22	0	15	0
Dyspnea	15	1.4	12	1.7
Metabolism and nutrition disorders				
Decreased appetite[2]	16	0.2	13	0
General disorders and administration-site Conditions				
Edema peripheral[2]	15	0	7	0
Pyrexia[2]	11	0.2	7	0
Nervous system disorders				
Dizziness[2]	13	0.2	8	0

Grading according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.
[1]Infections: urinary tract infections; respiratory tract infections; gastroenteritis; sepsis (1%).
[2]Only include a Grade 3 adverse reactions.
[3]Includes the following fatal adverse reactions: pneumonia (n = 1).

Clinically relevant adverse reactions in < 10% of patients in MONALEESA-3 receiving KISQALI plus fulvestrant included thrombocytopenia (9%) dry skin (8%), dysgeusia (7%), dry mouth (5%), vertigo (5%), dry eye (5%), lacrimation increased (4%), erythema (4%), hypocalcemia (4%), blood bilirubin increased (1%), syncope (1%), interstitial lung disease (0.4%), pneumonitis (0.4%), hypersensitivity pneumonitis (0.2%), and acute respiratory distress syndrome (0.2%).

Table 13: Select Laboratory Abnormalities (≥ 10%) in Patients in MONALEESA-3 Who Received KISQALI Plus Fulvestrant

Laboratory abnormality	KISQALI + Fulvestrant (n = 483)		Placebo + Fulvestrant (n = 241)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Hematology				
Leukocytes decreased	95	26	26	0.4
Neutrophils decreased	92	53	21	0.8
Lymphocytes decreased	69	16	35	4.1
Hemoglobin decreased	60	4.3	35	2.9
Platelets decreased	33	1.9	11	0
Chemistry				
Creatinine increased	65	1	33	0.4
Gamma-glutamyl transferase increased	52	8	49	10
Aspartate aminotransferase increased	50	7	43	2.9
Alanine aminotransferase increased	44	11	37	1.7
Glucose serum decreased	23	0	18	0
Phosphorous decreased	18	4.6	8	0.8
Albumin decreased	12	0	8	0

COMPLEEMENT-1: KISQALI in Combination with Letrozole and Goserelin or Leuprolide

Men with HR-positive, HER2-negative Advanced Breast Cancer for Initial Endocrine-Based Therapy

The safety of KISQALI in combination with letrozole was evaluated in men (n = 39) in an open-label, multicenter clinical study for the treatment of adult patients with HR-positive, HER2-negative, advanced breast cancer who received no prior hormonal therapy for advanced disease (COMPLEEMENT-1) *[see Clinical Studies (14) in the full prescribing information]*.

The median duration of exposure to KISQALI was 20.8 months (range, 0.5 to 30.6 months).

Other adverse reactions occurring in men treated with KISQALI plus letrozole and goserelin or leuprolide were similar to those occurring in women treated with KISQALI plus endocrine therapy.

6.2 Postmarketing Experience

The following adverse events have been reported during post-approval use of KISQALI. Because these events 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 drug exposure.

Respiratory disorders: Interstitial lung disease/pneumonitis

Skin and Subcutaneous Tissue Disorders: Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN), Drug-induced hypersensitivity syndrome (DiHS)/Drug reaction with eosinophilia, and systemic symptoms (DRESS)

7 DRUG INTERACTIONS

7.1 Drugs That May Increase Ribociclib Plasma Concentrations

CYP3A4 Inhibitors

Coadministration of a strong CYP3A4 inhibitor (ritonavir) increased ribociclib exposure in healthy subjects by 3.2-fold *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, and voriconazole) and consider alternative concomitant medications with less potential for CYP3A inhibition.

If coadministration of KISQALI with a strong CYP3A inhibitor cannot be avoided, reduce the dose of KISQALI to 400 mg once daily *[see Dosage and Administration (2.2) in the full prescribing information]*.

Instruct patients to avoid grapefruit or grapefruit juice, which are known to inhibit cytochrome CYP3A enzymes and may increase the exposure to ribociclib *[see Patient Counseling Information (17) in the full prescribing information]*.

7.2 Drugs That May Decrease Ribociclib Plasma Concentrations

CYP3A4 Inducers

Coadministration of a strong CYP3A4 inducer (rifampin) decreased the plasma exposure of ribociclib in healthy subjects by 89% *[see Clinical Pharmacology (12.3) in the full prescribing information]*. Avoid concomitant use of strong CYP3A inducers and consider an alternate concomitant medication with no or minimal potential to induce CYP3A (e.g., phenytoin, rifampin, carbamazepine, and St. John's wort (Hypericum perforatum).

7.3 Effect of KISQALI on Other Drugs

CYP3A Substrates with Narrow Therapeutic Index

Coadministration of midazolam (a sensitive CYP3A4 substrate) with multiple doses of KISQALI (400 mg) increased the midazolam exposure by 3.8-fold in healthy subjects, compared with administration of midazolam alone *[see Clinical Pharmacology (12.3) in the full prescribing information]*. KISQALI given at the clinically relevant dose of 600 mg is predicted to increase the midazolam AUC by 5.2-fold. Therefore, caution is recommended when KISQALI is administered with CYP3A substrates with a narrow therapeutic index. The dose of a sensitive CYP3A substrate with a narrow therapeutic index, including but not limited to alfentanil, cyclosporine, dihydroergotamine, ergotamine, everolimus, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus, may need to be reduced as ribociclib can increase their exposure.

7.4 Drugs That Prolong the QT Interval

Avoid coadministration of KISQALI with medicinal products with a known potential to prolong QT, such as antiarrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine, and sotalol), and other drugs that are known to prolong the QT interval (including, but not limited to, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide, and ondansetron) *[see Warnings and Precautions (5.3), Clinical Pharmacology (12.2) in the full prescribing information]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from animal studies and the mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) in the full prescribing information]*.

There are no available human data informing the drug-associated risk. In animal reproduction studies, administration of ribociclib to pregnant animals during organogenesis resulted in increased incidences of post implantation loss and reduced fetal weights in rats and increased incidences of fetal abnormalities in rabbits at exposures 0.6 or 1.5 times the exposure in humans, respectively, at the highest recommended dose of 600 mg/day based on AUC *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk of major birth defects is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies in the U.S. general population.

Data

Animal Data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of ribociclib up to 1000 mg/kg/day and 60 mg/kg/day, respectively, during the period of organogenesis.

In rats, 300 mg/kg/day resulted in reduced maternal body weight gain and reduced fetal weights accompanied by skeletal changes related to the lower fetal weights. There were no significant effects on embryo-fetal viability or fetal morphology at 50 or 300 mg/kg/day.

In rabbits at doses ≥ 30 mg/kg/day, there were adverse effects on embryo-fetal development, including increased incidences of fetal abnormalities (malformations and external, visceral, and skeletal variants) and fetal growth (lower fetal weights). These findings included reduced/small lung lobes, additional vessel on the descending aorta, additional vessel on the aortic arch, small eyes, diaphragmatic hernia, absent accessory lobe or (partly) fused lung lobes, reduced/small accessory lung lobe, extra/rudimentary 13th ribs, misshapen hyoid bone, bent hyoid bone alae, and reduced number of phalanges in the pollex. There was no evidence of increased incidence of embryo-fetal mortality. There was no maternal toxicity observed at 30 mg/kg/day.

At 300 mg/kg/day in rats and 30 mg/kg/day in rabbits, the maternal systemic exposures (AUC) were approximately 0.6 and 1.5 times, respectively, the exposure in patients at the highest recommended dose of 600 mg/day.

8.2 Lactation

Risk Summary

It is not known if ribociclib is present in human milk. There are no data on the effects of ribociclib on the breastfed infant or on milk production. Ribociclib and its metabolites readily passed into the milk of lactating rats. Because of the potential for serious adverse reactions in breastfed infants from KISQALI, advise lactating women not to breastfeed while taking KISQALI and for at least 3 weeks after the last dose.

Data

In lactating rats administered a single dose of 50 mg/kg, exposure to ribociclib was 3.56-fold higher in milk compared to maternal plasma.

8.3 Females and Males of Reproductive Potential

Based on animal studies and mechanism of action, KISQALI can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to starting treatment with KISQALI.

Contraception

Females

Advise females of reproductive potential to use effective contraception (methods that result in less than 1% pregnancy rates) during treatment with KISQALI and for at least 3 weeks after the last dose.

Infertility

Males

Based on animal studies, KISQALI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1) in the full prescribing information]*.

8.4 Pediatric Use

The safety and efficacy of KISQALI in pediatric patients has not been established.

8.5 Geriatric Use

Of 334 patients who received KISQALI in MONALEESA-2, 150 patients (45%) were ≥ 65 years of age and 35 patients (11%) were ≥ 75 years of age. Of 484 patients who received KISQALI in MONALEESA-3, 226 patients (47%) were ≥ 65 years of age and 65 patients (14%) were ≥ 75 years of age. Of 248 patients who received KISQALI in MONALEESA-7, no patients were ≥ 65 years of age. No overall differences in safety or effectiveness of KISQALI were observed between these patients and younger patients.

8.6 Hepatic Impairment

No dose adjustment is necessary in patients with mild hepatic impairment (Child-Pugh class A). A reduced starting dose of 400 mg is recommended in patients with moderate (Child-Pugh class B) and severe hepatic impairment (Child-Pugh class C) *[see Dosage and Administration (2.2) in the full prescribing information]*. Based on a pharmacokinetic trial in patients with hepatic impairment, mild hepatic impairment had no effect on the exposure of ribociclib. The mean exposure for ribociclib was increased less than 2-fold in patients with moderate (geometric mean ratio [GMR]: 1.44 for C_{max}; 1.28 for AUC_{inf}) and severe (GMR: 1.32 for C_{max}; 1.29 for AUC_{inf}) hepatic impairment *[see Clinical Pharmacology (12.3) in the full prescribing information]*.

8.7 Renal Impairment

Based on a population pharmacokinetic analysis, no dose adjustment is necessary in patients with mild (60 mL/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) < 90 mL/min/1.73 m^2) or moderate (30 mL/min/1.73 m^2 ≤ eGFR < 60 mL/min/1.73 m^2) renal impairment. Based on a renal impairment study in healthy subjects and non-cancer subjects with severe renal impairment (eGFR 15 to < 30 mL/min/1.73 m^2), a starting dose of 200 mg is recommended. KISQALI has not been studied in breast cancer patients with severe renal impairment *[see Dosage and Administration (2.2), Clinical Pharmacology (12.3) in the full prescribing information]*.

10 OVERDOSAGE

There is limited experience with reported cases of overdose with KISQALI in humans. General symptomatic and supportive measures should be initiated in all cases of overdose where necessary.

Distributed by:
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936

T2022-58

Special Report

Gut Health Has Impact on the Skin

The gut-brain-skin axis is more important to overall health than previously understood, and prebiotics and probiotics play a large role in the benefits. By Renata Block, MMS, PA-C

This article originally appeared on dermatologytimes.com

Literature and marketing about the body's microbiome and gut health have become popular topics among our health-conscious patients. As a result, the discussion of prebiotics and probiotics and their significant role in maintaining gut health has gained popularity in recent years. Although the research is in its infancy, it continues to point toward the gut-brain-skin connection. Additional data suggest that how much of what we eat or the supplements we take can affect our skin health—which leads us to explore the world of prebiotics and probiotics, and how they affect gut health to help us absorb these nutrients. This opens the door to the gut-skin axis and how it can affect our skin regarding inflammatory response diseases such as eczema, psoriasis, vitiligo, and acne.

Why Is the Microbiome Important?

The gastrointestinal tract contains microorganisms such as bacteria, viruses, and protozoa. Collectively, such microorganisms make up what is termed the gut microbiota, microbiome, or intestinal microflora. Their makeup and activity can play a significant role in health and disease.[1]

The balance of the microbiome on the skin and in our gut is an essential front line of defense, protecting us from germs. A good equilibrium helps break down food, releasing energy and vitamins to keep the body healthy. Since the body must coexist with the microbiome, it plays a crucial role in keeping our skin healthy. However, the body is exposed to daily external factors that can disrupt the homogeneous environment for optimal health. For example, disruptions from such causes as processed foods, antibiotics, stress, infection, disease, and exogenous organisms can drastically change the composition and activity of the gut microbiota.[2]

The microbiome's balance and effect on the skin were initially introduced in 2016. Recent research and literature reviews point to a solid relationship between the gut-brain-skin axis and the gut microbiome balance vital to maintaining health and optimal immunity.[3] We are discovering the importance of having a balanced gut microbiome and how any imbalance can lead to increased risk of inflammatory responses that can exacerbate acne, psoriasis, atopic dermatitis, urticaria, and vitiligo. In addition, a chronic unhealthy mix of microorganisms can lead to leaky gut syndrome, weakening the intestinal wall—an issue already linked to asthma and eczema.[4]

How Can We Feed Our Gut Microbiome?

The American diet has changed drastically since the introduction of processed foods. Adding a prebiotic and a probiotic can assist in creating a homogeneous environment of microorganisms in the gut. Breaking down the benefits of each aids understanding of why taking both is much more beneficial than taking either by itself.

Prebiotics

The fermentation process in the gut is important; prebiotics act as a primary carbon source in this metabolic process and the growth of beneficial bacteria such as *bifidobacteria* and *lactobacilli*. Overall, the health benefits of prebiotic dietary fibers can affect gut barrier permeability, decrease pathogenic bacteria populations and allergy risks, increase calcium absorption, and improve immune system defense.[2]

Examples include nondigestible specialized plant fibers such as spirulina, fructans, galacto-oligosaccharides, pectin, resistant starch,

and rhamnose. They naturally exist in different dietary food products, including asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke (*Helianthus tuberosus*), wheat, honey, banana, barley, tomato, rye, soybean, human and cow milk, peas, beans, and, recently, seaweeds and microalgae.[5]

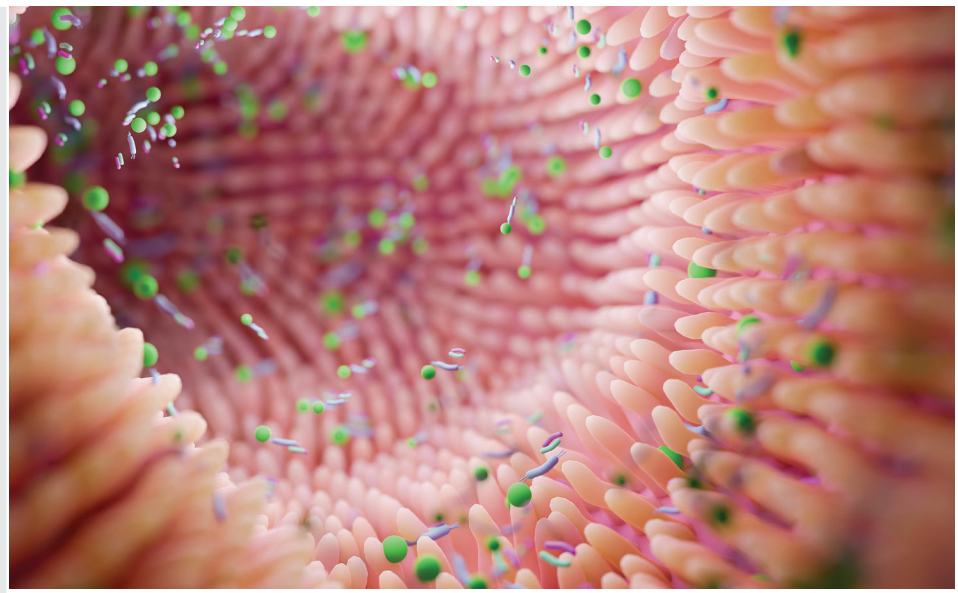
Research has found that the oral administration of microalgae can modulate the gut microbiota, activate the immune system in the gut, and have powerful anti-inflammatory benefits.[6] Generally, prebiotics play an essential role in human health and are found to be safe.

Probiotics

Live beneficial bacteria make up the definition of probiotics and are known to improve digestive health. The primary purpose is to "replace" the beneficial bacteria in the gut that a variety of factors, such as oral antibiotics, stress, and inflammation, can deplete.

Familiar probiotic foods include yogurt, kefir, sauerkraut, kombucha, pickles, sourdough, and miso. However, many more exist and are now widespread in supplement form, which may confuse the individual because certain strains of these supplements may do more harm than good. Knowing what strain is best for the condition is essential and the strain must have been shown to be effective in clinical trials. The most common are *Lactobacillus* and *Bifidobacterium*, but specific strains for treating certain conditions, such as acne, include *Lactobacillus rhamnosus* SP1. Other strains in the 7 core genera of microbial organisms include *Saccharomyces*, *Streptococcus*, *Enterococcus*, *Escherichia,* and *Bacillus*.[1]

Probiotics can be helpful as they are known to help digest food and fight off pathogens. In addition, clinical trials have shown probiotics to be beneficial in preventing allergies in children and atopic dermatitis. Probiotics differ from prebiotics because they contain live organisms and may need special storage. But, overall, they are found to be safe.



A healthy balance of gut microbiota is required for optimal skin health, creating metabolic and immune homeostasis.

Final Microbiome Thoughts

Many patients are more conscious about their diet, which supports their gut and digestive health. As clinicians, we are at the front line of this discussion regarding skin health. Research shows that a healthy balance of gut microbiota is required for optimal skin health, creating metabolic and immune homeostasis. More research points to how compositional gut microbiota changes have been linked with exacerbating inflammatory skin diseases such as eczema, psoriasis, and more. Daily prebiotics and probiotics help keep a homogenous microorganism environment for optimal skin health. ■

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FDA Approves First OTC Birth Control Pill in United States

Norgestrel will be available in store and online at leading drug, convenience, and grocery stores across the country.

By Killian Meara

The FDA has approved norgestrel (Opill) for OTC use to prevent pregnancy in all ages, making it the first birth control pill in the United States available without a prescription. The approval was granted to pharmaceutical company HRA Pharma, which was recently acquired by Perrigo.

Norgestrel has been approved for prescription use since 1973, and HRA Pharma applied for OTC approval in July 2022. The FDA requires an applicant to demonstrate that a product can be used by consumers safely and that a drug label can be easily read without any assistance. The OTC approval was based on several studies on label comprehension as well as the phase 3 ACCESS use trial (NCT04112095), which showed that consumers could use Opill correctly based on the label.[1]

"Today's approval marks the first time a nonprescription daily oral contraceptive will be an available option for millions of people in the United States," Patrizia Cavazzoni, MD, director of the FDA's Center for Drug Evaluation and Research, said in a news release.[2] "When used as directed, daily oral contraception is safe and is expected to be more effective than currently available nonprescription contraceptive methods in preventing unintended pregnancy."

The OTC availability of norgestrel is expected to help reduce barriers to access by allowing people to obtain the medication without needing to see a health care provider. There are over 6 million pregnancies in the United States each year, nearly half of which are unintended. Unintended pregnancies have been associated with several negative outcomes, including increased risk of preterm delivery and reduced likelihood of receiving early prenatal care.

> The approval of norgestrel (Opill) is expected to help reduce barriers to access by allowing people to obtain the medication without needing to see a health care provider.

Opill contains .075 mg of norgestrel and should be taken at the same time every day. Common adverse effects include cramps or bloating, irregular bleeding, abdominal pain, dizziness, nausea, headaches, and increased appetite. Those who have or have ever had breast cancer should not use norgestrel. Using medications that interact with norgestrel, including other hormonal birth control products, can result in decreased efficacy.

Norgestrel will be available in-store and online at leading drug, convenience, and grocery stores across the country beginning in the first quarter of 2024. Perrigo has not yet announced how much the medication will cost.

"Today's approval is a groundbreaking expansion for women's health in the US, and a significant milestone towards addressing a key unmet need for contraceptive access," Frederique Welgryn, Perrigo Global vice president for women's health, said in a news release.[3] "Perrigo is committed to making Opill, which is now the most effective method available OTC at preventing pregnancy, accessible and affordable to women and people of all ages." ■

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Review of FDA Approvals for Pediatric Obesity Management

GLP-1 receptor agonists, used to manage diabetes, are now being used for obesity in children and adolescents.

By Caitlyn Bradford, PharmD; Wade Tung, PharmD candidate; Justine Magalona, PharmD candidate; Natalie Catalan, PharmD candidate; and Danielle M. Alm, PharmD

This article originally appeared in the July issue of Contemporary Pediatrics® *and has been lightly edited.*

Pediatric obesity affects more than 14 million children and adolescents, equivalent to 1 in 5 children in the United States. Obesity prevalence continues to increase in the pediatric population. Certain racial and ethnic minority groups have seen a greater rise, with Hispanic individuals having the highest prevalence of obesity at 26.2% followed by non-Hispanic Black individuals at 24.8%. Biological sex does not seem to play a role in the risk of obesity; the prevalence of obesity is similar between boys (20.9%) and girls (18.5%).[1]

The American Academy of Pediatrics (AAP) defines obesity as a body mass index (BMI) greater than or equal to the 95th percentile for age and sex.[2] The CDC reported childhood obesity prevalence data from 2017 to 2020 at 12.7% among children aged 2 to 5 years, 20.7% among children aged 6 to 11 years, and 22.2% among individuals aged 12 to 19 years.[1]

Risk factors for development of childhood obesity include modifiable factors (eg, physical activity levels, certain medications, sleeping patterns) and nonmodifiable factors (eg, low socioeconomic status, certain disease states, specific racial and ethnic minority groups).[3] Pediatric obesity has been linked to an increased risk of hypertension, asthma, polycystic ovary syndrome, type 2 diabetes, low self-esteem, depression, and eating disorders.[4,5]

Caregivers can help prevent childhood obesity by instituting the following changes with their children: establishing a daily routine; adhering to the American Academy of Sleep Medicine's age-based sleep recommendations; providing balanced meals of whole grains, fruits, vegetables, healthy fats, and protein; limiting screen time to the AAP's age-based recommendations; and promoting approximately 300 minutes of physical activity weekly.[1,6,7] Caregivers should encourage a balanced diet of whole grains, fruits, vegetables, protein, and some fats. Limiting fruit juices and adding water to every meal should also be encouraged. The Kid's Healthy Eating Plate, created by Harvard T.H. Chan School of Public Health in Boston, Massachusetts, can be offered to caregivers as a guide for creating balanced meals.[8]

Clinicians should query caregivers about access to nutritious foods, time available to prepare meals, who is preparing the meals, and current support systems in place. Increasing accessibility, affordability, and subsequent enrollment into physical activity–based programs for children can help combat obesity secondary to a lack of physical activity. Organized sports teams and outdoor activities often come to mind; however, indoor physical activity within the home or school or via a community group should be offered to children limited by the safety of their neighborhood. Referring social workers for families challenged by living in high-crime areas is a great resource to employ for increased support, connection, and guidance as warranted.[9]

Treatment

First-line therapies for obesity management recommended by the AAP are motivational interviewing and creation of personalized treatment plans, which include dietary modifications, increased physical activity, behavioral modifications, and psychoeducation.[4] Pharmacological

Table. **FDA-Approved GLP-1 Receptor Agonists for Pediatric Weight Loss**[19,20]

	Liraglutide	Semaglutide
Brand name with FDA pediatric obesity indication	Saxenda	Wegovy
Dosing	• Initial: 0.6 mg subQ once daily • Second week: 1.2 mg subQ once daily • Third week: 1.8 mg subQ once daily • Fourth week: 2.4 mg subQ once daily • Maintenance: 3 mg subQ once daily	• Weeks 1-4: 0.25 mg subQ once weekly • Weeks 5-8: 0.5 mg subQ once weekly • Weeks 9-12: 1 mg subQ once weekly • Weeks 13-16: 1.7 mg subQ once weekly • Maintenance: 2.4 mg subQ once weekly
Contraindications	• Pregnancy • Family history of MTC • MEN2 • Hypersensitivity	• Pregnancy • Family history of MTC • MEN2 • Hypersensitivity
Warnings and precautions	• Risk of thyroid C-cell tumor • Acute pancreatitis • Acute gallbladder disease • Hypoglycemia • Acute kidney injury • Heart rate increases • Suicidal behavior and ideation	• Risk of thyroid C-cell tumor • Acute pancreatitis • Acute gallbladder disease • Hypoglycemia • Acute kidney injury • Heart rate increases • Suicidal behavior and ideation
Adverse drug reactions	• Nausea (39%-42%) • Diarrhea (21%-22%) • Vomiting (34%) • Injection site reactions (1%-14%) • Hypoglycemia (15%)	• Nausea (16%-44%) • Diarrhea (9%-30%) • Vomiting (36%) • Abdominal pain (6%-20%) • Injection site reactions (< 1%)
Clinical pearls	• Discontinue if BMI has not decreased ≥ 1% from baseline after 12 weeks on maintenance dose. • If a dose is missed for > 3 days, resume with a daily dose of 0.6 mg to minimize initiation reactions. • Patients do not have to reach the 3-mg target dose to achieve weight loss.	• Can decrease dose to 1.7 mg once weekly for 4 extra weeks if dose of 2.4 mg subQ is not tolerated. • Treatment should be discontinued if the patient cannot tolerate the 1.7-mg weekly dose.

BMI, body mass index; GLP-1, glucagon-like peptide-1; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid carcinoma; subQ, subcutaneous.

First-line therapies for obesity management... are motivational interviewing and creation of personalized treatment plans.... Pharmacological treatment may be considered adjunctively when nonpharmacological therapy alone does not achieve the desired results.

treatment may be considered adjunctively when nonpharmacological therapy alone does not achieve the desired results.[4] Thus far, the FDA has approved 4 medications for chronic weight management in pediatric populations: orlistat (Xenical),[10] phentermine and topiramate extended-release capsules (Qsymia),[11] liraglutide (Saxenda),[12] and semaglutide (Wegovy).[13] This review will focus on the newly approved glucagon-like peptide-1 receptor agonists (GLP-1 RAs).

GLP-1 RAs bind to the GLP-1 receptors in the pancreas, brain, and gastrointestinal tract to stimulate insulin release. Additionally, GLP-1 RAs delay gastric emptying, which in turn reduces food intake and promotes a feeling of fullness.[14]

The FDA granted approval for the first GLP-1 RAs in April 2005 for blood glucose control in adult patients with type 2 diabetes.[14] The medication class contains dulaglutide, exenatide, semaglutide, liraglutide, and lixisenatide. Of these, liraglutide and semaglutide are FDA approved for pediatric weight loss.[15,16] In December 2020, liraglutide received approval as an adjunctive agent to lifestyle modifications for chronic weight management in pediatric patients 12 years or older with body weight greater than 60 kg and an initial BMI greater than 30 kg/m^2.[15] In December 2022, the FDA approved semaglutide as an adjunctive agent to lifestyle modifications for chronic weight management in pediatric patients 12 years or older with an initial BMI equal to or greater than the 95th percentile standardized for age and sex.[16] The phase 3, interventional STEP TEENS clinical trial (NCT04102189) showed semaglutide was superior to placebo, with a change in BMI percentage by week 68 (a 16.1% reduction with semaglutide vs 0.6% increase with placebo). Patients commonly experienced nausea, vomiting, diarrhea, headache, and abdominal pain during the study. Discontinuation of the trial regimen occurred in 5% of patients in the semaglutide group and 4% in the placebo group, most commonly because of gastrointestinal events.[15] Liraglutide was evaluated in a placebo-controlled, 56-week clinical trial (NCT04102189). Results demonstrated a 2.65% reduction in body weight with liraglutide vs a 2.37% increase with placebo. Gastrointestinal events were common and were the most common reason for regimen discontinuation (10% vs 0% with liraglutide vs placebo).[16] Of note, exenatide has shown to significantly reduce BMI in adolescent patients with severe obesity compared with placebo; however, exenatide is not currently FDA approved for use in the pediatric population for this indication.[17] Medication information for liraglutide and semaglutide (Wegovy) can be found in the **Table**.[13,20]

GLP-1 RAs are administered via a subcutaneous injection in the abdomen, thigh, or upper arm. Patients and caregivers should be counseled on appropriate medication preparation and injection techniques. Liraglutide and semaglutide products come packaged in ready-to-use pens, whereas exenatide formulations require product manipulation prior to administration, necessitating additional patient education.[13,20]

Findings from studies within the adult population have shown semaglutide results in significantly greater weight loss vs liraglutide; however, no current studies are examining superiority between the GLP-1 RAs in the pediatric population.[21,22] More research is needed to better categorize the expected BMI reduction with each agent. Findings from available studies show up to 76% and 43.3% of adolescent patients reaching BMI reduction of 5% or more with semaglutide and liraglutide, respectively, within the designated study periods.[23,24]

As mentioned, GLP-1 RAs serve as an adjunctive agent to lifestyle modifications. A meta-analysis conducted by Ryan et al revealed a synergistic effect between the combined use of GLP-1 RAs and lifestyle interventions, which resulted in greater reductions in blood pressure levels, hemoglobin A_{1c} levels, and weight compared with using

GLP-1 RAs alone.[25] Other considerations when choosing between products may include cost and insurance formulary. Patient assistance programs and savings offers are available for both liraglutide and semaglutide through the manufacturer to offset high co-pays and ease private pay costs.

Conclusion

First-line therapies for the management of pediatric obesity focus heavily on nonpharmacological measures. Pharmacological treatment can be offered adjunctively when desired results are not achieved through nonpharmacological measures alone. Semaglutide and liraglutide are 2 FDA-approved medications for this indication that are generally well tolerated in the pediatric population.■

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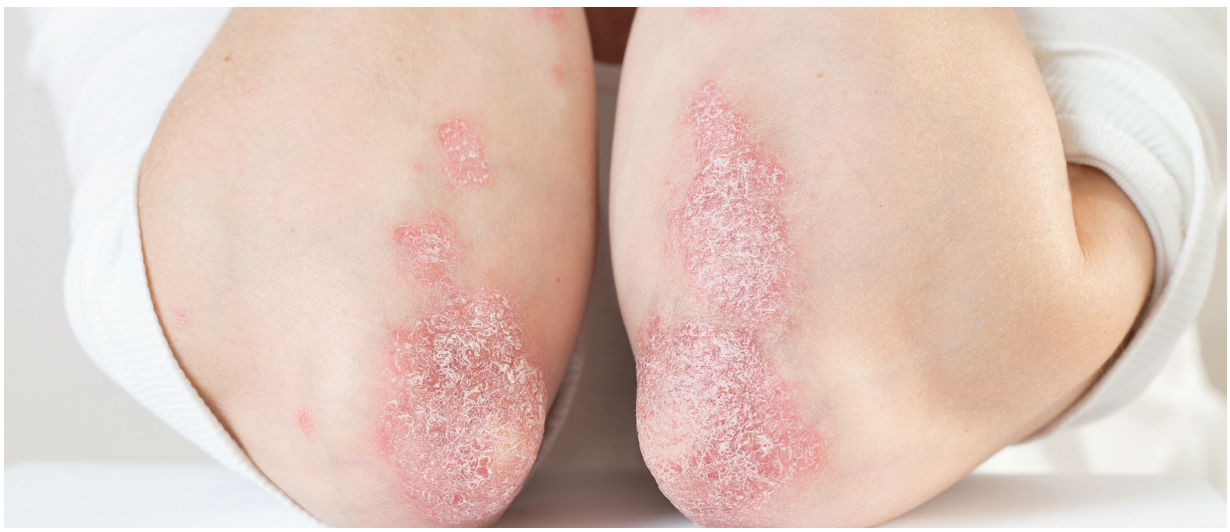
Biologics Offer Great Results in Treating Psoriasis—at a Cost

Highly effective medications for severe disease are expensive and administered invasively, whereas the development of treatments for milder disease has lagged.

By Rachael Zimlich, BSN, RN

This article originally appeared in Dermatology Times® *and has been lightly edited.*

During the past 2 decades, understanding of the pathogenesis of psoriasis has increased, opening new pathways to treatment. Although these treatments—such as biologics—are highly effective, they are also limited by cost and administration challenges. Despite these



discoveries, there has been little advancement in traditional, topical treatments, and there is still no cure for this chronic condition.

A review[1] published in the September 2022 issue of *Dermatology and Therapy* investigated some of the newest advances being collectively researched in clinical trials for psoriasis treatment during the previous year. A big theme, according to the study, was several small molecule oral medications in various phases of clinical trials that may help to reduce some of the limitations of biologic therapies.

Many of the newer, highly effective medications for treating psoriasis target the IL-23/IL-17 axis, the pathway where psoriatic inflammation is believed to be triggered. Medications like tumor necrosis factor α, IL-12/23, and IL-17 inhibitors target these pathways and have produced superior results in treating moderate to severe psoriasis, but the study also notes that progress on treating milder cases of psoriasis has stalled somewhat.

Treatments for mild psoriasis still focus on systemic medications with a high risk of toxicity such as methotrexate, or traditional topicals that are less effective and carry a risk for long-term consequences, the report noted.

So, although newer medications have led to better skin clearing and an improved quality of life, it comes at a higher cost and these medications usually involve injections or infusions that can create a barrier for many patients. The lack of progress in other systemic and topical medications highlights the treatment gaps in psoriasis, and the need for new treatments, according to the study.

Some treatments currently in trial phases were identified in the study and include therapies such as:

- IL-36 inhibitors
- IL-23 inhibitors
- IL-17 inhibitors
- Phosphodiesterase 4 inhibitors
- Janus kinase inhibitors
- Receptor-interacting serine protein kinase 1 inhibitors
- Retinoic acid receptor–related orphan receptor C inhibitors
- A_3 adenosine receptor agonists
- Aryl hydrocarbon receptor modulators
- CXC chemokine receptor 2 antagonists

Many of these medications are in the later stages of clinical trials and harness the efficacy of biologic medications but offer an oral administration option. There are also choices geared toward treating mild psoriasis instead of reserving these treatments for more severe forms of the disease.

There are also several medications in the early stages of clinical trials for which data is limited, but that also offer more oral treatment options. These include a reactive aldehyde species inhibitor (ADX-629); a calcitonin gene-related peptide receptor antagonist (rimegepant); and a sphingosine-1-phosphate receptor 1 agonist.

Finally, the study highlighted treatments recently approved by the FDA for psoriasis, a list that includes deucravacitinib, an oral tyrosine kinase 2 inhibitor; spesolimab, an anti–IL-36 receptor antibody; and other nonsteroidal topical agents.

The study authors estimated that progress in developing new treatments will continue at a rapid pace, especially as understanding of the disease evolves. The biggest focus with these new treatments, the research team noted, is data on long-term efficacy and safety. ■

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By Peter A. Kreckel, RPh

Dance With the Girl That Brung Ya

PBMs, retail chains, and pharmacy schools have all contributed to the current state of the profession. It's time they worked on fixing it.

Back in 1981, as a newly minted, fully fledged pharmacist, I was excited to take over a new location of Kopp Drug in Tyrone, Pennsylvania. I had worked for Rite Aid for 6 months and quickly found that patient counseling and care were not on their front burner. I was anxious to turn that page and begin anew, this time working at a small, independent community pharmacy.

Long before the days of computers, patients brought in their prescription bottles to fill. We reused the bottles over and over so as not to have to retype labels. One of my new patients was a gentleman named "Ted." Ted would come in and ask us to fill "$4 worth of Bentyl, $12 worth of Tagamet, and $4 worth of Lanoxin." Ted had exactly $20 in his well-worn wallet, so there was no wiggle room!

When the Pharmaceutical Assistance Contract for the Elderly prescription assistance program, known as PACE, started in Pennsylvania in 1984, I was delighted that cost would no longer be a variable in the patients' selection of a pharmacy. Through these prescription benefits, pharmacists would all be paid the same and patients would all be charged the same, making the performance of the pharmacist the deciding factor as to where the patients would take their business. The better the pharmacist was with providing patient counseling and compassionate care, the more volume they would generate. However, I learned all too quickly that this would not last forever: Eventually, the Tyrone School District signed up with Blue Cross to have its employees' prescriptions filled in Altoona, Pennsylvania, at the Phar-Mor store.

I was livid. I wrote a letter to the editor of the local newspaper, and I attended the school board meeting, to no avail. The fact that I provided wonderful service, counseled patients, offered free delivery, and even opened the store after hours didn't matter. The fact I lived in that town, and that my school taxes were being used to fund another pharmacy, didn't matter either. Little did I realize that things would only get worse.

Pharmacy schools need to establish a more intense community pharmacy–based curriculum; they must promote this wonderful profession that is on the front lines of health care.

Because the free market did so well for patients in selecting their pharmacies, I foolishly thought this idea would continue with insurance companies. We were reimbursed the average wholesale price plus $2.55 for filling prescriptions. This was significant, as most prescriptions were filled with newly introduced brand-name drugs; it wasn't until the late 1990s that generics took over the marketplace. Excellent service and compassionate care brought patients to the pharmacy, until pharmacy benefit managers (PBMs) and chain pharmacies took over.

Today, our profession is in crisis mode. Fewer students are enrolling in pharmacy school. Many schools brag that nearly 50% of their graduates match for residency, but less than 20% of the student population is committed to becoming a community pharmacist. It will be a matter of only a few years before every clinical slot is filled, and there will be even fewer students interested in the profession.

There is an old saying that goes, "Dance with the girl that brung ya." In our profession, I feel that this is as important as ever. With enrollment way down, I think it is vital to pharmacy that both pharmacy schools and the profession start "dancing with the girl that brung ya!" Pharmacy schools need to establish a more intense community pharmacy–based curriculum; they must promote this wonderful profession that is on the front lines of health care, and they need to hire more community pharmacy–focused faculty.

Chain pharmacies are struggling to keep pharmacists and employees. My class of 1981 at the University of Pittsburgh, was the first in which more women than men graduated. Chain pharmacies need to be cognizant of the flexibility that is needed for employees to enjoy family life. At the store where I worked for the first 26 years of my career, the owner hired several women on a part-time basis, allowing them the flexibility to accommodate their goals of having both a career and a family. My wife, Denise, was one of those able to achieve such balance.

The major chains, the PBMs, and the schools of pharmacy have all had a hand in creating the current state of community pharmacy. It is time they get it fixed, because the downfall of the community pharmacy profession will lead to the collapse of the profession. It is time to get started, before "the girl that brung ya" leaves the dance floor. ■

Peter A. Kreckel, RPh, practices pharmacy in Lemont Furnace, Pennsylvania.

Conference Recap:

NACDS Total Store Expo

The theme of this year's National Association of Chain Drug Stores Total Store Expo (NACDS TSE) was *converge*, and that's exactly what retailers, exhibitors, and pharmacists did. Attendees came together August 12 to 14 in San Diego, California, for 3 exciting days of meetings and education.

Check out excerpts from our conference below, and scan the QR code or visit drugtopics.com/conference/nacds to read more.

In a Post-Dobbs World, Pharmacists Still Face Uncertainty

By Lauren Biscaldi, MS

Since the 19th century—well before the 1973 Supreme Court decision in *Roe v Wade*—there have been abortion laws on the books. And after the landmark decision, these laws were never repealed, creating a set of legal challenges following the *Dobbs v Jackson Women's Health Organization* decision on June 24, 2022.

Perhaps more crucially for pharmacists, though, is that "none of those laws had to do with medication abortion," said Scot Hasselman, cochair at Reed Smith LLP—creating additional confusion when some of those laws when into effect following the Dobbs decision. "It's very challenging being a retail pharmacy, especially being a chain that is across numerous jurisdictions because you're trying to figure out, 'What is the law today? What can we do today? What are our obligations [around] providing health care?'"

The Federal Government Responds

On the day of the Dobbs decision, the Department of Justice and Attorney General Merrick B. Garland released a statement responding to the ruling that clarified what, legally, states and the federal government could and could not do:

- States cannot ban an approved medication based on a disagreement with the FDA.
- States cannot impose either criminal or civil liability on a federal employee acting within the scope of their employment.
- Federal agencies may continue to provide reproductive health services.

On July 11 and July 13, the Department of Health and Human Services (HHS) issued its own responses to the Supreme Court decision. First, Secretary Xavier Becerra reaffirmed that compliance with the Emergency Medical Treatment and Labor Act includes offering lifesaving abortion services to patients who are experiencing medical emergencies. Two days later, HSS also issued guidance to retail pharmacies with a reminder about Section 1557 of the Affordable Care Act, which prohibits discrimination on the basis of race, color, national origin, age, disability, or sex, which includes pregnancy, sexual orientation, gender identity, and sex characteristics, through covered health programs or activities.

Another issue that retail pharmacies must contend with is the Comstock Act, an "antivice" law put on the books in 1873 that criminalized using the United States Postal Services to mail contraceptives and abortifacients, along with other substances.

State-Level Reactions

Copresenter Lesley Reynolds, a partner at Reed Smith LLP, noted that with the Dobbs decision, the Supreme Court overruled both *Planned Parenthood v Casey* and *Roe v Wade*, finding that "there was no federal constitutional right to abortion, and that this was an issue for the states," Reynolds said. "The majority opinion noted that [the goal was] to get the

courts out of the issue of abortion. That's not really what has come [to be].

"[Abortion] has been litigated at an incredible rate," she continued, "due to the numerous laws being challenged and legislators enacting new proposals." In some states, such as Kentucky, Louisiana, Mississippi, and Oklahoma, among others, trigger laws banning abortion went into immediate effect; in Georgia, Wyoming, and Indiana, legislation proposing a variety of additional restrictions was proposed, some of which is still pending. And in Idaho, legislators have criminalized bringing minors across state lines to receive abortion care—including medication that will induce abortion—in a law dubbed "abortion trafficking."

State attorneys general have also taken public positions on these state and federal laws. Earlier this year, 20 Republican attorneys general signed letters to both CVS and Walgreens warning the pharmacy chains that their intention to distribute abortion pills through the mail was illegal under the Comstock Act, directly contradicting earlier DOJ guidance. In response, Walgreens agreed that it would not dispense abortion pills—either in the pharmacy or by mail—in those states, a list that includes several states where both abortion and abortion medications remain legal. In response, a group of Democratic state attorneys general issued their own letter urging Walgreens and CVS to ignore these threats of legal action.

For pharmacists—and especially for pharmacists practicing near state lines—these conflicting directives have further muddied the waters around an extremely contentious issue. "Alaska is a state that has a state constitution where… reproductive rights are protected; essentially there's a right to abortion in Alaska," Hasselman said. "There are also laws on the books in Alaska that limit the performance of an abortion to certain locations, and they must be performed by certain individuals—certain types of providers—so you have a law that essentially doesn't really provide a pathway for dispensing abortifacients in a pharmacy, arguably."

According to Hasselman, the question then becomes, "How do you sort of square those two?" The Alaska state attorney general has taken the view that pharmacists cannot dispense abortifacients in a retail pharmacy, which is not technically inconsistent with the state constitution. "The constitution…just says that there is a right, and there's a statute that says that right is limited to certain locations and certain practitioners, and that doesn't include retail pharmacy," said Hasselman.

"So you're a dispensing pharmacist in Alaska, what do you do?" asked Hasselman. Pharmacists who defy these statues risk discipline, such as a loss of their license or legal action, and administrative hearings challenging disciplinary action can languish in court for years.

Mifepristone Under Challenge

Pharmacists are also likely familiar with the recent legal challenge of mifepristone, where the Alliance for Hippocratic Medicine and the American Association of Pro-Life Obstetricians and Gynecologists, among others, brought a lawsuit claiming that the FDA was inappropriate in their approval of mifepristone in 2000.

On August 16, a panel of judges in the 5th US Circuit Court of Appeals ruled that access to mifepristone must be restricted and ordered a ban on both telemedicine prescriptions and shipments of the drug by mail. The decision will need to be reviewed by the Supreme Court, and the DOJ has stated that the Biden administration will be appealing the ruling.

In the meantime, what are retail pharmacists supposed to do? According to Hasselman and Reynolds, that answer remains unclear. "The answer depends…on the state in which you're sitting," Reynolds said. "In some states, pharmacists cannot dispense and would be subject to…licensure actions [or] other criminal statutes depending on the state."

"There are a lot of states where we've advised pharmacies not to dispense at all," Hasselman said.

REFERENCE

Hasselman S, Reynolds L. Post Dobbs for pharmacy. Presented at: NACDS TSE 2023; August 12-14, 2023; San Diego, CA.

Food Is Medicine: Pharmacists Can Advance Policies for Healthier Communities

Will pharmacists soon be filling prescriptions for fruits and vegetables? As policy developments around the food-as-medicine movement continue, *Drug Topics* sat down with Holly Freishtat, senior director of Feeding Change at the Milken Institute to discuss her thoughts around food as medicine and how pharmacists can implement food-based solutions using their clinical expertise. Freishtat was a panelist on the NACDS Institute session titled, "Pharmacies Feeding Innovation: Creative Community Solutions to Advance Food Is Medicine."

Bringing Health Care Closer to Home

Drug Topics sat down with Julie Akers, PharmD, FWSPA, to discuss ways that pharmacists can maximize the work they put into developing innovative care models in their communities.

Akers, associate dean of external relations and an associate professor at Washington State University College of Pharmacy and Pharmaceutical Sciences in Spokane, was a panelist at the session, "Bringing Healthcare Closer to Home: Innovative Pharmacy Care Models to Better Serve Communities."

2023 Pharmacy Trends Forecast

Drug Topics caught up with Doug Long, vice president of industry relations at IQVIA, to discuss the latest trends and issues as well as the forecast for 2023 and beyond. Long's session was titled "2023 Pharmaceutical Trends, Issues, and Forecasts."

Pharmacists Are on the Front Line of Women's Health and Wellness

Drug Topics sat down with Summer Williams Kerley, vice president, clinical market access solutions, Rite Aid Corporation, to hear her insights in the women's health space. During the conference, Kerley was a panelist at the session "Closing the Gap in Health and Wellness for Women."

This interview has been lightly edited for clarity.

Drug Topics: **What are the areas within women's health that are most lacking in terms of funding and research?**

Summer Williams Kerley: I'm going to say all areas. Only 4% of the money that is used for research and development focuses on women's health. If you think about that—I think the majority of shoppers for wellness products are usually women, but there's a lack of research in general for women's health conditions.

How can we start encouraging more discussion about women's health?

When it comes to women's health, historically, people are uncomfortable. They're very uncomfortable sometimes, talking about fertility issues and sexual wellness, or even things that women that may suffer from, like hypothyroidism, or how they may have thinning hair. It's really important that our pharmacists are being proactive and understanding, and not just focusing on the needs of their customers from 1 prescription, but really all of their health care needs. That's why it's important for pharmacists to get to know their customers, so that that comfort level is there to talk about conditions that patients may not be comfortable talking to their physician about.

What actions can pharmacists take today to generate support for, and understanding of, the importance of women's health issues?

Just like any topic that a pharmacist would need to learn about, I think it's really important for pharmacists to look at the whole person. Again, a man in his 40s may be suffering from something completely different than a woman in her 40s. It's about really making sure that they can talk to those customers, and it's about continuing education in that area. ■