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Patient Care in the COVID-19 Era Calls for Enhanced Communication, Education

Even in the middle of the ongoing pandemic crisis, pharmacists stay connected to their patients. Whether it’s from a safe 6-foot distance, from behind a glass barrier, or through remote telecommunication, this interaction remains a crucial piece of patient care.

For many patients, especially those with chronic conditions, disease management is not as simple as filling a prescription. Mismanagement, or lack of overall management, of prescription medications leads to 1.5 million adverse events every year. In this issue’s cover story, we explore how independent pharmacies can incorporate medication therapy management (MTM) into practice to help patients prevent medication-related problems and optimize their medication use.

Not only does MTM improve patient care, but offering MTM services can also be a cost-effective business opportunity for pharmacies. Read more on how to set up and get paid for MTM services on page 8.

With flu season looming, immunization is on every health care provider’s mind, whether it’s figuring out how to safely administer flu vaccinations in the pharmacy or wondering about the status of coronavirus disease 2019 (COVID-19) vaccines in development. To keep you up-to-date on the latter, MJH Life Sciences™ recently held a webinar with virology experts to discuss the latest details in vaccine development and what they mean for health care providers on the front line. Read the full recap on page 12.

On page 18, Jennifer Gershman discusses the prevention and management of pneumonia, providing an overview of different types of pneumonia, including pneumonia associated with COVID-19.

On page 20, we discuss the rise of artificial intelligence (AI) in the pharmacy world, and why many in the industry are embracing AI offerings today. In the COVID-19 era, these technology innovations are primed to produce quick solutions. As Vin Singh, MBA, MS, said in the article, “The benefits that AI can bring to help tackle the COVID pandemic have yet to be fully realized.”

As always, visit drugtopics.com for more relevant and timely pharmacy news.

Thank you for reading,

Mike Hennessy Sr, Chairman and Founder of MJH Life Sciences™
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Coalition of Health Groups Push for Pharmacist Provider Status

By Christine Blank

In an open letter, several health organization urged the Trump Administration and Congress to recognize pharmacists as medical providers.

The National Forum for Heart Disease & Stroke Prevention and a coalition of more than 20 other groups representing patients, the medically underserved, and diverse health care providers sent the letter to the bipartisan Congressional leadership and the Trump Administration. The letter urged for action to be taken to allow more pharmacies to ramp up patients’ access to coronavirus disease 2019 (COVID-19) testing and to help prevent delays in giving vaccines when they become available.

The groups represent more than 200 million Americans who have conditions that leave them particularly at risk of COVID-19 complications. According to the Coalition, Congress should issue emergency pharmacist provider status under Medicare Part B to provide COVID-19 and influenza testing and vaccinations.

New Hampshire Passes Bill Allowing Pharmacist-Provided COVID-19 Vaccinations

By Gabrielle Ientile, Assistant Editor

New Hampshire joined New York and Minnesota in allowing coronavirus disease 2019 (COVID-19) vaccine access through pharmacies through pharmacist-provided vaccinations once the vaccine becomes available.

Governor Christopher Sununu signed the bill, HB1639, into law in August. Pharmacy organizations have praised state bills expanding the scope of pharmacists amid the pandemic, as well as national initiatives that have recognized the value of pharmacists. Because many individuals in the United States do not have reliable access to a physician, pharmacists are uniquely positioned to provide health care for these populations, and this includes providing access to a COVID-19 vaccine.

Although vaccination rates have waned during the pandemic, the CDC recently notified Americans about the importance of continuing to stay on schedule for receiving their vaccinations to prevent dual infections with COVID-19.

To listen to this podcast and others, visit www.drugtopics.com/podcasts.

CANNABIS SERIES: FDA Support, Research in the Works

In the first episode of Drug Topics® podcast’s Cannabis Series, we discuss the burgeoning medical marijuana landscape, featuring FDA guidelines and research on the diverse benefits of cannabis and cannabidiol products as medicine.

Definitive data on cannabis, the compounds found in cannabis, and their effects on the endocannabinoid system, is currently a bit of a lunar landscape. Although there are a lot of CBD and hemp products on the market, they are not FDA approved. Recently though, the FDA has expressed its commitment to supporting medical cannabis and cannabis-compound research.

Jeff Lombardo, PharmD, BCOP, research assistant professor for University of Buffalo Center for Integrated Global Biomedical Sciences, provides perspective on the research landscape and availability of products state-by-state.

For US Secures Deal With Moderna for 100 Million Doses of COVID-19 Vaccine, see page 17
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A Plus for Both Patients and Pharmacists
One in 4 Americans used 3 or more prescription medications during the last 30 days. Such medications may have been prescribed by multiple specialists and filled at various pharmacies, combined with supplements or OTC medications, leading to potential adverse effects (AEs) or less than optimal results. Such mismanagement—or rather a lack of overall management—leads to 1.5 million preventable adverse events every year.

That’s where medication therapy management (MTM) can help. By incorporating MTM into their practice, independent pharmacists can help patients prevent medication-related problems and optimize their medication use.
A Cost-Effective Business Opportunity

Providing this service is not only useful to patients and members of the health care team. It can be a good way for independent pharmacies to expand their business, as a variety of payers are prepared to cover the costs of such oversight.

“Since Medicare Part D payers are required to cover MTM services for eligible patients, this is an opportunity for pharmacies to provide a billable service and expand beyond solely dispensing functions, hence further building up their business,” Abraham said. Additionally, some adherence problems are simple to diagnose, and an MTM session can prevent serious problems, and reduce costs for both the patient and health care system over time.

Emilah Tubuo, PharmD, RPh, and owner of Powell Pharmacy, had one patient bring 6 bottles of metformin to an MTM session. When asked why she had so many bottles of her diabetes medication, the patient described her last doctor’s visit, where she was praised for her progress in controlling the disease. After 3 months of taking the medication, she assumed she was cured and had not taken any more of the treatment for 2 months.

“The doctor was encouraging her because she is on a positive path and she thought, I’ve treated my diabetes and I’m good to go,” said Tubuo. “Fortunately, we did CMR on that day and I told her, this is a journey, one step at a time. She had not asked the doctor whether she should stop taking it. She just assumed. She would have gone back in 3 or 4 months to see the doctor and would have been back to where she started.”

Occasionally, a patient may have 2 prescriptions for the same condition with potentially dangerous consequences. “We also see people who see multiple doctors for different things, and we start to see duplicates of medication—not even the same meds,” said Brianne L. Porter, PharmD, MS, assistant professor of clinical pharmacy.

The Ohio State University College of Pharmacy. “So, someone goes to a heart doctor and gets a drug for their heart, a β-blocker, and they are out of refills and the doctor is not responding. They might call their general practitioner and their general practitioner says, ‘I don’t want you to run out of it, I’ll refill it just for this month,’ and then the heart doctor restarts it. Then suddenly the patient is on the same kind of med from 2 different doctors, and they don’t know because they are not talking to each other.”

As well as making recommendations for medication safety and efficiency, during a review, a pharmacist might also suggest a vaccine. Patients with diabetes might be urged to get a flu vaccine, whereas patients over 50 years of age may be reminded about the shingles vaccine.

“We then send the recommendations to the physician, saying, we saw your patient and these are the things we discussed,” Tubuo said. “Here are our recommendations. Let us know what you think, print it out, sign it and send it back to us. If we have a patient with diabetes, we can ask if they want to add a statin. Sometimes we initiate it, sometimes they make a different decision, ‘no, not at this time.’ We work together as a team to take care of the patient. Don’t look at it as the pharmacist doing the doctor’s job. No one can do it all.”

Nonpharmacological options are also addressed. “You come in and you’re taking a statin and chances are that you’re looking at what else you can do which will help your cholesterol and lower your chances of having a cardiovascular event,” said Tubuo. “As a pharmacist, we also focus on those non-pharmacological options, optimizing those medication outcomes, because if you look at the guidelines, they always say in addition to lifestyle and diet changes. We forget that. Those are hard. Those are where we need to hold each other’s hands.”

5 Core Elements of Medication Therapy Management

1. Review and optimize medication therapy
2. Examine the patient’s personal medication record
3. Develop an action plan
4. Make necessary interventions and/or referrals
5. Document and follow up

“People want to be listened to. Typically when you come to the pharmacy, you pick up your prescription, you make a payment and walk out the door. People go home with so many questions.”

EMILAH TUBUO, PHARMD, RPH

Setting Up a Plan

A pharmacist can help set up a specific plan. “Once the medications are reviewed, pharmacists address barriers to
compliance, review the patient’s pertinent vitals, lab values and set up clinical goals,” said Sokhal. “Pharmacists also review relevant lifestyle changes and set up SMART goals (specific, measurable, achievable, relevant, time-bound) for the patients. We utilize our dispensing software to document the interventions, action plan, and follow-up plan and also to submit pharmacist eCare plans.”

Vendor-supplied documentation platforms, such as Outcomes and SinfoniaRX, provide centralized information and can make documentation easier.

“When I pull you up, if you filled your prescription at any of the chains, I will see your prescription history for the past 12 months.” Tubuo said.

Many patients are not aware that the MTM service exists or that it is often free.

“Marketing MTM services is important so that members realize they have a service available to them that may improve their therapeutic outcomes while reducing the risk of adverse events,” said Abraham. “It’s also important to emphasize that MTM services are free and may save you money since pharmacists help optimize medication use with cost-effective drug choices.”

**Getting Paid**

There are several ways pharmacies can get paid for this service.

“As a new pharmacy wanting to provide MTM services and get paid for it, I would definitely start looking at the American Pharmacists Association’s MTM Resources,” Abraham said. “There are some basic requirements which you probably already have as a pharmacy, such as obtaining a National Provider Identifier number. The easiest way is to consult with all of your contracted payers to determine how MTM services should be billed.”

In some cases, the payer uses its own employee pharmacists to provide MTM and does not contract for the services, but in other cases the payer contracts with pharmacies or individual pharmacists to provide the services.

“We receive MTM-eligible members from the health plan and then basically provide outreach to them so that we can provide them with their MTM opportunities remotely at their convenience,” said Abraham.

**Offering MTM During COVID-19**

MTM sessions can serve a critical function during the coronavirus disease 2019 (COVID-19) pandemic, which has made it more difficult but even more important for vulnerable patients to manage chronic diseases such as diabetes, hypertension, heart failure, and asthma.

“Patients have decreased access to care and are scared to visit their doctors’ offices,” said Abraham. “Many of them have questions about their medications, uncontrolled chronic disease conditions, general health, and nowhere to go. Access to care has dramatically decreased in the COVID era, and the provision of MTM services provides patients increased access to care from their home at their convenience.”

The pandemic has resulted in more remote health care communication. To set up remote MTM meetings, on a basic level, pharmacists need a computer/laptop, phone, and documentation platform to provide MTM services. Technology resources such as Doximity, Microsoft Teams, Zoom, and Cisco Webex, have proven helpful.

Providing MTM services also opens opportunities for other clinical pharmacy services such as comprehensive medication management (CMM) services, where pharmacists are able to provide chronic disease state management to patients in partnership with their health plan and primary care providers.

In Tubuo’s experience, when patients find out MTM is a free service, they almost always want to do it.

“People feel rushed every time they are around a medical provider. If you go online and look for physician reviews, the best review is, ‘This doctor actually sat down and talked with me. I did not feel like he just wanted to hurry me out of the room.’ People want to be listened to. Typically when you come to the pharmacy, you pick up your prescription, you make a payment and walk out the door. People go home with so many questions.”

For references, visit drugtopics.com.
Experts Discuss the Race for a COVID-19 Vaccine

Webinar participants review the history and hurdles. By Lois Levine

Recently, MJH Life Sciences™ hosted the webcast “COVID-19: Race for a Vaccine,” with 3 world-renowned scientists leading a lively discussion on the history of vaccines, past and future efficacies within the vaccine world, and just what a coronavirus disease 2019 (COVID-19) vaccine might look like in the near future. The panel included Walter A. Orenstein, MD, professor and associate director of the Emory Vaccine Center at Emory University School of Medicine; Angela Rasmussen, PhD, associate research scientist at the Center for Infection and Immunity at Columbia University; and Gregory A. Poland, MD, editor-in-chief of Vaccine and director of the Mayo Vaccine Research Group.

Community pharmacies are the ideal locations to provide a vaccine for COVID-19. Although there are still barriers to overcome, pharmacists should prepare now to administer it, and that requires staying up-to-date on the most recent developments.

Rasmussen noted that at present, although more than 150 vaccines against the coronavirus are being researched, just 6 are in phase 3. Three leading the vaccine race include mRNA, replicating RNA (replicon), and DNA. Although all these share the benefits of being easy to manufacture (none require the infectious virus to build the vaccine), Rasmussen pointed out that each one comes with disadvantages, as well. Both mRNA and replicon are not temperature stable/more reactogenic, whereas DNA is proving difficult to deliver to target cells.

Poland offered insight on massive controversies in the medical media landscape, with the reminder that “you can have your own opinions, but not your own facts—science is not a democracy.” He said it is essential to reinforce the principles of scientific evidence, which is intentional, explicit, peer reviewed, and agnostic to results.

Additionally, Poland noted the public’s collective temperature in response to the vaccine race, citing concerns about cutting corners, vaccines being produced at warp speed, and vaccine allocation (utilitarian or egalitarian). With multiple national and international tabletop exercises and 3 novel coronaviruses that crossed the species barrier in the past 16 years, there is no excuse for not being ready, prepared, and in sync for COVID-19 right now, Poland said. He noted that despite the public pressure for treatments and vaccines, there is also no substitute for careful clinical studies and trials. The scientific community should be mindful not to overpromise, he said, emphasizing that despite what first comes to market, the ideal vaccine should be able to be mass-produced quickly, have an excellent safety profile, be stable at room temperatures, and be able to be stored indefinitely.

Orenstein continued with a frank look at questions that may be unanswered even at the time of the first COVID-19 licensing. These include who the priority groups for the vaccine would include, risk factors for vaccine failure and waning immunity, and the impact of the vaccine in reducing transmission. On a brighter note, Orenstein offered a reminder that “vaccine safety continues to be monitored even after the public begins using the vaccine” through a number of watchdog groups.

Orenstein wrapped up with a reminder to all clinicians to follow recommendations of the Advisory Committee on Immunization Practices and continue to report cases of COVID-19 to local and state health departments, including vaccination status.

“You can have your own opinions, but not your own facts—science is not a democracy.”

Gregory A. Poland, MD
Adult Pneumonia Management and Prevention

Pharmacists can play an important role in pneumonia management and prevention.  
By Jennifer Gershman, PharmD, CPh

Pneumonia is a lung infection that can result in mild to severe illness across all ages, and common causes include viruses, bacteria, and fungi. Individuals at high risk of experiencing pneumonia include adults 65 years or older, children younger than 5 years, those with underlying health conditions, and smokers. Common causes of viral pneumonia are influenza and respiratory syncytial virus. Bacterial pneumonia is commonly caused by Streptococcus pneumoniae (pneumococcus), and it is important for patients to get the pneumococcal vaccine for prevention.

Community-Acquired Pneumonia (CAP) Treatment Recommendations
Pharmacists can ensure that patients receive appropriate treatment for community-acquired pneumonia (CAP), which is acquired outside of the hospital setting. The CAP treatment guidelines were recently updated to recommend amoxicillin as a first-line agent unless patients have a penicillin allergy. Healthy outpatient adults with CAP who do not have underlying health conditions or risk factors for antibiotic resistant pathogens should receive 1 of the following treatments: amoxicillin 1 g 3 times daily (first line), or doxycycline 100 mg twice daily, or a macrolide (azithromycin 500 mg on the first day then 250 mg daily, or clarithromycin 500 mg twice daily, or clarithromycin extended release 1000 mg daily).

Evidence suggests that pneumococcal resistance (over 30%) can be associated with macrolides so this should be taken into consideration when selecting CAP treatments. Pharmacists should also educate patients about cardiac risks associated with azithromycin, including QTc prolongation, and assess for any potential drug interactions.

Patients with CAP and comorbidities should receive broader spectrum treatment in the outpatient setting. Combination therapy with amoxicillin/clavulanate or a cephalosporin (cef-podoxime, cefuroxime) and a macrolide (azithromycin, clarithromycin) or doxycycline should be started for initial treatment. Reserve fluoroquinolone monotherapy (levofloxacin, moxifloxacin, or gemifloxacin) for patients with drug-resistant CAP or ß-lactam allergies.

Individuals hospitalized with CAP will typically need combination therapy with a ß-lactam (ampicillin plus sulbactam, or cefotaxime, ceftriaxone, or cefpodoxime) and a macrolide. Fluoroquinolone monotherapy (levofloxacin or moxifloxacin) can also be used. Patients with contraindications to macrolides and fluoroquinolones can receive combination therapy with a ß-lactam and doxycycline.

Hospital-Acquired Pneumonia (HAP) and Ventilator-Associated Pneumonia (VAP)
Nosocomial pneumonia, or hospital-acquired pneumonia (HAP), may occur during a hospital stay, and patients may experience ventilator-associated pneumonia (VAP) after being on a ventilator. Melissa Santibañez, PharmD, BCCCP, a critical care pharmacist and an assistant professor in the department of clinical and administrative sciences at Larkin University College of Pharmacy in Miami, Florida, said that patients can present to the intensive care unit (ICU) with pneumonia due to any causative organism, including bacterial, viral, and fungal. Patients admitted to critical care units are also more likely to have complicating comorbidities, baseline immunosuppression, or other risk factors for multidrug-resistant organisms (eg, mechanical ventilation, indwelling venous catheters, parenteral nutrition, renal replacement therapy, or nursing home residence).

“The pharmacists’ role in these cases is essential, as they can ensure that patients receive ventilator pneumonia precaution order sets and that certain medications are being replaced regularly to prevent bacterial colonization (eg, administration lines for propofol and lipids),” said Santibañez. Pharmacists can play an integral role in proper antimicrobial prophylaxis against expected opportunistic infections for immunocompromised patients. “If a patient has been...
Adult Pneumococcal Vaccine Recommendations

Pharmacists should consult the CDC’s PneumoRecs VaxAdvisor free mobile app as a point-of-care resource to determine which pneumococcal vaccines patients require.

Adults aged 19–64 years (not previously vaccinated)

- Patients with cerebrospinal fluid leaks or cochlear implants should receive 1 dose of pneumococcal conjugate vaccine (PCV13 or Prevnar13) followed by a dose of pneumococcal polysaccharide vaccine (PPSV23 or Pneumovax 23) at least 8 weeks later.

Immunocompromised adults aged 19–64 years (not previously vaccinated)

- Conditions: sickle cell disease or other hemoglobinopathies, asplenia, congenital or acquired immunodeficiency, HIV infection, chronic renal failure or nephrotic syndrome, cancer (e.g., leukemia, lymphoma, multiple myeloma, Hodgkin disease), iatrogenic immunosuppression (e.g., immunosuppressive drugs, radiation therapy, solid organ transplant)
- Individuals should receive 1 dose of PCV13 first, followed by the first PPSV23 dose at least 8 weeks later. The second PPSV23 dose should be given at least 5 years after the first PPSV23 dose.

Adults aged 19–64 years with the following chronic health conditions (not previously vaccinated) should receive 1 dose of PPSV23:

- Alcoholism
- Chronic heart disease
- Chronic liver disease
- Chronic lung disease (e.g., COPD, emphysema, asthma)
- Diabetes
- Complications from cigarette smoking

Adults 65 years and older without an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak:

- Receive 1 dose of PPSV23
- Updated recommendation to engage in shared clinical decision making regarding PCV13 administration (for individuals who have not previously received the vaccine)
- Patients who received any doses of PPSV23 before age 65 should have 1 final dose at 65 years or older.
- The last dose should be administered at least 5 years after the prior PPSV23 dose.

Adults 65 years or older with an immunocompromising condition, cochlear implant, or cerebrospinal fluid leak (not previously vaccinated):

- Administer 1 dose of PCV13 first.
- Give 1 dose of PPSV23 at least 8 weeks after any prior PCV13 dose and at least 5 years after any prior PPSV23 dose.
- Patients who received any PPSV23 doses before 65 years should receive 1 final vaccine dose at 65 years or older.

For references, visit drugtopics.com.
Awareness of artificial intelligence (AI) is increasing throughout health care. Relative to pharmacy, the American Society of Health-Systems Pharmacists Foundation’s “Pharmacy Forecast 2020: Strategic Planning Advice for Pharmacy Departments in Hospitals and Health Systems” specifically lists the emergence of AI in its report, inspiring industry discussion and guiding the strategic planning processes of health system pharmacy leadership across the country.¹

For pharmacy, AI provides information on drug interactions, drug therapy monitoring, formulary selection, costs, usage trends, and more.

“AI is already transforming health care but will become increasingly valuable as investments in systems that can capture and manage data are made and clinical informatics entities work more collaboratively to address current data shortfalls,” said Doug Zurawski, PharmD, senior vice president of clinical strategy at Kit Check, Inc, maker of radio frequency identification (RFID)/AI technology for hospital pharmacies to help with medication management. “It is incumbent upon us, in this industry and in this field, to take the lead and learn more, invest in systems that support AI and machine learning, and prepare for the future with access to artificial intelligence.”

Deborah Sadowski, MHA, RPh, director of pharmacy services at Deborah Heart and Lung Center in Browns Mills, New Jersey, said IBM estimated back in 2011 that there were over 161 billion gigabytes of data in the entire health care arena, which she projects has easily doubled by now.

“It is impossible to manage that much information safely and efficiently with the human mind, so it is essential that we incorporate AI as a tool to help us better care for patients—be it preventing medication errors, managing pharmacogenomics applications for better medication choices, or doing prospective cost analysis for treatment choices—all by processing billions of bits of information efficiently and quickly,” she said. “It is key to remember however that AI is a tool to supplement knowledge and should be used in conjunction, not a replacement for, the clinical judgment and human experience that the pharmacist or other health care provider brings to the table.”

Vin Singh, MBA, MS, the CEO of Gaithersburg, Maryland–based BullFrog AI Holdings, Inc, a precision pharmaceutical company built around an AI platform, noted that pharmaceutical companies have been plagued for years with vast amounts of data, but most do not have the proper technologies to analyze it all.

“We are seeing more and more pharmaceutical companies looking to leverage AI and machine learning solutions to translate their data into therapies that have a better chance of benefiting patients,” he said. “By combining experts in machine learning and AI with subject matter experts in pharmaceutical and health industries, we can approach it with an open mind and share strategies from a multifunctional perspective.”

Wolf Ruzicka, MBA, chairman and IT innovator for Washington, DC–based EastBanc Technologies, said AI can be used to search for similar chemical molecules to already known drugs in huge existing databases.

A new application is to use AI technologies to analyze large clinical trial data sets to link certain responses and adverse effects to individual genetic markers.

“The goal is to find new drugs with similar treatment properties but less expensive or with less [adverse effects],” he said. “As a result, we can determine which patients could be treated successfully, in some cases life-saving, while for other patients the drug may not be useful.”

New AI Tools
AI represents an innovative way in which entrepreneurs and health care professionals are reinventing the US health care system to better serve patients, which is why many in the pharmacy industry are embracing AI offerings today.

Health care technology company DrFirst recently released its next-generation, patented SmartSig AI technology to improve the quality of patient medication history when it is imported into hospitals’ and health systems’ electronic health records (EHRs).

SmartSig 2.0 accurately translates...
nearly 93% of incoming prescription information, saving up to 30 seconds of work for each drug entered during the medication reconciliation process.

Rebecca Sulfridge, PharmD, an emergency medicine clinical specialist with Covenant HealthCare in Saginaw, Michigan, credits the new technology with helping to minimize additional patient risks and protecting staff from unnecessary face-to-face exposure during the coronavirus disease 2019 (COVID-19).

“We are spending less time reconciling medication histories manually, and in the first month of use, we recaptured an additional 15% productivity per shift, which represents approximately $650,000 per month, while also improving patient safety and outcomes,” she said.

Tom Knight, MBA, MS, the CEO of Invistics Corp, a Peachtree Corners, Georgia–based software company working with AI, explained that machine learning is being used to create drug diversion prevention software solutions that are self-learning.

“This is very important to pharmacies and health care facilities as they work to detect and prevent employees from stealing medications, also known as drug diversion,” he said. “Machine learning allows solutions to learn from past diversion incidents, so they become better and better at detecting potential diversion incidents.”

For example, machine learning technology can pick up on isolated incidents that are aligned with known patterns of diversion, such as if a pharmacist is filling prescriptions for oxycodone 3 times more frequently than their colleagues, and synthesize that information with other data, such as reports of suspicious activities from pharmaceutical technicians, and create alerts for managers, or drug diversion specialists. Therefore, drug diversion incidents that might have taken weeks to discover before can be found in hours.

Kara Earle, MBA, MS, senior drug diversion specialist at FairWarn, which works with hospital pharmacies on their drug diversion programs by using AI to help prevent new diversion cases, said she’s seeing a strong push from pharmacies looking to replace older technologies that require manual processes with new, AI-powered technology to streamline workflows.

For example, Mount Sinai in New York, New York, employs FairWarning’s Drug Diversion Intelligence to monitor all daily transactions and detect irregular behavior such as unusual access of controlled substances, medication access after termination, and inventory discrepancies.

“AI has the ability to handle large quantities of data and cross-reference data from multiple systems, so it helps to automate manual steps and increase visibility into the movement of medications to create a broader monitoring picture,” Earle said.

A Look Ahead
Although the impact of AI is growing, Zurawski noted that a lack of standardization in EHRs and regulatory hurdles sometimes hinder access to sufficient volumes of reliable data to effectively inform advanced computing applications.

In the years ahead, he believes clinical informatics, vendor cooperation, and collaboration will help address some of the gaps in data access.

Earle noted AI will continue to evolve, and models will become more effective at identifying diversion before major problems arise.

“The goal is to prevent diversion from happening at all, and employing AI-powered technology is a huge step toward this goal—it can catch policy violations and program loopholes before a diversion even occurs,” she said. “For instance, incorrectly provisioned security settings on dispensing cabinets, users not following proper wasting procedures, or nurse managers failing to follow up on open discrepancies are all typical policy violations that may indicate diversion. Identifying those policy gaps early can prevent diversion and save lives.”

said. “The benefits that AI can bring to help tackle the COVID pandemic have yet to be fully realized, and it has the potential to serve as a valuable and irreplaceable tool. Global infectious disease challenges will continue to spawn, and having AI tools that can prevent or minimize the damage to public health is essential.” Additionally, the change in workflows during COVID-19, such as staff assignments and the addition of contract, travel, and float nurses, have made manual monitoring methods almost obsolete.

“Pharmacies need the ability to track medication usage across departments, and even system-wide and near to real time as possible, which AI is capable of accomplishing,” Earle said. “One of our Drug Diversion Intelligence customers was able to identify diversion and medication tampering by a travel nurse who was hired during COVID-19 within 10 days.”
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Prevent Medication Errors in Autoimmune Disease

Pharmacists can play an important role in educating patients about autoimmune drugs to prevent medication errors. By Jennifer Gershan, PharmD, CPh

Autoimmune diseases affect more than 24 million individuals in the US, and the most common conditions are type 1 diabetes, multiple sclerosis (MS), lupus, inflammatory bowel disease (IBD), and rheumatoid arthritis (RA). Pharmacists can play a vital part of patient care by educating individuals about their autoimmune therapies to prevent drug-related problems at home. Evidence demonstrates that pharmacists can also decrease medication-related errors after hospital discharge and reduce emergency department visits.

Autoimmune Drug Medication Errors and Counseling Pearls

**Methotrexate**

According to the National Coordinating Council for Medication Error Reporting and Prevention, “a medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.” Methotrexate (Rheumatrex) is prescribed for RA and psoriasis, and it is critical to ensure proper dosing and patient education for this medication to prevent adverse events. Dosing of methotrexate for RA or psoriasis is once weekly as low-dose therapy, but is generally administered daily when used for cancer treatment. Harmful or fatal errors with low-dose oral methotrexate have been reported to the Institute for Safe Medication Practices (ISMP), with the most common involving accidental daily dosing intended for weekly administration. Therefore, ISMP considers methotrexate a high-alert medication in both the hospital and community settings. Patients should receive both verbal and printed instructions emphasizing the importance of once per week dosing for methotrexate prior to hospital discharge. ISMP’s ConsumerMedSafety.org website includes a free educational handout. Pharmacies can also dispense methotrexate as a weekly dose pack. Patients should pick a day of the week that they will be taking methotrexate, and the pharmacy can include this with the instructions.

**NSAIDs**

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often used to reduce pain associated with RA or lupus. Educating patients to read the OTC product’s Drug Facts label is important to ensure they are not taking multiple NSAID products, which can lead to an increased risk of gastrointestinal bleeding. Corticosteroids are generally used for RA, IBD (short term), and lupus. Patients should avoid abruptly stopping therapy if they have been taking these medications for 3 or more weeks as they need to be tapered slowly to prevent disease flares and adrenal insufficiency.

**Other Common Autoimmune Therapies**

Levothyroxine (Synthroid) is commonly used to treat hypothyroidism, which can be caused by the autoimmune condition Hashimoto disease. Patients should be counseled to take levothyroxine on an empty stomach 30 to 60 minutes before breakfast for optimal absorption. Also, certain medications including calcium, antacids, and iron can bind to levothyroxine and potentially reduce the efficacy, so they should be separated by at least 4 hours.

Insulins used for type 1 diabetes are considered high-alert medications, and it’s important that patients know their dose to prevent administration errors. The U-500 insulin is concentrated and contains 5 times more insulin per ml than standard insulin. Patients should also be cautioned about severe worsening of MS after stopping the medication fingolimod (Gilenya). It is important for patients to consult their pharmacist and physician prior to discontinuing the therapy.

For references, visit drugtopics.com.
A Look at the Year in GENERICS

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A Look at the Year in Generics

Notable generics have entered the market in the past year, but more can be done to improve access and affordability.  

By Keith Loria

The generic pipeline continues to provide significant value to payers and patients as key products in top therapeutic classes lose patent protection.

Matt Gibbs, PharmD, president of commercial markets for Capital Rx, Inc, said although the second generic wave peaked in 2018, many impactful generics entered the market over the past 12 months—most notably, the launch of multiple generics for pregabalin (Lyrica; Pfizer) in July 2019.

“Because there wasn’t a single generic with a 180-day exclusivity period, it resulted in an immediate significant price drop for payers and patients,” he said. “Fourth quarter 2019 also saw the first generic for popular contraceptive NuvaRing enter the market, providing patients who prefer a non-hormonal contraceptive a generic option. This will also benefit payers providing $0 contraceptive coverage to their members under the Affordable Care Act, as brand NuvaRing is a key driver of plan spend in the contraceptive category.”

Early 2020 saw the return of generics to the market for albuterol rescue inhalers ProAir HFA and Ventolin HFA. Generic albuterol inhalers utilizing chlorofluorocarbon propellants existed in the market by the late ’90s, but the requirement to change to alternate propellants shifted these products back to brands. “The availability of generics in the class will benefit both patients and plans in mitigating spend in the asthma category,” Gibbs said.

He feels the biggest notable generic coming in 2020 is the availability of generic emtricitabine/tenofovir (Truvada; Gilead) for use in HIV preexposure prophylaxis (PrEP).

“As plans begin to implement $0 ACA coverage for PrEP, the availability of generic Truvada will significantly decrease overall cost to plans as we see awareness of and access to PrEP improve across the US,” Gibbs said. “This improved awareness and focus on access to PrEP is one step in the global and US goals of getting to zero new HIV transmissions by 2030.”

Slow to Develop

Ryan Schmidt, associate director of formulary services for Madison, Wisconsin—based Navitus Health Solutions, says that overall, the generic market this past year has been relatively slow.

“There haven’t been many blockbuster generic releases, and the ones that hit the news are generally ‘authorized generics,’ where the manufacturer of the generic product either has an agreement with the brand manufacturer, or in some instances is the brand manufacturer,” he said. “The other thing that limits impact of these releases is a lot of them have come from classes with multiple alternative generic options already meaning the amount of use in the brand space has been limited.”

Ross Goetz, PharmD, director of business development and national pharmacy compliance administrator for Healthcare4U.com, noted that digital companies with direct-to-consumer models have increased access to generic medications at an affordable price, making generic drugs more desirable to the consumers opting to manage their own cost portfolio.

Still, when referring to abbreviated new drug application (ANDA) approvals, or first-time approvals of generic drugs, he calls 2020 “a weak year,” citing a few HIV therapies pending generic launch, and the generic for varenicline (Chantix; Pfizer), which has been delayed since the initial date. At press time, the FDA has so far approved 35 first-time generics. In 2019, the FDA approved 107 first generic drugs out of a total of 1014 approved or tentatively approved ANDAs, according to the 2019 Office of Generic Drugs annual report.

Shashank Upadhye, JD, a pharmaceutical patent attorney with Chicago, Illinois—based Upadhye Cwik LLP, who has practiced in generic drug law for more than 20 years, said it’s been a tough year for companies that are in just traditional, simple solid oral dosage forms.

An exception, he noted, is Mylan, which obtained recent approval for its biosimilar for insulin glargine—called Semglee, which is a biosimilar to Sanofi’s Lantus insulin.

“Mylan had won some patent litigation and thus had removed the patent obstacle. But it finally won FDA approval for its pen and vial product,” he said. “Mylan [and its production partner Biocon] had some troubles getting approval. It is a complex product, and thus it was not a question of simply copying the Lantus product. Now patients have new options, with hopefully better pricing, now that the FDA has approved more insulins.”

Financial Matters

The most notable generic products, Schmidt shared, have not had the major financial impact one would typically expect over the last year.

“Generic insulin products offer significant price decreases for those...
Generic IR formulations. The study cost savings of $2.6 billion by switching Medicaid beneficiaries, in which the burden associated with extended-release (ER) versus immediate-release (IR) formulation among Medicare and Medicaid beneficiaries, in which the findings showed a potential annual savings for greater access to generic medications are quite significant. Experts agree that there is an unmet need for more less expensive, generic versions of complex medications in the market.

Significant savings to payers and the federal government from approving more generic versions of complex medication could be realized; Bob Lobo, PharmD, director of clinical programs at Vanderbilt University Medical Center, Nashville, Tennessee, told Drug Topics® in a previous interview. He cited a recent study on the economic burden associated with extended-release (ER) versus immediate-release (IR) formulation among Medicare and Medicaid beneficiaries, in which the findings showed a potential annual cost savings of $2.6 billion by switching certain ER drugs to comparable generic IR formulations. The study looked at only 20 ER oral medications, but it suggests that the annual savings from greater access to generic medications are quite significant.

According to Schmidt, the drug with one of the largest effects on spending in the past 12 months has been pregabalin, the generic equivalent to Lyrica.

There were multiple manufacturers ready to go at launch, meaning costs for the generics were significantly lower than the brand at launch,” he said. “This is important as it helps patients without insurance, reducing prices to where they were back in 2012,” he explained. “However, rebates offered on the original brand products still make the brand medications less expensive to plans in most situations, meaning we haven’t seen these have impact on overall spend.”

Similarly, a number of generic inhalers have come to market for common products such as Advair, Symbicort, Proair, and Ventolin. Although the increased competition has had some impact on overall spending, major savings opportunities haven’t risen yet, as the complexity of these devices have prevented a scenario where multiple low-cost generic products are available.

Experts agree that there is an unmet need for more less expensive, generic versions of complex medications in the market.

“There were multiple manufacturers ready to go at launch, meaning costs for the generics were significantly lower than the brand at launch,” he said. “This is important as it helps drive down patient cost, regardless of copay or coinsurance, helping to facilitate conversion to the generic product, saving both the patient and the plan money right away.”

Conversely, ramelteon, Rozerem’s equivalent, was first released at a similar time, but due to lack of competition in the market, has retained a higher cost relative to other generic medications in the class.

“Pregabalin has dropped in price by over 95% compared with brand Lyrica, [which also took an approximately 5% price increase on January 1, 2020,] and is covered nearly universally,” Schmidt said. “Ramelteon, on the other hand, still costs close to $100 per month.”

Goetz agreed that pregabalin has been the most significant generic over the past year.

“When you look into medications for nerve pain, there is not a great depth of options. Outside of narcotic pain medications, gabapentin stood as the most cost-effective option,” he said. “Although gabapentin comes tied with challenges like a notable [adverse effect] profile, it is often the drug of choice on insurance formularies. For those who rely on their insurance coverage to afford medications, paying for brand name Lyrica was simply not an option. Now available as generic pregabalin, patients can more comfortably elect to switch away from gabapentin without a major cost burden, if any.”

**A Shifting Market**

Due to the coronavirus disease 2019 (COVID-19), the FDA has stopped conducting foreign inspections. Given that more than 80% of the generic drugs sold in the United States are made outside the country, the lack of inspections has resulted in delayed or aborted new generic drug launches.

Upadhye said COVID-19 has caused several problems, including decreased profitability for existing generic companies’ products; increased price pressures by the buyers who themselves are facing business pressures; pressures on existing patent litigation to either do very little to advance the case or to settle the case quickly on whatever terms being offered; and the FDA’s refusal to conduct foreign inspections, resulting in delayed or aborted new generic drug product launches or delays in relaunches.

It’s not a surprise that the pandemic is affecting the generic drug market, as when the disease was spreading rapidly in March, there was a major rush to refill medications, leading to a large increase in claims and even shortages. This was immediately followed by a drop-off in overall claims volume, which is now returning closer to normal.

“One major shift is from 30-day claims to more patients getting 90-day supplies via delivery or mail order,” Schmidt said. “The interesting component of this is that maintenance medications seem to have rebounded well, whereas acute medications aren’t rebounding quite as quickly. This isn’t as surprising, as many elective clinical visits are being delayed, and general improved health precautions are likely leading to less non-COVID infections.”

From a new product perspective, the FDA is still in full swing, and the industry has continued to see new approvals of both brand and generic products. The impact of these new releases may be seen a couple of years down the road as some clinical trials have gone on hold or been delayed due to COVID-19.

Goetz believes the market is shifting heavily toward convenience and safety over price alone.

“Utilization of telehealth services reached an all-time high in April 2020, while ambulatory prescriber practices were down roughly 60% in office visits,” he said. “Now that patients are more aware of the options available, it can be expected that they will consider the financial and personal impact of each option as they weigh their plans for their future. As we have seen with many areas of modern commerce, the power is no longer with the large chains with storefronts in every area; it falls with the companies who can provide a service at a fair price, with a larger focus on convenience than ever before.”

For references, visit drugtopics.com.
Biosimilars May Lead to Improved Competition and Lower Costs

How will biosimilars continue to affect the prescription product market in 2021? By John Schieszer

Biosimilars, which offer the potential for more treatment options and less expensive alternatives, are having a good year in 2020 and may have a significant impact on the prescription product market in 2021. With the approval of more biosimilar medications, experts hope that greater competition may occur and help lower overall costs. “As intellectual property protections for biological products continue to expire in the US, we can expect many more applications for potential biosimilar and interchangeable products, and increased uptake of approved products too,” said Sarah Yim, MD, the director of the Office of Therapeutic Biologics and Biosimilars at the FDA’s Center for Drug Evaluation and Research, in Bethesda, Maryland.

Some of the key issues affecting biosimilar uptake involve reimbursement factors and insurance coverage, according to Yim. However, she said, business and intellectual property concerns also have contributed to the delayed launch of some FDA-approved biosimilars. In 2009, the Biologics Price Competition and Innovation Act created an abbreviated regulatory pathway for biological products demonstrating to be biosimilar or interchangeable with an FDA-approved drug. Since then, the FDA has approved biosimilar medications to treat a host of conditions, including cancer, colitis, Crohn disease, rheumatoid arthritis, and psoriasis.

Biologics are medicines that generally come from living organisms, which include animals and microorganisms (yeast and bacteria). A biosimilar is defined by the FDA as a biologic that has no clinically meaningful differences from another biologic that is already FDA approved. Biosimilars are made with the same types of natural sources as the original medication and are delivered the same way. They have the same strength and dosage and the same potential adverse effects.

The FDA has outlined 4 key strategies in its Biosimilars Action Plan (BAP) to accelerate biosimilar competition. The 4 strategies are:

1. Improve the development and approval process for biosimilar and interchangeable products.
2. Maximize scientific and regulatory clarity for the developers of biosimilar products.
3. Improve the understanding of biosimilars among patients, clinicians, and payers.
4. Support market competition by reducing gaming of FDA requirements and other attempts to unfairly delay competition.

Right now, there are 28 FDA-approved biosimilar products, and 17 are on the market. “We have seen a jump in the past year of launched products. In addition, the biosimilars that are on the market have typically launched with initial list prices 15% to 35% lower than the list prices of the reference products,” Yim said.

Over the next 6 to 18 months, the landscape will be evolving for biosimilar and interchangeable insulin products and other transition biological products. Under new regulations, insulin and other biological products such as human growth hormone (somatropin), pancrelipase, choricion gonadotropin, follitropin alfa, and menotropins are regulated by the FDA in biologics license applications. This means that manufacturers can submit marketing applications for proposed biosimilar and interchangeable products that reference transitioned biological products. “If approved, these products will help bring competition to those markets, and patients may have more affordable access to the medications they need,” Yim said. “I am hopeful that we will see the FDA’s first interchangeable biosimilar product during the time period [6 to 18 months].”

Once an interchangeable product is approved and available on the market, Yim said it can then be substituted for the reference product without the intervention of the prescriber. It is hoped that this will lead to increased access and lower costs for patients. There are more than 80 biosimilars in the development pipeline. Five biosimilars have been approved in the last year, with adalimumab-fkjp (Hulio) and pegfilgrastim-apgf (Nyvepria) most recently approved (Table 1).

Sandoz Inc has 8 approved biosimilars worldwide and 4 in the United States. Sheila Frame, the vice president of marketing, market access, and patient services at Sandoz in Princeton, New Jersey, said reimbursement...
policies do not support the use of biosimilars, and despite progress in certain therapeutic areas, some hesitancy remains among many clinicians to switch to a biosimilar. "To realize the full promise of biosimilars in the US, we need to support policies that increase their adoption and help create a more balanced and competitive marketplace," Frame told Drug Topics®.

She said that within Medicare Part D, Sandoz supports reducing administrative burdens for patients and providers by removing redundant prior authorization for a biosimilar when one has been granted for the reference biologic. Widespread adoption of biosimilars in clinical practice has faced headwinds, in part because of targeted misinformation campaigns, Frame said.

"We are encouraged by action from the FDA and the FTC [Federal Trade Commission] to combat pervasive misinformation, but it is the responsibility of all stakeholders to challenge biosimilar disparagement and misinformation when encountered. Clear and unbiased scientific messaging is crucial to helping patients and clinicians better understand the value of biosimilars," Frame said. She added that the cost savings from biosimilar medicines could be enormous, saving the US health care system billions of dollars in the coming years.

Andrew Powaleny, director of public affairs at the Pharmaceutical Research and Manufacturers of America in Washington, DC, said the rich pipeline of biosimilar products in development and market experience suggest there still is significant potential for cost savings in the marketplace.

A recent analysis of the market dynamics of 4 biologics and their biosimilars demonstrated that the net prices of all the originator biologics decreased following the entry of biosimilars. In the Medicaid program, discounts increased by between 20.1 and 35.2 percentage points. "As the market experience with biosimilars increases, we expect product usage to play an expanded role in options for patients and further decrease prescription drug spending. Experts have argued that the coming wave of biosimilars will penetrate the market even more quickly than those already available for patients," Powaleny said.

**COVID-19 Pandemic and Prescription Drug Costs**

Currently, the coronavirus disease 2019 (COVID-19) pandemic is crippling the economy. Frame said everyone is looking toward rebuilding, so any and all cost savings are on the table. "Supporting and advancing policies that increase access and use of lower-cost biosimilars can help," she said.

At the University of California, San Francisco (UCSF), Health, leadership has endorsed the adoption of biosimilars for clinical care, according to Candy Tsourenouis, PharmD, a professor in the department of clinical pharmacy at the UCSF School of Pharmacy. As a member of the department’s Medication Outcomes Center, Tsourenouis is involved in providing evidence-based reviews of recently approved prescription medications and performing medication utilization analyses for UCSF Health. She said the endorsement of biosimilars aligns with the national adoption of biosimilars across health systems to ensure safe and cost-effective therapies are available.

"We anticipate significant cost savings while maintaining high-quality care and ensuring similar clinical outcomes. Over the next 6 to 18 months, we hope to show similar clinical outcomes but with significant reductions in drug spending, not only within UCSF Health, but also more broadly for UC Health," which oversees and provides strategic direction across all 6 health systems, including UCSF Health, Tsourenouis told Drug Topics®.

Brian Komoto, PharmD, past president of the California Pharmacists Association in Visalia, California, said biosimilars could help improve patient access and reduce copays. "Hopefully, physicians are receptive and the use of biosimilars can increase," Komoto told Drug Topics®. "This should also allow pharmacies that are not able to get contract pricing, the ability to work with manufacturers of biosimilar products."

Francis B. Palumbo, PhD, JD, a professor and executive director at the University of Maryland School of Pharmacy’s Center on Drugs and Public Policy in Baltimore agrees that at this time clinician acceptance is vital. The trend appears positive, and it seems that biosimilars are having a significant impact in terms of patient access and lowering overall costs. 'Biosimilars are now being approved at an increasing pace and have most likely reached some level of critical mass where they can exert real influence on the market,' Palumbo told Drug Topics®.

For references, visit drugtopics.com.
The Pharmacist’s Role in Generic Substitution

By Karen Berger, PharmD

The FDA reports that in 2019, 9 out of 10 prescriptions filled in the United States were for generic drugs.¹ This places pharmacists in a unique position to recommend cost-saving generics and counsel patients on generic substitution.

Jennifer Palazzolo, RPh, pharmacist-in-charge and owner of Flatirons Family Pharmacy in Longmont, Colorado, feels that pharmacists can play an important role in helping patients with generics. “In the day of electronic prescriptions, patients often have no idea what is sent to the pharmacy and often have sticker shock when the prescription is not covered or has a high copay.” Palazzolo recommended that “the best thing to do in this case is to reach out to the patient before proceeding with filling an expensive brand-name prescription. There are often acceptable generics available that are cost-saving to the patient and health care as a whole, and the pharmacist can teach patients to advocate for themselves if the cost of medication is an issue.”

Palazzolo often educates patients on generics, beginning with OTC products. For example, if a patient is asking for a recommendation and reaching for the brand-name product, Palazzolo will explain to the patient that the generic contains the same active ingredient and will have the same therapeutic outcome. Palazzolo said, “Sure, there are times the patient can’t get past the pretty packaging, but 9 times out of 10, once explained, the patient will opt for the cost-saving option.”

She finds that in conversation, patients will sometimes share the economic burden of copays. If a patient is requesting a brand-name product when a generic is available, she asks why in a nonconfrontational way, and explains that it may not be covered or may be very expensive. Often, the patient simply doesn’t want medication from another country. Palazzolo takes the opportunity to educate patients on the manufacturing processes and quality assurance practices, as well as the standards generics have to follow. Once she does this, the patient often feels more comfortable trying the generic, as long as they know they can still switch back to brand if need be, which they rarely do.

Wendi Medved, PharmD, pharmacist-in-charge and owner of Coast to Coast Compounding in Golden, Colorado, takes the time to look for opportunities to save patients money with generics. She recommends pharmacists review patient profiles to look for possible generic substitutions, and reach out to patients and their prescribers for a new prescription, “keeping in mind federal and state laws, and which medications are listed in the Orange Book as Narrow Therapeutic Index (NTI) medications.” She also looks for additional opportunities to save the patient even more money.

Medved stressed the importance of keeping an open line of communication with patients, and letting the patient be involved in the decision-making process. This way, she said, the patient is not surprised or taken aback by a medication that appears different.

She also noted that pharmacists should recognize the difference between generic substitution and therapeutic interchange, as a therapeutic interchange using a generic product in place of a brand can save a significant amount of money.“Drugs in therapeutic interchange programs should be targeted based on scientific evidence for similar levels of clinical effectiveness and positive medical outcomes,” she said. For example, the physician may prescribe a newer, brand-name hypertension drug, but a drug in the same class that is available in generic form may work just as well for treating the patient’s hypertension. In the community pharmacy setting, Medved suggests initiating a conversation with both the patient and prescriber about the possibility of a therapeutic interchange.

By helping patients save money, pharmacists can help them improve adherence and outcomes, and avoid complications and hospitalizations.

REFERENCE

A Partnership to Optimize Medication Use and Patient Outcomes

Initiative promotes adoption of value-based care models in community pharmacy settings.

By Todd D. Sorensen, PharmD and Carrie Martin Blanchard, PharmD, MPH

Outcomes-based programs, also sometimes referred to as value-based programs, focus on quality of care, rather than quantity of patient visits, to encourage providers to deliver interventions that improve patient care and outcomes.

HealthPartners (HP), a regional health plan based in Minnesota, embodies this “pay for value” philosophy through its Partners in Excellence (PIE) program. Pharmacists are eligible to participate in the medication therapy management (MTM) program by providing comprehensive medication management (CMM), as defined by the CMM patient care process, encounters, and value-based compensation through clinical performance and engagement performance metrics.

The HealthPartners’ PIE program is a performance and recognition program for physicians, medical groups, and pharmacies that achieve top marks in patient-centered metrics including health, experience, and affordability. The health plan evolved and expanded its MTM program after internal analyses demonstrated a significant return on investment when high-risk patients receive CMM services. Pharmacy providers are eligible for performance-based payments associated with achievements in blood pressure control, diabetes control (A1C), and a tobacco-free lifestyle. Pharmacy entities meeting performance benchmarks for clinical metrics are then eligible for a second-tier performance payment based on plan member engagement in CMM services.

HP views community pharmacists as an integral part of building a strong network of CMM providers for patients; however, these pharmacists often experience competing priorities and unique barriers that limit participation.

The Slice of PIE initiative is a collaborative effort between HP, the University of Minnesota (UMN), the University of North Carolina (UNC), and the Alliance for Integrated Medication Management designed to improve and increase delivery of CMM within the HP CMM provider network. Twelve Minnesota community pharmacy organizations, representing over 100 pharmacies, are engaged in the initiative. Implementation supports that help expand patient access include lists from HP identifying patients in most need of CMM interventions, a community of learning that connects participants across the initiative, frequent meetings with implementation coaches, monthly learning events (webinars), and additional strategies designed to help support expansion of patient access.

Slice of PIE will investigate research questions defined under 3 separate study aims. First, the initiative will evaluate the effectiveness of the learning collaborative as an implementation strategy to drive the adoption and sustainability of CMM delivery. The second aim will be to rigorously evaluate the implementation inputs and patient outcomes of initiating the PIE program in community pharmacies. Third, the research team will determine the clinical effectiveness and sustainability of the interventions delivered by Slice of PIE participants.

This initiative has the opportunity to change the trajectory of outcomes-based care nationally, thereby allowing patients across the country access to enhanced care and better health outcomes.
Indication for AirDuo RespiClick/Authorized Generic

AirDuo RespiClick is indicated for the treatment of asthma in patients aged 12 years and older. AirDuo RespiClick is only for patients uncontrolled on an inhaled corticosteroid (ICS) or whose disease severity clearly warrants an ICS/Long-acting beta₂-agonist (LABA).

Important Limitation of Use: AirDuo RespiClick is NOT indicated for the relief of acute bronchospasm.

Important Safety Information for AirDuo RespiClick/Authorized Generic

- **Contraindications:** AirDuo RespiClick is contraindicated in:
  - Primary treatment of status asthmaticus or other acute episodes of asthma requiring intensive measures
  - Patients with known severe hypersensitivity to milk proteins or any ingredients of AirDuo RespiClick

Please see additional Important Safety Information and Brief Summary of Full Prescribing Information on the following pages.
AirDuo RespiClick® (fluticasone propionate and salmeterol) Inhalation Powder:

**ASTHMA CONTROL WITH LESS MEDICINE**

Recommended starting dose: 1 inhalation twice daily¹⁻³

<table>
<thead>
<tr>
<th></th>
<th>AirDuo RespiClick</th>
<th>Authorized Generic</th>
<th>ADVAIR DISKUS®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluticasone propionate + Salmeterol</td>
<td>Fluticasone propionate + Salmeterol</td>
<td>Fluticasone propionate + Salmeterol</td>
</tr>
<tr>
<td>Low</td>
<td>55 mcg + 14 mcg</td>
<td>55 mcg + 14 mcg</td>
<td>100 mcg + 50 mcg</td>
</tr>
<tr>
<td>Medium</td>
<td>113 mcg + 14 mcg</td>
<td>113 mcg + 14 mcg</td>
<td>250 mcg + 50 mcg</td>
</tr>
<tr>
<td>High</td>
<td>232 mcg + 14 mcg</td>
<td>232 mcg + 14 mcg</td>
<td>500 mcg + 50 mcg</td>
</tr>
</tbody>
</table>

**IMPORTANT SAFETY INFORMATION for AirDuo RespiClick/Authorized Generic (continued)**

- **Serious Asthma-Related Events – Hospitalizations, Intubations, Death:** Use of LABA as monotherapy (without ICS) for asthma is associated with an increased risk of asthma-related death. Available data from controlled clinical trials also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA monotherapy. When LABA are used in fixed-dose combination with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone.

- **Deterioration of Disease and Acute Episodes:** AirDuo RespiClick should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. AirDuo RespiClick is not indicated for the relief of acute bronchospasm. An inhaled, short-acting beta₂-agonist, not AirDuo RespiClick, should be used to relieve acute symptoms such as shortness of breath.

- **Excessive Use and Use with Other Long acting Beta₂-Agonists:** AirDuo RespiClick should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using AirDuo RespiClick should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol) for any reason.

Please see additional Important Safety Information throughout and Brief Summary of Full Prescribing Information on the following pages.
IMPORTANT SAFETY INFORMATION for AirDuo RespiClick/Authorized Generic (continued)

- **Local Effects of ICS:** Oropharyngeal candidiasis has occurred in patients treated with AirDuo RespiClick. If this occurs, treat with appropriate local or systemic (i.e., oral) antifungal therapy while treatment with AirDuo RespiClick continues, but at times therapy with AirDuo RespiClick may need to be interrupted. Advise the patient to rinse his/her mouth with water without swallowing following inhalation.

- **Immunosuppression:** Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use with caution in patients with the above because of the potential for worsening of these infections.

- **Transferring Patients from Systemic Corticosteroid Therapy:** Particular care is needed for patients who have been transferred from systemically active corticosteroids to ICS because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available ICS. Taper patients slowly from systemic corticosteroids if transferring to AirDuo RespiClick.

- **Hypercorticism and Adrenal Suppression** may occur with high doses of ICS, including fluticasone propionate, or at the recommended dose in susceptible individuals. If such changes occur, discontinue AirDuo RespiClick slowly.

- **Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors:** The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, ketoconazole) with AirDuo RespiClick is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

- **Paradoxical Bronchospasm and Upper Airway Symptoms:** If paradoxical bronchospasm occurs, discontinue AirDuo RespiClick immediately and institute alternative therapy.

- **Hypersensitivity Reactions, Including Anaphylaxis:** Immediate hypersensitivity reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of AirDuo RespiClick. Discontinue AirDuo RespiClick if such reactions occur.

- **Cardiovascular and Central Nervous System Effects:** Salmeterol, a component of AirDuo RespiClick, can produce clinically significant cardiovascular effects in some patients as measured by pulse rate, blood pressure, and/or symptoms. If such effects occur, AirDuo RespiClick may need to be discontinued. AirDuo RespiClick should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

- **Reduction in Bone Mineral Density (BMD):** Decreases in BMD have been observed with long-term administration of products containing ICS. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

- **Effect on Growth:** ICS, as well as poorly controlled asthma, may cause a reduction in growth velocity, and the long-term effect on final adult height is unknown. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma. Monitor growth of pediatric patients.

- **Glauccoma and Cataracts:** Long-term use of ICS, including fluticasone propionate, a component of AirDuo RespiClick, may increase the risk for cataracts or glaucoma. Regular eye exams should be considered.

- **Eosinophilic Conditions and Churg-Strauss Syndrome:** Systemic eosinophilic conditions, such as Churg-Strauss syndrome, may occur. Be alert to eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, and/or neuropathy.

- **Coexisting Conditions:** Use with caution in patients with conivulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

- **Hypokalemia and Hyperglycemia:** Beta-adrenergic agonist medicines may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects.

Please see additional Important Safety Information on the previous pages and Brief Summary of Full Prescribing Information on the following pages.
AirDuo RespiClick® (fluticasone propionate and salmeterol) Inhalation Powder:

**ASTHMA CONTROL WITH LESS MEDICINE**

Not all strengths are depicted above. Additional strengths of AirDuo RespiClick and its authorized generic are 55/14 (fluticasone propionate 55 mcg and salmeterol 14 mcg) and 232/14 (fluticasone propionate 232 mcg and salmeterol 14 mcg).

<table>
<thead>
<tr>
<th>Total Daily Dose¹-³</th>
<th>AirDuo RespiClick</th>
<th>Authorized Generic</th>
<th>ADVAIR DISKUS®</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluticasone propionate + Salmeterol</td>
<td>Fluticasone propionate + Salmeterol</td>
<td>Fluticasone propionate + Salmeterol</td>
</tr>
<tr>
<td>Low</td>
<td>110 mcg + 28 mcg</td>
<td>110 mcg + 28 mcg</td>
<td>200 mcg + 100 mcg</td>
</tr>
<tr>
<td>Medium</td>
<td>226 mcg + 28 mcg</td>
<td>226 mcg + 28 mcg</td>
<td>500 mcg + 100 mcg</td>
</tr>
<tr>
<td>High</td>
<td>464 mcg + 28 mcg</td>
<td>464 mcg + 28 mcg</td>
<td>1000 mcg + 100 mcg</td>
</tr>
</tbody>
</table>

ADVAIR DISKUS® is a registered trademark of the GSK group of companies. Table is intended to show differences in dosing only and should not be construed to imply safety or efficacy similarities or differences.

**IMPORTANT SAFETY INFORMATION for AirDuo RespiClick/Authorized Generic (continued)**

- **Adverse Reactions:** Most common adverse reactions (reported in greater than or equal to 3% of patients) include nasopharyngitis, oral candidiasis, headache, cough and back pain

Please see Important Safety Information on the previous pages and Brief Summary of Full Prescribing Information on the following pages.

**References**


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BRIEF SUMMARY OF PRESCRIBING INFORMATION FOR AIRDUO® RESPICLICK®

(FLUTICASONE PROPIONATE AND SALMETEROL) INHALATION POWDER

FOR ORAL INHALATION AND NEBULIZATION

Initial U.S. Approval: 2000

1 INDICATIONS AND USAGE

AIRDUO® RESPICLICK® is indicated for the treatment of asthma in patients aged 12 years and older. AIRDUO RESPICLICK should be used for patients not adequately controlled on a long term asthma control medication such as an inhaled corticosteroid or whose disease warrants initiation of treatment with both an inhaled corticosteroid and a long-acting beta adrenergic agonist (LABA).

Limitations of Use: AIRDUO RESPICLICK is NOT indicated for the relief of acute bronchospasm.

2 CONTRAINDICATIONS

4.1 Status Asthmaticus

AIRDUO RESPICLICK is contraindicated in the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required (see Warnings and Precautions (5.10)).

5 WARNINGS AND PRECAUTIONS

5.1 Serious Asthma-Related Events – Hospitalizations, Intubations, Death

Use of LABA as monotherapy (without inhaled corticosteroids) for asthma is associated with an increased risk of asthma-related event (see Salmeterol Multicenter Asthma Research Trial [SMART]). The results of SMART also suggest that use of LABA as monotherapy increases the risk of asthma-related hospitalization in pediatric and adolescent patients. These findings are considered a class effect of LABA. When LABA are used in fixed-dose combinations with ICS, data from large clinical trials do not show a significant increase in the risk of serious asthma-related events (hospitalizations, intubations, death) compared with ICS alone (see Serious Asthma-Related Events with Inhaled Corticosteroid/Long-acting Beta-2-Agonists (LABA) With Fixed Dosage Combination).

4 Large, 28-week, randomized, blinded, active-controlled clinical safety trials were conducted to evaluate the risk of serious asthma-related events when LABA were used in fixed-dose combination with ICS compared with ICS alone in subjects with asthma. Three (3) trials included adult and adolescent subjects aged 12 years and older. A trial compared budesonide/formoterol to budesonide, 1 trial compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder, and 1 trial compared mometasone furoate/formoterol to mometasone furoate. The fourth trial included pediatric subjects aged 4 to 11 years and compared fluticasone propionate/salmeterol inhalation powder to fluticasone propionate inhalation powder. The primary safety endpoint for all 4 trials was serious asthma-related events (hospitalizations, intubations, death). A blinded adjudication committee determined whether events were asthma-related. The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in the risk of serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS alone.

Table 1. Meta-analysis of Serious Asthma-Related Events in Subjects with Asthma Aged 12 Years and Older

<table>
<thead>
<tr>
<th>Event Type</th>
<th>ICS/LABA (n = 17,537)</th>
<th>ICS (n = 17,552)</th>
<th>ICS/LABA vs. ICS Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious asthma-related eventa</td>
<td>116</td>
<td>109</td>
<td>1.10 (0.85, 1.44)</td>
</tr>
<tr>
<td>Asthma-related death</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Asthma-related intubation (endotracheal)</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Asthma-related hospitalization (≥24-hour stay)</td>
<td>115</td>
<td>105</td>
<td></td>
</tr>
<tr>
<td>ICS = Inhaled Corticosteroid; LABA = Long-acting Beta-2-adrenergic Agonist.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Randomized subjects who had taken at least 1 dose of study drug. Planned treatment used for analysis.

b Estimated using a Cox proportional hazards model for time to first event with baseline hazards stratified by each of the 3 trials.

c Number of events that occurred within 6 months after the first use of study drug or 7 days after the last day of study drug, whichever date was later. Subjects can have one or more events, but only the first event was counted for analysis. A single, blind, independent adjudication committee determined whether events were asthma related.

The pediatric safety trial included 6,208 pediatric patients aged 4 to 11 years who received ICS/LABA (fluticasone propionate/salmeterol inhalation powder) or ICS (fluticasone propionate inhalation powder). In this trial 27/3,107 (0.9%) of patients treated with ICS/LABA and 21/3,101 (0.7%) of patients treated with ICS experienced a serious asthma-related event. There were no asthma-related deaths or intubations.

5.2 Deterioration of Disease and Acute Episodes

AIRDUO RESPICLICK should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma. AIRDUO RESPICLICK has not been studied in subjects with acutely deteriorating asthma. The initiation of AIRDUO RESPICLICK in this setting is not appropriate.

5.3 Excessive Use of AIRDUO RESPICLICK and Use with Other Long-Acting Beta-2-Agonists (LABA)

AIRDUO RESPICLICK should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medications containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using AIRDUO RESPICLICK should not use another medicine containing a LABA (e.g., albuterol) for treatment of acute symptoms, despite regular twice-daily use of AIRDUO RESPICLICK.

When beginning treatment with AIRDUO RESPICLICK, patients who have been taking oral or inhaled, short-acting beta-agonists on a regular basis (e.g., 4 times a day) should be instructed to discontinue the regular use of these drugs.

5.4 Local Effects of Inhaled Corticosteroids

In clinical trials, the development of localized infections of the mouth and pharynx with Candida albicans has occurred in subjects treated with AIRDUO RESPICLICK. When such an infection develops, it should be treated with appropriate local therapy. A single, blind, independent adjudication committee determined whether events were asthma-related.

The 3 adult and adolescent trials were designed to rule out a risk margin of 2.0, and the pediatric trial was designed to rule out a risk margin of 2.7. Each individual trial met its pre-specified objective and demonstrated non-inferiority of ICS/LABA to ICS alone. A meta-analysis of the 3 adult and adolescent trials did not show a significant increase in the risk of serious asthma-related event with ICS/LABA fixed-dose combination compared with ICS alone (Table 1). These trials were not designed to rule out all risk for serious asthma-related events with ICS/LABA compared with ICS alone.

5.5 Immunomodulation

Persons who are using drugs that suppress the immune system are more susceptible to infections than healthy individuals. Chickenpox and measles, for example, can have more serious or even fatal courses in susceptible adolescents and adults using corticosteroids. In such patients who have not had these diseases or who have not been properly immunized, particular care should be taken to avoid exposure. How the dose, route and duration of corticosteroid administration affect the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known. If a patient is exposed to Chickenpox, prophylaxis with varicella-zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG) may be indicated. If a patient is exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IMIG) may be indicated. (See respective package inserts for complete VZIG and IVIG prescribing information.) If chickenpox develops, treatment with antiviral agents may be considered.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infections of the respiratory tract; systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

5.6 Transferring Patients from Systemic Corticosteroid Therapy

When systemic corticosteroids are needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function.
AIRDUO® RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

Patients who have been previously maintained on 20 mg or more of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, or infection (particularly gastroenteritis), or other conditions associated with severe electrolyte loss. Although AIRDUO RESPICLICK may improve control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a medical identification warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or a severe asthmatic attack.

Patients requiring systemic corticosteroids should be weaned slowly from systemic corticosteroids by a gradual reduction to AIRDUO RESPICLICK. Lung function (mean forced expiratory volume in 1 second [FEV1], or morning peak expiratory flow [AM PEF]), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of systemic corticosteroids, some patients may experience symptoms of systemic active corticosteroid withdrawal (e.g., joint/muscular pain, lassitude, depression) despite maintenance or even improvement of respiratory function.

5.5 Paradoxical Bronchospasm and Upper Airway Symptoms

Fluticasone propionate, a component of AIRDUO RESPICLICK, can produce paradoxical bronchospasm, which may be life-threatening. If paradoxical bronchospasm occurs following dosing with inhaled fluticasone propionate/salmeterol medicines, it should be treated by discontinuation of treatment with AIRDUO RESPICLICK and the patient may require hospitalization. If the paradoxical bronchospasm is severe, the patient should receive systemic corticosteroids. If bronchospasm is life-threatening or not responsive to treatment, resuscitative measures should be employed. Treatment should be accompanied by close monitoring of the patient's respiratory status, and further systemic corticosteroids should be administered when indicated.

5.6 Drug Interactions with Strong Cytochrome P450 3A4 Inhibitors

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, neflinavir, saquinavir, ketocazole, telithromycin) with AIRDUO RESPICLICK is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur [see Drug Interactions (7.1)].

5.7 Hypersensitivity Reactions, Including Anaphylaxis

In rare instances, severe local or systemic reactions (e.g., urticaria, angioedema, rash, bronchospasm, hypotension), including anaphylaxis, may occur after administration of AIRDUO RESPICLICK. There have been reports of anaphylactic reactions in patients with severe milk protein allergy after inhalation of dry powder containing lactose; therefore, patients with severe milk protein allergy should not use AIRDUO RESPICLICK [see Contraindications (4)].

5.8 Cardiovascular and Central Nervous System Effects

Excessive beta-adrenergic stimulation has been associated with seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia [see Overdosage (10)]. Therefore, AIRDUO RESPICLICK, like all products containing sympathomimetic amines, should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

AIRDUO® RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

Salmeterol, a component of AIRDUO RESPICLICK, can produce a clinically significant reduction in serum potassium, which may be measured by some participants and may cause cardiac arrhythmias, weakness, fatigue, malaise, and insomnia. Although such effects are uncommon after administration of salmeterol at recommended doses, if they occur, the drug may need to be discontinued. In addition, AIRDUO RESPICLICK is reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QT interval, and ST segment depression. The clinical significance of these findings is unknown. Large doses of inhaled or oral salmeterol (12 to 20 times the recommended dose) have been associated with clinically significant prolongation of the QT interval, which has the potential for producing ventricular arrhythmias. Fatality has been reported in association with excessive use of inhaled sympathomimetic drugs.

5.12 Reduction in Bone Mineral Density

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. The clinical significance of small changes in BMD with regard to long-term consequences such as fracture is unknown. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

5.13 Effect on Growth

Orally inhaled corticosteroids, including AIRDUO RESPICLICK, may cause a reduction in growth velocity when administered to pediatric patients. Monitor the growth of pediatric patients receiving AIRDUO RESPICLICK routinely (e.g., via stadiometry). To minimize the suppression of systemic inhaled corticosteroids, including AIRDUO RESPICLICK, titrate each patient's dosage to the lowest dosage that effectively controls his/her symptoms [see Use in Specific Populations (8.4)].

5.14 Glaucoma and Cataracts

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients following the long-term administration of inhaled corticosteroids, including fluticasone propionate, a component of AIRDUO RESPICLICK. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Effects of treatment with other fluticasone Propionate and Salmeterol Inhalation Powder 500 mcg/50 mcg, fluticasone propionate 500 mcg, salmeterol 50 mcg, or placebo on development of cataracts or glaucoma was evaluated in a subset of 658 subjects with chronic obstructive pulmonary disease (COPD) in the 3-year survival trial. Ophthalmologic examinations were conducted at baseline and at 48, 106, and 158 weeks. Conclusions about cataracts cannot be drawn from this trial because the high incidence of cataracts at baseline (61% to 71%) resulted in an inadequate number of subjects available for comparison with other fluticasone Propionate and Salmeterol Inhalation Powder 500 mcg/50 mcg who were eligible and available for evaluation of cataracts at the end of the trial (n = 53). The incidence of newly diagnosed cataracts was 2% with other Fluticasone Propionate and Salmeterol Inhalation Powder 500 mcg/50 mcg, 5% with fluticasone propionate, 0% with salmeterol, and 2% with placebo.

5.15 Eosinophilic Conditions and Churg-Strauss Syndrome

In rare cases, patients on inhaled fluticasone propionate, a component of AIRDUO RESPICLICK, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome, a condition that is often treated with systemic corticosteroid therapy. These events usually, but not always, have been associated with the reduction and/or withdrawal of oral corticosteroid therapy following the introduction of fluticasone propionate. Cases of serious eosinophilic conditions have also been reported with other inhaled corticosteroids in this clinical setting. Physicians should be alert to eosinophilia, vasculitis, rash, worsening pulmonary symptoms, cardiac complications, and/or neuropsychopathy in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.16 Coexisting Conditions

AIRDUO RESPICLICK, like all medicines containing sympathomimetic amines, should be used with caution in patients with convulsive disorders or thyrotoxicosis and in patients who are sensitive to sympathomimetic amines. A causal relationship between fluticasone propionate, a component of AIRDUO RESPICLICK, may present with systemic eosinophilic conditions. Some of these patients have clinical features of vasculitis consistent with Churg-Strauss syndrome. Physicians should be alert to eosinophilia, vasculitis, rash, worsening pulmonary symptoms, cardiac complications, and/or neuropsychopathy in their patients. A causal relationship between fluticasone propionate and these underlying conditions has not been established.

5.17 Hypokalemia and Hyperglycemia

Beta-adrenergic agonist medications may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation. Clinically significant changes in blood glucose and/or serum potassium were seen infrequently during clinical trials with AIRDUO RESPICLICK at recommended doses.

6 ADVERSE REACTIONS

Use of LABA may result in the following:

• Serious asthma-related events – hospitalizations, intubations, death [see Warnings and Precautions (5.1)].

• Cardiovascular and central nervous system effects [see Warnings and Precautions (5.1)].

• Systemic and local corticosteroid use may result in the following:

  • Candida albicans infection [see Warnings and Precautions (5.4)]
  • Immunompression [see Warnings and Precautions (5.5)]
  • Increased corticosteroid and adrenal suppression [see Warnings and Precautions (5.1)]
  • Reduction in bone mineral density [see Warnings and Precautions (5.12)]
  • Growth effects in pediatrics [see Warnings and Precautions (5.13)]
  • Glaucoma and cataracts [see Warnings and Precautions (5.14)].
6.1 Clinical Trials Experience in Asthma

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In two placebo-controlled, 12-week, clinical studies (Trials 1 and 2), a total of 1,364 adolescent and adult patients with persistent symptomatic asthma despite ICS or ICS/LABA therapy were treated twice daily with either placebo; fluticasone propionate 113 mcg or 232 mcg ARMONAIR RESPICLICK (hereafter referred to as fluticasone propionate MDPI); or AIRDUO RESPICLICK 55 mcg/14 mcg, 113 mcg/14 mcg, or 232 mcg/14 mcg. Sixty percent of patients were female and 80% of patients were white. The average duration of exposure was 82 to 84 days in the fluticasone propionate MDPI and AIRDUO RESPICLICK treatment groups compared with 75 days in the placebo group. Table 2 displays the incidence of most common adverse reactions in pooled Trials 1 and 2.

Table 2: Adverse Reactions with ≥3% Incidence with AIRDUO RESPICLICK, and More Common than Placebo in Subjects with Asthma (Trials 1 and 2)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Fluticasone Propionate MDPI 55 mcg (n=243)</th>
<th>Fluticasone Propionate MDPI 113 mcg (n=243)</th>
<th>Fluticasone Propionate MDPI 222 mcg (n=146)</th>
<th>AIRDUO RESPICLICK 55 mcg/14 mcg (n=228)</th>
<th>AIRDUO RESPICLICK 113 mcg/14 mcg (n=228)</th>
<th>AIRDUO RESPICLICK 232 mcg/14 mcg (n=146)</th>
<th>Placebo (n=270)</th>
<th>% ( \geq 3 ) Incidence with AIRDUO RESPICLICK, and % Incidence with Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea and/or Vomiting</td>
<td>5.4</td>
<td>3.2</td>
<td>7.3</td>
<td>0.9</td>
<td>1.7</td>
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* Oral candidiasis includes oropharyngeal candidiasis, oral fungal infection, and oropharyngitis funga.

Other adverse reactions not previously listed (and occurring in ≥3% of patients and in three or more patients on AIRDUO RESPICLICK) that were reported more frequently by patients with asthma treated with AIRDUO RESPICLICK compared with patients treated with placebo include the following:

- Sinusitis, oropharyngeal pain, pharyngitis, dizziness, influenza, rhinitis allergic, rhinitis nonallergic, conjunctivitis, conjunctivitis chlamydial, conjunctivitis herpeticum, conjunctivitis adenovirus, conjunctivitis adenovirus upper, myalgia, pain in extremity, dyspepsia, laceration, dermatitis contact, and palpitations.

6.2 Postmarketing Experience

In addition to adverse reactions reported from clinical trials, the following adverse reactions have been identified during post approval use of fluticasone propionate and/or salmeterol or a combination of these factors.

- Headache, laryngeal spasm, irritation, or swelling such as stridor or choking.

Respiratory, Thoracic, and Mediastinal Disorders: Chest congestion; chest tightness, dyspnea; facial and oropharyngeal edema, immediate bronchospasm; paradoxical bronchospasm; tracheitis; wheezing; reports of upper respiratory symptoms of laryngeal spasm, irritation, or swelling such as stridor or choking.

Skin and Subcutaneous Tissue Disorders: Ecchymoses, photodermatitis.

Nervous System Disorders: Paresthesia, restlessness.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Endocrine Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

Metabolic and Nutritional Disorders: Hyperglycemia, weight gain.

Musculoskeletal, Connective Tissue, and Bone Disorders: Arthralgia, cramps, myositis, osteoporosis.

7. DRUG INTERACTIONS

AIRDUO RESPICLICK has been used concomitantly with other drugs, including short-acting beta-agonists, and inhaled corticosteroids, commonly used in patients with asthma via MDPI, ARMONAIR RESPICLICK, or ARMONAIR RESPICLICK. No formal drug interaction trials have been performed with AIRDUO RESPICLICK.

7.1 Inhibitors of Cytochrome P450 3A4

Fluticasone propionate and salmeterol, the individual components of AIRDUO RESPICLICK, are substrates of CYP3A4. The use of strong CYP3A4 inhibitors (e.g., ritonavir, atazanavir, clarithromycin, itraconazole, nefazodone, neflinivir, saquinavir, protease inhibitors) with AIRDUO RESPICLICK is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

- Ritonavir: In a drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that ritonavir (a strong CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects. Patients with a history of Raynaud's syndrome and adrenal suppression.

- Itraconazole: Fluticasone Propionate: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC) but had no effect on urinary excretion of cortisol.

- Ketoconazole: Fluticasone Propionate: Coadministration of orally inhaled fluticasone propionate (1,000 mcg) and ketoconazole (200 mg once daily) resulted in a 1.9-fold increase in plasma fluticasone propionate exposure and a 45% decrease in plasma cortisol area under the curve (AUC) but had no effect on urinary excretion of cortisol.

- Saquinavir: In a drug interaction trial with fluticasone propionate aqueous nasal spray in healthy subjects has shown that saquinavir (a moderate CYP3A4 inhibitor) can significantly increase plasma fluticasone propionate exposure, resulting in significantly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and saquinavir, resulting in systemic corticosteroid effects.

7.2 Monoamine Oxidase Inhibitors and Tricyclic Antidepressants

AIRDUO RESPICLICK should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 14 days of discontinuation of such agents, because the action of some of these agents is potentiated by the use of AIRDUO RESPICLICK.

7.3 Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of AIRDUO RESPICLICK, but may also produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents for these patients. Caution should be used in administering these drugs to patients being treated with AIRDUO RESPICLICK.

7.4 Non-Potassium-Sparing Diuretics

Diuretics, change and/or hypertensive crisis that may result from the administration of non–potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, such as salmeterol, a component of AIRDUO RESPICLICK. Patients should be closely monitored and treated for any signs of hyperglycemia or exacerbation of diabetes while being treated with AIRDUO RESPICLICK.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of AIRDUO RESPICLICK or individual components, fluticasone propionate and salmeterol, in pregnancy in women. There are no clinical considerations with the use of AIRDUO RESPICLICK in pregnant women [see Clinical Considerations]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol as well as individual components. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate and/or salmeterol, respectively. Although the clinical significance of these effects is not known, caution is advised in the coadministration of AIRDUO RESPICLICK with non–potassium-sparing diuretics.

8.2 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of AIRDUO RESPICLICK or individual components, fluticasone propionate and salmeterol, in pregnancy in women. There are no clinical considerations with the use of AIRDUO RESPICLICK in pregnant women [see Clinical Considerations]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol as well as individual components. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate and/or salmeterol, respectively. Although the clinical significance of these effects is not known, caution is advised in the coadministration of AIRDUO RESPICLICK with non–potassium-sparing diuretics.

8.2 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no randomized clinical studies of AIRDUO RESPICLICK or individual components, fluticasone propionate and salmeterol, in pregnancy in women. There are no clinical considerations with the use of AIRDUO RESPICLICK in pregnant women [see Clinical Considerations]. Animal reproduction studies are available with the combination of fluticasone propionate and salmeterol as well as individual components. In animals, teratogenicity characteristic of corticosteroids, decreased fetal body weight and/or skeletal variations, in rats, mice, and rabbits were observed with subcutaneously administered maternal toxic doses of fluticasone propionate and/or salmeterol, respectively. Although the clinical significance of these effects is not known, caution is advised in the coadministration of AIRDUO RESPICLICK with non–potassium-sparing diuretics.
In two embryo/fetal development studies, pregnant rats received salmeterol by oral administration at doses ranging from 100 to 1,000 mcg/kg/day during the period of organogenesis. Salmeterol produced no maternal toxicity or embryonic/fetal effects at doses up to 3,500 times the MRHIDI (on a mcg/m² basis at maternal oral doses up to 10,000 mcg/kg/day).

In an embryo/fetal development study in pregnant rats dosed by the oral route from late gestation through delivery and lactation, salmeterol at a dose 3500 times the MRHIDI (on mcg/m² basis with a maternal oral dose of 10,000 mcg/kg/day) was teratogenic and increased the rate of stillbirths.

In an embryo/fetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout the period of organogenesis, fluticasone propionate produced decreased fetal body weights and skeletal variations, in the presence of maternal toxicity, at a dose approximately 0.2 times the MRHIDI (on a mcg/m² basis with a maternal subcutaneous dose of 30 mcg/kg/day). Clef palate and skeletal variations were observed in rabbit fetuses, in the presence of maternal toxicity at a dose approximately 0.6 times the MRHIDI (on a mcg/m² basis with a maternal subcutaneous dose of 45 mcg/kg/day). The mouse NOAEL was observed with a dose approximately 0.16 times the MRHIDI (on a mcg/m² basis with a maternal subcutaneous dose of 25.7 mcg/kg/day); however, there was no evidence of teratogenicity. The NOAEL was observed with a dose approximately 0.1 times the MRHIDI (on a mcg/m² basis with a maternal inhalation dose of 5.5 mcg/kg/day). In an embryo/fetal development study in pregnant rabbits that were dosed by the subcutaneous route throughout organogenesis, fluticasone propionate produced reduced fetal body weights, in the presence of maternal toxicity, at a dose approximately 0.02 times the MRHIDI and higher (on a mcg/m² basis with a maternal subcutaneous dose of 0.57 mcg/kg/day). Teratogenicity was evident based upon a finding of cleft palate in 1 fetus at a dose approximately 0.2 times the fluticasone propionate/mouse mcg/m² basis with a maternal subcutaneous dose of 4 mcg/kg/day). The NOAEL was observed in rabbit fetuses with a dose approximately 0.004 times the MRHIDI (on a mcg/m² basis with a maternal subcutaneous dose of 0.08 mcg/kg/day).

In a pre- and post-natal development study in pregnant rats dosed by the subcutaneous route from late gestation through delivery and lactation (Gestation Day 17 to Postpartum Day 22), fluticasone propionate was not associated with decreases in pup body weight, and had no effects on developmental landmarks, learning, memory, reflexes, or fertility at doses up to approximate equivalence to the MRHIDI (on a mcg/m² basis with a maternal oral dose of 15 mcg/kg/day). Fluticasone propionate crossed the placenta following subcutaneous administration to mice and rats and oral administration to rabbits. Salmeterol, of embryo/fetal development studies, pregnant rabbits received oral administration of salmeterol at doses ranging from 100 to 10,000 mcg/kg/day during the period of organogenesis. In pregnant Dutch rabbits administered salmeterol doses approximately 1,000 times the MRHIDI (on mcg/m² basis at maternal oral doses of 1000 mcg/kg/day and higher), fetal toxic effects were observed characteristically resulting from beta-adrenoceptor stimulation. These included precocious eyelid openings, clef palate, and limb and paw flexures, and delayed ossification of the frontal and parietal cranial bones. No such effects occurred at a salmeterol dose approximately 420 times the MRHIDI (on a mcg/m² basis at a maternal oral dose of 600 mcg/kg/day). New Zealand White rabbits, which are less sensitive since they delayed ossification of the parietal and cranial bones were seen at a salmeterol dose approximately 7,000 times the MRHIDI (on a mcg/m² basis at a maternal oral dose of 10,000 mcg/kg/day).
AIRDUO® RESPICLICK® (fluticasone propionate and salmeterol) inhalation powder

Salmeterol

The expected signs and symptoms with overdosage of salmeterol are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the signs and symptoms of beta-adrenergic stimulation (e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, muscle cramps, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, insomnia, hyperglycemia, hypokalemia, metabolic acidosis). Overdosage with salmeterol can lead to clinically significant prolongation of the QTc interval, which can produce ventricular arrhythmias.

As with all inhaled sympathomimetic medicines, cardiac arrest and even death may be associated with an overdose of salmeterol.

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This brief summary is based on the AIRDUO® RESPICLICK® full prescribing information AIRDPI-005.
As the pandemic dominates headlines, the United States continues to face another major public health crisis—the opioid epidemic. One bright spot is at Boston Medical Center, where the city’s safety net hospital’s pharmacy team has reduced inpatient opioid use among surgical patients by 41% since 2017 and cut discharge opioid prescribing for surgery patients by 25%. The initiative involved pharmacists across the hospital’s ambulatory, inpatient, and retail pharmacy departments.

Kevin Horbowicz, PharmD, BCPS, associate director of inpatient clinical pharmacy services, described witnessing the opioid overdose epidemic as his driving force. “It was very central to us at Boston Medical Center… where it’s having a big impact on our patients, many of whom struggle with opioid use disorder and other disorders,” he said.

Success depended on coordinating with the hospital’s information technology team and more than 20 surgical specialties. Today, surgeons can order sets in the electronic health record that prompt them to prescribe agents such as acetaminophen to manage patients’ pain. Horbowicz said. That’s dangerous for an individual who might become dependent or whose medication is accessible to other household members, he explained.

Pharmacist participation during rounds with the surgical team is key, McAneny said. The pharmacist can provide insight on topics such as appropriate medications, when to stop antibiotics, and when to switch from an intravenous to an oral route. McAneny, who mostly performs endocrine surgery, said he hasn’t prescribed opioids for postsurgical recovery in 10 years.

He also emphasized the importance of patient education. For example, McAneny tells patients who have had thyroid surgery that neither oxycodone nor acetaminophen will take away the resulting sore throat, which should subside by the end of the day.

Lessons Learned

Developing a consensus among more than 20 surgery subspecialties proved the most difficult part of implementing the program, according to Horbowicz. The fields of orthopedics, plastic surgery, and trauma have very different needs, he said.

Another challenge involved scheduling a meeting with the chair of neurosurgery to discuss the program, he added. Still, he highlighted Boston Medical Center’s “collaborative, multidisciplinary culture,” with physicians, nurses, and pharmacists working well together. “That was part of the secret sauce,” Horbowicz said.

As a result of Horbowicz’ leadership, Boston Medical Center’s Opioid Utilization Improvement Team won the Pharmacy Health-System Award from the Massachusetts Society of Health-System Pharmacists.

By Aine Cryts

Boston Medical Center’s pilot program included procedures such as abdominal surgeries, which tend to involve large incisions and “a lot of pain,” said David McAneny, MD, the medical center’s chief surgical officer. He was so impressed by how well using agents such as angiotensin-converting enzyme inhibitors and acetaminophen managed postsurgical pain that he supported including all surgeries in the program.

In line with this effort, the hospital was implementing the enhanced recovery after surgery (ERAS) protocols, McAneny said. This multimodal, multidisciplinary approach to the care of surgical patients includes surgeons, anesthesiologists, and surgical care staff. ERAS protocols generally include minimally invasive approaches rather than large surgical incisions, and early mobilization.
Since I’ve been teaching a class of 55 physician assistants for the past 15 years, I’ve come to know some of them very well. One of my former students and I were discussing the coronavirus disease 2019 (COVID-19) mayhem. He said, “It has taught me the difference between essential versus expendable personnel.”

He went on to say that since the lockdown began in this country, essential personnel have been going to work. Whether you are a kid stocking shelves at the grocery store, a police officer patrolling the streets, a physician seeing patients, or a pharmacist filling prescriptions, we are all described as being essential. Sounds like a big compliment. However, my physician assistant friend suggested that “expendable” is a more appropriate term.

My friend went on to add that the truly “essential” personnel are walled off safely in their homes, sitting on their couches with their laptops, working remotely. They must be important—say, more important than those of us at work—because they are afforded much more protection than those of us stocking shelves, seeing patients, patrolling streets, or filling prescriptions, he said.

I was amazed to find out that even the folks who run the pharmacy benefit managers (PBMs) are working from home. It is too dangerous for them to come to our stores to do an audit, so they fax us a “bench audit” to fill out. They can continue to underpay us, for example, by $60 for a sight-saving medication, as I discussed in my June essay, from the comfort of their living room couch.

Yes, the managed care organizations are also working from home, away from this deadly virus. From the safety of their homes, they continue to underpay us, for example, by $0.79 for a lisinopril prescription. So, we pharmacies lose $60 providing a sight-saving drug, get paid less than a buck for a month’s worth of blood pressure medications, and lose over a grand on a bench audit. What do we get for our efforts?

One student pharmacist I was talking with told me her boyfriend was making his bonus $600 a week for unemployment. That is $15 an hour for a 40-hour week. My “essential” pharmacy technicians are salivating at that figure. The government decided to give hazard pay of $3 an hour to those who worked during the shutdown, except for pharmacy technicians. I immediately contacted our state senator, Judy Ward, who quickly sent a letter to Pennsylvania’s governor.

“We find it hard to believe that the program considers food retail facilities (grocery and convenience stores) an eligible industry but not pharmacies and drug stores,” wrote senators Lisa Boscola, D-Bethlehem, and Ward, R-Hollidaysburg. “The employees of pharmacies/drug stores were just as much on the front line as employees in grocery stores during the COVID-19 pandemic and faced an equally high risk given that these businesses remained open during the emergency order when other businesses were closed.”

My pharmacy technicians who worked diligently through this crisis, never missing a day of work, waiting on sick people, and providing lifesaving medications, were not considered “essential.”

Pharmacy technicians work alongside pharmacists to meet unprecedented demands during these times. They are not expendable.

“If we are essential, who is expendable? We are.”

For references, visit drugtopics.com.

Peter A. Kreckel, RPh, practices community pharmacy in Altoona, Pennsylvania.
Dravet syndrome is a rare and chronic form of epilepsy characterized by severe and unrelenting seizures. This debilitating disease typically manifests within the first year of life with frequent and prolonged seizures often triggered by hyperthermia, developmental delays, and other health problems. Initial therapy of Dravet syndrome has been limited to the use of valproate in combination with agents such as clobazam and stiripentol, with limited efficacy data in the United States. On June 25, 2020, fenfluramine (Fintepla), a Schedule IV amphetamine derivative that exhibits agonist activity at the 5-HT2 receptor, was approved for the treatment of seizures associated with Dravet syndrome in patients 2 years and older. Although the mechanism by which it exerts its therapeutic effect is unknown, patients treated with fenfluramine have consistently shown significantly greater reductions in the frequency of convulsive seizures than those receiving placebo in clinical trials.

Two randomized, double-blind placebo-controlled clinical trials were conducted in 202 patients with Dravet syndrome between the ages of 2 and 18 years. Study 1 (N = 117) compared 3 treatment groups; 0.7 mg/kg/day of fenfluramine, 0.2 mg/kg/day of fenfluramine, and placebo, respectively, in patients on 1 to 4 antiepileptic drugs, excluding stiripentol, who were inadequately controlled. Study 2 (N = 85) compared 0.4 mg/kg/day of fenfluramine with placebo in patients inadequately controlled on 2 to 4 antiepileptic drugs including stiripentol and either clobazam, valproate, or both. Both studies only included patients with a baseline of 6 or more convulsive seizures over 6 weeks, and observed a primary efficacy end point of a change from this baseline, per 28 days, during the 14- or 15-week treatment periods.

In both studies, the reduction in frequency of convulsive seizures was significantly greater for all dose groups of fenfluramine, compared with placebo. This reduction was seen within 3 to 4 weeks of starting fenfluramine, and the effect was seen throughout the duration of both studies. The majority of patients using all doses of fenfluramine experienced a 50% or greater reduction in monthly convulsive seizures.

Fenfluramine has a boxed warning for valvular heart disease and pulmonary arterial hypertension. Fenfluramine is only available under a risk evaluation and mitigation strategy and requires an echocardiogram assessment prior to initiation of therapy, frequently throughout, and after therapy. Furthermore, 37% and 19% of patients in clinical trials reported decreased appetite and decreased weight, respectively. Fenfluramine is associated with sedation, suicidal ideation, hypertension, and glaucoma. This medication is contraindicated in patients with concomitant use, or use within 14 days of, monoamine oxidase inhibitors due to the increase in risk of serotonin syndrome. Fenfluramine should be gradually titrated to discontinuation to minimize the risk of a rebound in seizure frequency and status epilepticus.

Fenfluramine is administered as an oral solution with or without food and is dispensed as a 2.2 mg/mL (360 mL) vial with 2 oral syringes. Initial dosing for both pediatric and adult patients begins at 0.1 mg/kg/dose twice daily and can be titrated on a weekly basis up to 0.2 mg/kg/dose, and then 0.35 mg/kg/dose twice daily, based on response and tolerability. The maximum recommended dose for adult and pediatric patients is 26 mg/day and 13 mg/day, respectively. The labeling does not provide dose adjustments in renal impairment, and use is not recommended in hepatic impairment. Of note, these dosing recommendations are for adults without concomitant stiripentol therapy and for pediatric patients 2 to 18 years old on at least 1 other antiepileptic drug.

Youssef Bessada, PharmD, is a PGY-1 pharmacy resident at UConn John Dempsey Hospital at UConn Health, Farmington, Connecticut.

Kevin W. Chamberlin, PharmD, FASCP, is university director of pharmacy residency programs at UConn Health.

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BRIEF SUMMARY

SHINGRIX (Zoster Vaccine Recombinant, Adjuvanted)

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

1 INDICATIONS AND USAGE

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

Limitations of Use:

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

2 DOSAGE AND ADMINISTRATION

2.2 Administration Instructions

For intramuscular injection only.

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

2.3 Dose and Schedule

Two doses (0.5 mL each) administered intramuscularly according to the following schedule: A first dose at Month 0 followed by a second dose administered anytime between 2 and 6 months later.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Preventing and Managing Allergic Vaccine Reactions

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

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

The safety of SHINGRIX was evaluated by pooling data from 2 placebo-controlled clinical studies (Studies 1 and 2) involving 29,305 subjects aged 50 years and older who received at least 1 dose of SHINGRIX (n = 14,645) or saline placebo (n = 14,660) administered according to a 0- and 2-month or 0- and 6-month schedule. At the time of vaccination, the mean age of the population was 69 years; 7,286 (24.9%) subjects were aged 50 to 59 years, 4,488 (15.3%) subjects were aged 60 to 69 years, and 17,531 (59.8%) subjects were aged 70 years and older. Both studies were conducted in North America, Latin America, Europe, Asia, and Australia. In the overall population, the majority of subjects were white (74.3%), followed by Asian (18.3%), black (1.4%), and other racial/ethnic groups (6.0%); 58% were female.

 Solicited Adverse Events

In Studies 1 and 2, data on solicited local and general adverse events were collected using standardized diary cards for 7 days following each vaccine dose or placebo (i.e., day of vaccination and the next 6 days) in a subset of subjects (n = 4,886 receiving SHINGRIX, n = 4,881 receiving placebo with at least 1 documented dose). Across both studies, the percentages of subjects aged 50 years and older reporting each solicited local adverse reaction and each solicited general adverse event following administration of SHINGRIX (both doses combined) were pain (78.0%), redness (38.1%), and swelling (25.9%); and myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (25.8%), fever (20.3%), and gastrointestinal symptoms (17.3%), respectively.

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

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

<table>
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<td></td>
<td>SHINGRIX %</td>
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<td>SHINGRIX %</td>
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<td>1.7</td>
<td>0.2</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
<td>0.7</td>
<td>0.6</td>
</tr>
</tbody>
</table>

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

7 Days included day of vaccination and the subsequent 6 days.

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

Placebo was a saline solution.

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

Grade 3 myalgia, fatigue, headache, shivering, GI: Defined as preventing normal activity.

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

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

(continued on next page)
The incidence of solicited local and general symptoms was lower in subjects aged 70 years and older compared with those aged 50 to 69 years. 

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

There were no differences in the proportions of subjects reporting any or Grade 3 solicited local reactions between Dose 1 and Dose 2. Headache and shivering were reported more frequently by subjects after Dose 2 (28.2% and 21.4%, respectively) compared with Dose 1 (24.4% and 13.8%, respectively). Grade 3 solicited general adverse events (headache, shivering, myalgia, and fatigue) were reported more frequently by subjects after Dose 2 (2.3%, 3.1%, 3.6%, and 3.5%, respectively) compared with Dose 1 (1.4%, 1.4%, 2.3%, and 2.4%, respectively).

Unsolicited Adverse Events

Unsolicited adverse events that occurred within 30 days following each vaccination (Day 0 to 29) were recorded on a diary card by all subjects. In the 2 studies, unsolicited adverse events occurring within 30 days of vaccination were reported in 50.5% and 32.0% of subjects who received SHINGRIX (n = 14,645) and placebo (n = 14,660), respectively (Total Vaccinated Cohort). Unsolicited adverse events that occurred in <1% of recipients of SHINGRIX and at a rate at least 1.5-fold higher than placebo included chills (3.5% versus 0.2%), injection site pruritus (2.2% versus 0.2%), malaise (1.7% versus 0.3%), arthralgia (1.7% versus 1.2%), nausea (1.4% versus 0.5%), and dizziness (1.2% versus 0.8%).

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

Serious Adverse Events (SAEs)

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

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

Deaths

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

Potential Immune-Mediated Diseases

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

Dosing Schedule

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

6.2 Postmarketing Experience

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

General Disorders and Administration Site Conditions

Decreased mobility of the injected arm which may persist for 1 or more weeks.
HOW IMPORTANT IS IT TO COMPLETE THE 2-DOSE SERIES?

VERY IMPORTANT

MAKE SURE YOU ADMINISTER A SECOND DOSE OF SHINGRIX 2–6 MONTHS AFTER THE FIRST.

DOSE 1
Administer now

DOSE 2
Administer 2–6 months later

Indication
SHINGRIX is a vaccine indicated for prevention of herpes zoster (shingles) in adults aged 50 years and older. SHINGRIX is not indicated for prevention of primary varicella infection (chickenpox).

Important Safety Information
• SHINGRIX is contraindicated in anyone with a history of a severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine or after a previous dose of SHINGRIX.
• Review immunization history for possible vaccine sensitivity and previous vaccination-related adverse reactions. Appropriate medical treatment and supervision must be available to manage possible anaphylactic reactions following administration of SHINGRIX.
• Solicited local adverse reactions in subjects aged 50 years and older were pain (78.0%), redness (38.1%), and swelling (25.9%).
• Solicited general adverse reactions in subjects aged 50 years and older were myalgia (44.7%), fatigue (44.5%), headache (37.7%), shivering (26.8%), fever (20.5%), and gastrointestinal symptoms (17.3%).
• SHINGRIX was not studied in pregnant or lactating women, and it is unknown if it is excreted in human milk. Therefore, it cannot be established whether there is vaccine-associated risk with SHINGRIX in pregnant women or if there are effects on breastfed infants or milk production/excretion.
• Vaccination with SHINGRIX may not result in protection of all vaccine recipients.

Reference: Prescribing Information for SHINGRIX.

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

Get the facts at
visitSHINGRIXpharm.com

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