Trends in Oncology Management: Care Model and Innovative Strategies

Digital Therapeutics: Advances in Healthcare Innovation

Rare Disease Management: Pipeline and Managed Care Implications

Pharmacogenetics in Managed Care: Opportunities and Barriers to Adoption

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Spring 2019

Migraine Management:

Gaps in Care and Therapeutic Advances

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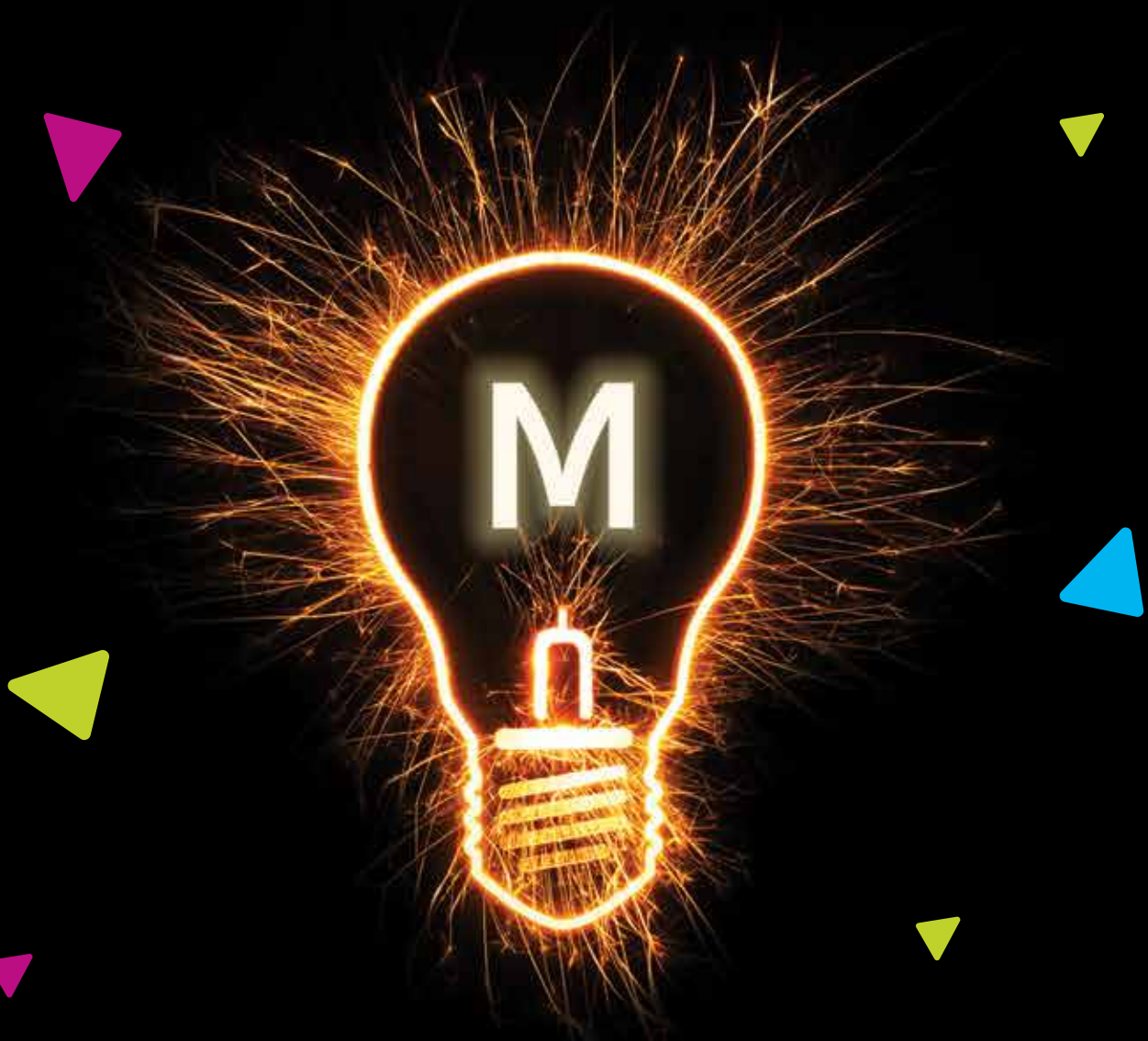

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Published By

Magellan Rx Management
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Scottsdale, AZ 85260

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ISSN:2159-5372 10444M

Features

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Dear Managed Care Colleagues,

Welcome to our spring issue of the Magellan Rx™ Report! In the fast-paced managed care environment, it is important to stay up to date on Food and Drug Administration (FDA) approvals of new agents and treatments, as well as innovative management strategies. In 2018, Magellan addressed 68 novel and notable FDA approvals and took action on 32 Class I and Class II drug recalls. At Magellan, we pride ourselves on providing our clients with the resources needed to remain at the forefront of this evolving world. Likewise, with each Report, we are excited to share with our readers the most up-to-date and valuable managed care and clinical perspectives, from discussions of innovative payment strategies to pipelines and product spotlights.

In this issue of the Report, the cover story reviews the ever-changing needs in the management of migraine. Featuring a discussion of both current treatments and the pipeline, this article highlights gaps in migraine treatment and considerations in the management of this patient population.

A second feature article delves into rare disease management, outlining the current landscape of rare disease treatment as well as future trends with rare disease therapies, and considers the resulting impact on managed care.

Other timely topics featured in this issue include a dive into oncology management and the impact of the Centers for Medicare and Medicaid Service's Oncology Care Model; an exploration of the landscape of precision medicine; a discussion of the innovative field of digital therapeutics; and a spotlight on the most recent offering in a Magellan webinar series, *Clinical Connections*, focused on hemophilia management.

No issue of the Report would be complete without a pharmaceutical pipeline review to help you track promising new agents that may receive FDA approval in the near future.

Finally, it is my pleasure to introduce the Chief Medical Officer for Magellan Rx Management, Dr. Caroline Carney. Having recently transitioned from her position as Senior Vice President and Chief Medical Officer for Behavioral Health and Specialty Medicine at Magellan Healthcare, Dr. Carney brings a wealth of expertise. With experience from an extraordinary clinical and research career as well as managed care leadership, Dr. Carney will be an excellent addition to the publication team, guiding us in bringing the quality and content of the Report to the next level.

To learn more about Magellan Rx Management and our support of payor initiatives of the future, please feel free to contact us at MagellanRxReport@magellanhealth.com. As always, I value any feedback that you may have, and thanks for reading!

Sincerely,

Mostafa Kamal
Chief Executive Officer
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Caroline Carney
Chief Medical Officer
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Managed Care Newsstand

HHS Releases 2017 U.S. Healthcare Spending Report

On December 7, the Department of Health and Human Services (HHS), through the Centers for Medicare & Medicaid Services (CMS) Office of the Actuary, released its annual report on U.S. healthcare spending in 2017. According to the report's highlights, total national health expenditures rose to $3.5 trillion, or $10,739 per capita and 17.9% of gross domestic product. Healthcare spending growth in 2017 was similar to average growth from 2008 to 2013 (3.9%) and below the 4.8% growth rate in 2016 — one of the slowest rates of growth in a decade. Spending on prescription drugs was nearly flat, rising 0.4% in 2017, to $333 billion.

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ICER Releases Clinical Effectiveness, Value Report with Policy Recommendations for Extended-Release Opioid Use Disorder Treatment

On December 4, the Institute for Clinical and Economic Review (ICER) released a Final Evidence Report and Report-at-a-Glance assessing the comparative clinical effectiveness and value of extended-release medications for the treatment of opioid use disorder, including buprenorphine implants (Probuphine®, Titan), an extended-release naltrexone injection (Vivitrol®, Alkermes), and two extended-release buprenorphine injections (Sublocade™ [Indivior] and Brixadi™ [Braeburn]), which received tentative approval from the FDA in December 2018.

The New England Comparative Effectiveness Public Advisory Council (CEPAC) found that the evidence is not adequate to demonstrate any of these extended-release treatments provides superior net health benefit over buprenorphine or naloxone, nor is the evidence adequate to distinguish between the four extended-release treatments. However, the CEPAC argued that access to multiple treatment options for patients with opioid use disorder is a clinical and policy priority.

Probuphine, Vivitrol, and Sublocade are all more expensive than buprenorphine or naloxone, and their current prices each exceed commonly cited cost-effectiveness thresholds. While there is no announced price yet for CAM20138, ICER calculated a value-based price benchmark for the therapy would fall between $4,100 and $5,300 per year. CEPAC also made the following public policy recommendations:

1. Drug manufacturers should align the price of these medications with their benefits to patients and, once that is done, payers should make these treatments easier for patients to access.
2. Regulators and government policymakers should consider eliminating restrictions on prescribing extended-release treatments and avoid legislative action favoring one treatment over the others.

CMS Innovation Center Announces Updated MA VBID Model and New Part D Payment Modernization Model

On January 18, CMS' Innovation Center announced it will be making updates to the MA Value-Based Insurance Design (VBID) Model for 2020 and 2021 and will begin a new Part D Payment Modernization Model for 2020.

The MA VBID Model builds on the existing model with new interventions: targeting by socioeconomic status (low-income subsidy or dual eligible status); a more robust MA and Part D rewards and incentives program; allowing plans to use telehealth services to meet some network requirements; and new care coordination requirements. In 2021, the model will test, newly including the hospice benefit in MA.

The new Part D Payment Modernization Model, which is intended to reduce government spending for Medicare Part D enrollees during the catastrophic phase of the benefit, would run January 2020 through December 2024. The model is available to standalone Prescription Drug Plans and MA-Prescription Drug plans and would introduce two-sided risk by comparing actual reinsurance costs to a CMS-established benchmark. PDP sponsors would share in savings if they stay below that target and be accountable for losses if exceeding it.

CMS Proposes 2020-21 MA and Part D Changes

On November 1, CMS published a proposed rule containing revisions to the Medicare Advantage (MA) and Part D prescription drug benefit programs for plan years 2020 and 2021. Major highlights of the 2020-21 MA and Part D Proposed Rule include:

1. Implement select provisions from the Bipartisan Budget Act of 2018, including more flexibility for MA plans to offer additional telehealth benefits as part of the basic benefit; new definitions and minimum criteria for Dual Eligible Special Needs Plans (D-SNPs); and a unified grievance and appeals procedure at the plan level for D-SNPs and Medicaid managed care organizations
2. Proposal for Prescription Drug Plan sponsors' access to Medicare Parts A and B claims data extracts
3. Changes to the precluded prescriber requirements
4. Changes to the Star Ratings System, including enhancements to the current hierarchical clustering methodology used to set cut points for certain measures and changes to measures for 2022 and 2023
5. Extrapolation of errors in MA Risk Adjustment Data Validation audits without a fee-for-service (FFS) adjuster. (CMS also released a summary and a technical appendix on the FFS adjuster).

Trump, Azar announce Medicare Part B proposal

In Q4 of 2018, President Trump announced a new proposal aimed at linking certain Medicare Part B drug payments to prices charged for prescription drugs in other countries. In his remarks, the president stated: "We are taking aim at the global freeloading that forces American consumers to subsidize lower prices in foreign countries through higher prices in our country." HHS Secretary Alex Azar further defended the model, sharing new federal data showing prices charged by drug makers in the U.S. are 1.8 times higher than in other countries. Following the announcement, Senior Advisor to the Secretary for Drug Pricing Reform Dan Best, who served as senior advisor to the Secretary for Drug Pricing Reform until his death on Nov. 1, 2018, penned a blog further defending the model, suggesting it would save Medicare and Medicaid more than $50 billion in its first eight years.

CMS indicated it may issue a proposed rule in spring 2019 and launch a five-year model phase-in of selected geographic areas as early as spring 2020.

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Major Highlights of the Medicare Part B IPI Model

1. Establishing an International Pricing Index Model to reimburse certain Part B drugs based on a Target Price derived from pricing data for a basket of 14 Organization for Cooperation and Economic Development countries, such as the U.K. and Japan. Medicare would pay the Target Price if that price is lower than the average sales price (ASP).
2. In lieu of reimbursing physicians and hospitals for the cost of purchasing a Part B drug, CMS would instead reimburse selected national vendors based on a phased-in Target Price or ASP, whichever is lower. Potential model vendors may include Part D sponsors and specialty pharmacies.
3. Model vendors would be prohibited from paying rebates or volume-based incentives to physicians and hospitals.
4. Physicians and hospitals would be paid a set payment amount per encounter or per month for an administered drug, which CMS would base on 6% of the included drugs' ASP.

Trends in Oncology Management:

Oncology Care Model and Innovative Management Strategies

The pace of innovation in the oncology arena is seemingly unmatched by any other therapeutic area in the pharmaceutical pipeline, and it continues to accelerate. In the past five years, the Food and Drug Administration (FDA) has approved more than 60 novel cancer drugs that have impacted the way we treat more than 20 different cancer types.[1]

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In 2014, pembrolizumab was the first programmed death-1 (PD-1) checkpoint inhibitor to receive FDA approval.[2] Subsequently, there have been five other checkpoint inhibitors approved which utilize the PD-1 or programmed death ligand-1 (PD-L1) pathway to harness the power of the patient's own immune system to destroy their cancer cells.[2] The six approved PD-1/PD-L1 inhibitors are now approved to treat 14 unique types of cancer.[1] There has also been a trend toward the development of oncology agents with greater specificity, which are able to target cancer cells with specific biomarkers present. In the majority of these cases, there is a known correlation between the tumor type and the specific biomarker. However, in May 2017, pembrolizumab became the first agent to receive FDA approval based on the presence of a specific biomarker regardless of the tissue of origin. Subsequently, in November 2018, a second agent, larotrectinib (Vitrakvi®), became the second "tumor agnostic" agent to be approved by the FDA.[3]

More recently, chimeric antigen receptor T-cell (CAR-T) therapy has presented a new approach to harnessing the patient's own immune system. Currently available CAR-T therapies differ from traditional immuno-oncology agents because they are created from the patient's own T-cells.[4] T-cells are first harvested from the patient's blood, then genetically modified to produce chimeric antigen receptors (CARs) on the cell surface. The modified T-cells are then expanded in the laboratory before ultimately being infused back into the patient where they target the cancer cells. In August 2017, tisagenlecleucel (Kymriah®, Novartis) became the first CAR-T therapy to receive FDA approval. Specifically, it was approved for the treatment of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (ALL). In clinical trials, CAR-T therapy has been highly effective in very difficult-to-treat cancers, with 83% of patients in remission three months after a single intravenous infusion in the pivotal ELIANA trial.[4]

While recent developments in the

While recent developments in the pipeline present significant advancements in the treatment of a wide variety of cancers, they also present significant challenges to payors due to the high costs associated with them.

pipeline present significant advancements in the treatment of a wide variety of cancers, they also present significant challenges to payors due to the high costs associated with them.[5] When the CAR-T therapies came to market, they sent shockwaves through the payor and provider communities with their unprecedented high costs for a one-time intravenous infusion. Payors were motivated to change the way they managed oncology agents to ensure lifesaving innovations such as these would be available to the patients that needed them.[5]

Challenges in Oncology Management

Historically, many payors have refrained from tightly managing oncology agents for a number of reasons, including the seriousness of the disease as well as the fact that oncology agents generally fell under the medical benefit.[6,7] For many payors, the pharmacy and medical benefits worked in silos, and drugs billed under the medical benefit went largely unmanaged. There is also a great degree of heterogeneity in oncology, with slight differences in indications between approved products that limit competition amongst products. In addition, under Medicare Part D, oncology is considered a protected class and payors are required to accept the clinical recommendations of professional compendia such as the National Comprehensive Cancer Network (NCCN).[7]

For the relatively few claims that may have been billed through the pharmacy benefit, payors may have utilized prior authorization criteria to ensure appropriate utilization, with criteria confirming appropriate diagnosis and tumor biomarkers, as applicable.[6,7]

A New Frontier

The cost of cancer care in the U.S. is approaching $150 billion annually, and it is projected to reach $180 billion annually in 2020.[1] As a result, the need for innovative strategies to mitigate the financial impact of these high cost healthcare expenditures is greater than ever. With the increasing use of highly targeted and personalized therapy, the management of cancer is increasingly complex and expensive. Even prior to the introduction immuno-oncology and CAR-T therapy, the use of imaging, diagnostic tests, and the frequent use of multiple therapeutic modalities, such as surgical resection, radiation, chemotherapy, and biologics, led to total costs of care that easily exceeded $100,000 within the first year following a cancer diagnosis.[1] Prior to the introduction of immuno-oncology and CAR-T therapy, office-based administration of cancer drugs (including both oral and intravenous therapies) and hospitalization made up two-thirds of the annual cancer costs among Medicare patients.[8] The unprecedented high costs of the newer agents will only continue to increase the total cost of care.

Tackling a Growing Problem

Of the 1.7 million individuals diagnosed with cancer in the U.S. each year, a significant portion of those affected are 65 years of age and older and Medicare beneficiaries.[9] In an effort to address the skyrocketing cost of caring for patients with a cancer diagnosis, the Centers for Medicare and Medicaid Services (CMS) implemented the five-year CMS Oncology Care Model (OCM) in July 2016. The OCM is an innovative multipayor model designed to provide higher quality and more coordinated oncology care. According to CMS, the three main goals of this program are to achieve "better care, smarter spending, and healthier people."[9]

Through this care model, physician group practices have entered into payment arrangements with CMS that include both financial and performance accountability for episodes of care related to the administration of chemotherapy. Physician group practices participating in the OCM are responsible for providing enhanced services to Medicare beneficiaries, such as care coordination and navigation, as well as evidence-based care in accordance with national treatment guidelines.[9]

There are over 175 physician groups participating in the OCM. Practice participants were selected following an open application and selection period, and participating physician groups include Medicare-enrolled groups that are composed of one or more physicians who treat Medicare beneficiaries who are diagnosed with cancer.[9] There is a wide variety of physician groups participating, ranging in size from single practicing oncologists to large practices with hundreds of providers, as well as practice locations that cover urban, suburban, and rural areas. In addition to CMS, there are also 12 commercial insurers participating in the OCM who will align their oncology payment models with Medicare's model. These commercial insurers will also help to support the OCM physician groups in their efforts to transform practice under the OCM.[9]

The OCM utilizes financial incentives, such as performance-based payments, to pay providers for the quality of service provided, not the quantity provided. The performance-based model is designed to promote better care coor-

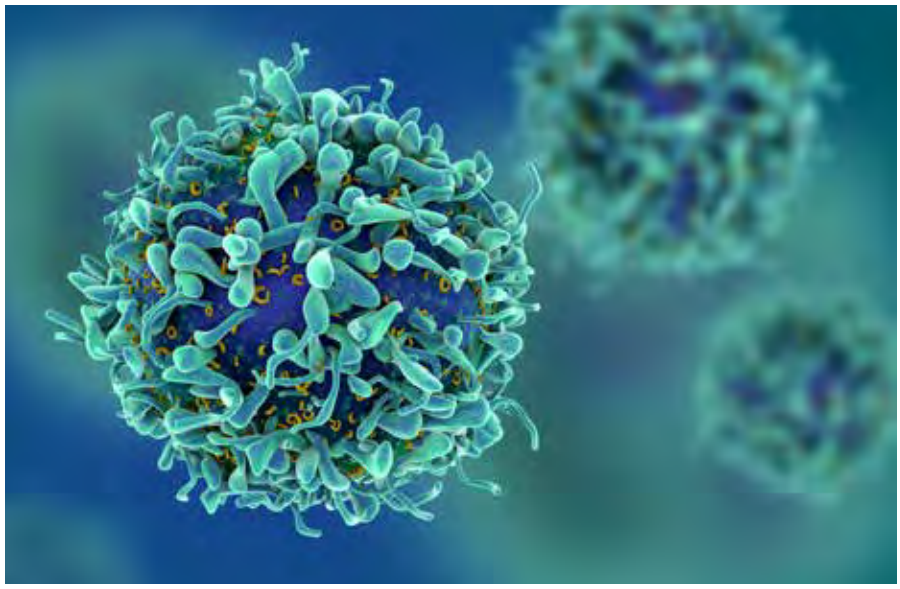
dination, more appropriate selection of therapy, and improved access for fee-for-service (FFS) Medicare beneficiaries who are receiving chemotherapy. If successful, the OCM will improve patient outcomes and deliver high-quality services at either the same or lower cost to Medicare.[9]

The target population for the OCM includes FFS Medicare beneficiaries who are receiving chemotherapy, and it covers the range of care patients receive during a six-month period, or "episode," that starts with chemotherapy.[9] More specifically, an episode begins on the date of an initial Medicare Part B or Part D chemotherapy claim and does not include services provided prior to that date. In the six months following the initial chemotherapy claim, the OCM FFS episode includes all Medicare Part A and Part B services that the beneficiary receives during that time, and certain Part D expenditures may also be included. Beneficiaries who continue to receive chemotherapy after the end of an episode will begin a new six-month episode starting the date of the subsequent chemotherapy claim.[9]

While participating in the OCM, providers continue to receive regular Medicare FFS payments, as well as a two-part payment approach to incentivize participating practices to improve the quality of care and provide enhanced services for beneficiaries undergoing chemotherapy.[9] These financial incentives include a monthly enhanced-oncology-services payment of $160 per beneficiary for providing enhanced services and a performance-based payment for OCM episodes. While the general approach to practice transformation is consistent across all participating payors, the specific payment amounts and episode definition may vary among the commercial insurers.[9]

The OCM is scheduled to run through June 30, 2021.[9] With the complexity and the scope of the model, the amount of data generated over five years will be immense. If proven successful at reducing Medicare expenditures while preserving or even improving the quality of care provided, the OCM is likely to have a profound impact on the way cancer care is paid for in the U.S., both by government and commercial payors.[8,9]

In addition to the OCM, a handful of other major health insurance providers have oncology-payment initiatives aimed at improving health outcomes at the lowest costs possible. The Anthem Cancer Care Quality Program is a quality initiative with the goal of bringing evidence-based cancer-treatment information to physician practices that will give physicians the information needed to compare the planned cancer treatment regimen to evidence-based clinical criteria.[10] The program also identifies evidence-based cancer treatment pathways (Anthem Cancer Treatment Pathways); these pathways are more specific than consensus guidelines, identifying treatments based on efficacy, toxicity profile, and cost. For in-network providers that use treatment regimens that align with an Anthem-approved pathway, Anthem may provide additional reimbursement.[10,11]



Aetna, in collaboration with Regional Cancer Care Associates (RCCA) of Maryland and New Jersey, launched an oncology medical home model in September 2016.[12] The goal of this medical home model is to provide continuous, proactive care to patients diagnosed with cancer, as well as physician incentives to promote improved health, affordability, and patient experience. The oncology medical home model was built on five basic principles, which include a focus on the patient as a whole, use of evidence-based and personalized care, provision of coordinated and integrated care, emphasis on quality and safety, and improvements in access to care. When it comes to caring for the patient from a holistic point of view, the RCCA physician is tasked with collaborating with other healthcare professionals to meet the individual's healthcare needs, ranging from preventative care to end-of-life care.[12] In terms of evidence-based and personalized care, all treatment decisions take into consideration both the clinical evidence and patient-specific factors. The model promotes coordinated and integrated care by ensuring all patients receive appropriate care across the healthcare continuum, taking into consideration patient-specific factors, such as their linguistic

and cultural needs. To achieve optimal quality and safety, the oncology medical home emphasizes evidence-based medicine that uses clinical decision support tools and accountability for quality improvement. Lastly, the model strives to improve patient access to care by promoting open scheduling, expanded hours of operation, and improvements in communication between patients and their providers.[12]

UnitedHealthcare, in collaboration with the Institute for Cancer Care Innovation at MD Anderson, launched a three-year pilot program in 2014 that was similar to the OCM in that it used an episode-of-care (also referred to as "bundled") payment structure.[9,13] In this pilot program that was limited to patients diagnosed with head and neck cancers, UnitedHealthcare made a single annual payment to MD Anderson to cover all inpatient and outpatient services provided to a patient. MD Anderson was then tasked with providing the patient the highest-quality care possible for as little money as possible. The pilot program ended in 2017 after enrolling 88 patients.[13] Given the small number of patients enrolled, the focus on a single cancer type, and the fact that MD Anderson has a reputation for providing exceptional care in oncology, it is unclear whether the outcomes of this small pilot would be broadly applicable to other healthcare systems and cancer types. Despite the program's limitations, Thomas W Feeley, MD, head of the Institute for Cancer Care Innovation at MD Anderson, reported that it was a success and that he would like to see more of these programs in place.[13]

The American Society of Clinical Oncology (ASCO) has drawn ideas from many of the pilot programs described above and has incorporated them into its Patient-Centered Oncology Payment (PCOP) model, which is similar to the OCM.[10,14,15] As many of these pilot programs do, the PCOP model focuses on providing higher-quality, lower-cost care with improved access to the critical services needed by individuals with cancer. The PCOP model was developed by medical oncologists, practice administrators, and experts in physician-payment and business analysis. Prior to implementation, ASCO elicited extensive feedback from their members, policymakers, and a variety of stakeholders from the oncology community, including patient advocates.[14] Under the PCOP model, higher upfront payments are issued to cover additional diagnostic services, care planning, and management to promote adherence, as well as evaluations for clinical trials. The PCOP model has been operating in collaboration with a commercial payor. In September 2018, ASCO proposed that CMS's Physician-Focused Payment Model Technical Advisory Committee (PTAC) consider implementation of PCOP as an advanced Alternative Payment Model (APM).

ASCO's recommendation underscores the challenges faced as the organization notes the need for additional advanced APMs, to promote ongoing patient access to and foster new value-based approaches to cancer care.[14,15] The search for innovative approaches to decreasing Medicare spending while bettering quality of care continues. In December 2018, PTAC recommended implementation of the Making Accountable Sustainable Oncology Networks (MASON) model. This program, adopted from the Community Oncology Medical Home (COME HOME), aims to have cancer care administered across clinic and hospital settings. MASON is positioned as a means of guiding delivery of evidence-based care by community-based oncologists while creating incentives to reward quality of care and cost savings.[16]

In addition to the innovative care coordination models that are being investigated, another trend among payors is shifting high-cost, physician-administered medications typically billed through the medical benefit into the pharmacy benefit.[16] Payors pursuing this strategy believe it will improve opportunities for utilization management of these agents, by permitting use of traditional management strategies such as prior authorization and step therapy.[6,17]

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Future Directions

One theme that has been apparent throughout the various pilot programs that have been tested is that there is an appetite for greater care coordination, with payors and clinicians approaching the patient holistically to improve patient outcomes.[13] Another theme is the importance of data collection. As a part of Horizon Blue Cross Blue Shield of New Jersey's episode-of-care program for breast cancer, following each episode, a retrospective review is conducted to determine whether quality metrics were met and whether expenditures were less than anticipated, which would result in shared cost savings. The data collected is entered into a data platform that categorizes the

cancer according to molecular subtype, and the information from that database is used to select the treatment that is most likely to work for an individual patient, decreasing the likelihood that time and money are wasted on ineffective treatments.[13] The ability to ultimately put that kind of data in the hands of clinicians on the front lines of treatment could transform the way we treat cancer. Given its significant advantages, experts in the field predict that oncology care will eventually shift entirely to an episode-of-care payment structure and suggest that perhaps other areas of healthcare should follow suit.[13]

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Digital Therapeutics:

Advances in Healthcare Innovation

The area of digital health is rapidly growing, with widespread adoption of health-related mobile applications, or "apps," and a variety of wearable sensors that are available to consumers. In 2017, there were an estimated 318,500 different health-related apps available, with approximately 200 new apps being created each day.

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Although wellness apps continue to account for the majority of available health-related apps, those focused on patient care, referred to as digital therapeutics, are growing at an increased rate and now account for approximately 40% of all available health-related apps.[1]

The use of digital therapeutics represents a new approach to the prevention and management of disease. By definition, digital therapeutics encompass a category of apps that can be used by the patient with the goal of modifying behavior and providing remote monitoring of their disease state to promote improved health outcomes.[2] For example, apps can be used to promote weight loss by helping patients adhere to diet and exercise plans. While there are many wellness apps currently on the market that can be used for a similar purpose, the key difference between digital therapeutics and wellness apps is that digital therapeutics are used to implement treatment programs that are specific to an individual patient's disease state(s). Chronic disease states such as diabetes or hypertension may offer ideal targets for digital therapeutics because these diseases may be significantly influenced by patient behavior.

Perhaps one of the greatest potential advantages of digital therapeutics, if proven effective, is that they may improve an individual's health without the high cost and potential side effects that may be associated with drug therapy. There is also a great deal of interest in the development of these applications from the technology industry, as they represent an opportunity to provide a therapeutic benefit to patients without the significant costs associated with bringing an actual medication to market.[3]

Could these apps ultimately replace the need for medications?

While the idea of using technology to treat disease in lieu of medication may sound appealing to many, it is highly unlikely that these apps would ever completely replace the need for medications. Experts in the field of digital therapeutics describe two different categories that these apps may fall into, including those that either augment or replace medication.[3] As the name suggests, apps designed for medication augmentation are intended for use in addition to pharmacotherapy to manage a disease. For example, use of an app to promote better diet and exercise

By definition, digital therapeutics encompass a category of apps that can be used by the patient with the goal of modifying behavior and providing remote monitoring of their disease state to promote improved health outcomes.

in a patient with high cholesterol that is also using a statin could potentially improve patient outcomes. Conversely, apps that are intended for medication replacement are designed to provide a similar benefit to the patient as a medication, allowing the patient to decrease or discontinue pharmacotherapy altogether. For example, an online therapy program called Sleepio incorporates visualization exercises to help patients suffering from insomnia achieve better sleep, without the need for medication therapy.[3]

What does the current body of literature say about the efficacy of digital therapeutics?

In order to differentiate digital therapeutics from general wellness apps, companies may conduct clinical trials and ultimately seek regulatory approval from the Food and Drug Administration (FDA). Although FDA approval of digital therapeutics is not required, regulatory approval may be beneficial to the company, as it suggests that the product has demonstrated a therapeutic benefit in clinical trials.[3]

Although there is a scarcity of published data evaluating the use of digital therapeutics, the technology companies behind these apps have shared publicly some of the key outcomes. One such study was conducted by Virta Health, evaluating an app designed to reverse diabetes without concomitant use of pharmacotherapy or surgery.[3] The app promotes a high-fat, low-carb diet in conjunction with online coaching. Virta Health reported that of the 262 patients with type 2 diabetes included in the 10-week study, approximately half of the study participants were able to achieve blood glucose levels that were considered below the clinical definition of diabetes.[3]

Because FDA-approval of digital therapeutics is not currently a requirement, there is flexibility in the way the clinical trials are designed. Some companies with digital therapeutics in development have used the template established by the drug industry, which includes the use of a placebo group. For example, Big Health compared their insomnia app to a placebo version, giving one group of study participants access to sham visualization exercises, while the other group utilized cognitive behavioral therapy. While detailed data is not currently available, Big Health reported that the digital therapeutic performed significantly better compared to the sham app.[1,3]

How is the FDA adapting to the influx of digital therapeutics?

As previously mentioned, the FDA does not currently require regulatory review for digital therapeutics prior to market entry. Despite the lack of regulations surrounding these apps, leaders in the digital-health industry formed the Digital Therapeutics Alliance in an effort to better define the new digital health industry. The Alliance, which currently includes 13 member companies, has expressed interest in the development of a formal process for the testing and subsequent approval of digital therapeutics.[4,5] In 2015, Pear Therapeutics, a member of the Digital Therapeutics Alliance, requested that the FDA review their software-based substance abuse therapy called reSET.[5] The FDA granted approval in September 2017. [6]

In 2017, the 21st Century Cures Act was passed by Congress and included the FDA's Digital Health Innovation Action Plan. According to this plan, the FDA stated its intention to encourage digital health innovation by redesigning policies and processes, as well as modernizing their tools to meet the need of the expanding digital health technology industry. In addition, the FDA specified it would provide clarity on policies and processes for the developers of digital therapeutics to deliver guidance on potential requirements to achieve regulatory approval.[5]

Following the declaration of the Digital Health Innovation Action Plan, the Digital Health Software Precertification Program pilot launched in September 2017.[5] The pilot program includes a variety of digital health companies, healthcare stakeholders, patients and caregivers, all collaborating on the development of the policies and processes to be used in the Precertification Program. The goal of the Precertification Program is to precertify the health technology company that developed the app, not the app itself. According to FDA Commissioner Scott Gottlieb, the FDA will review systems for software design, validation, and maintenance. If the company meets the necessary quality standards, they would receive precertification, which could potentially allow the company to submit less information to the FDA than what is currently required, or in some cases, precertified companies may be able to market their digital therapeutic without a premarket regulatory submission at all. Such an exemption may apply to certain lower-risk apps for companies that have demonstrated that the underlying software and internal

processes are sufficiently reliable. The company would then be responsible for immediately beginning post-marketing data collection that could be used by the FDA to confirm that the digital therapeutic remains safe and effective.[5] Following successful implementation of the Precertification pilot program, the FDA launched Developing a Software Precertification Program: A Working Model v1.0 in January 2019.[7]

In a January 8, 2019, announcement, the FDA introduced a draft regulatory framework to test new approaches for the review of digital health device applications. According to the FDA Commissioner, the new framework aims to "promote the development of novel, beneficial technology while ensuring patients have access to high-quality, safe and effective digital health devices."[8]

What are some of the challenges and unanswered questions associated with digital therapeutics?

Perhaps one of the greatest challenges with the implementation of new digital therapeutics is that the majority of physicians have never used such applications and they may not be familiar with applications that may be available for treating their patients.[9] As a result, the adoption of digital therapeutics by physicians will likely be slow and require education to ensure it is being used in an effective manner. In a survey conducted by Personal Connected Health Alliance, the majority of physicians surveyed said they would use digital therapeutics in combination with existing drug therapy for their patients, indicating an openness to the addition of digital therapeutics into a patient's treatment plan, but not necessarily a willingness to try replacing traditional prescription medicines with such applications.[9]

As with any therapy, digital therapeutics have a cost associated with them, and the out of pocket cost to the patient can greatly impact whether the patient initiates treatment and whether they will continue to use it. With traditional drug products, patients tend to be more likely to adhere to therapy if their insurance company covers a significant portion of the cost. At this time, it is unclear whether or how insurance companies would consider coverage of digital therapeutics, as they are non-drug products, and most plans do not have a benefit design that supports the review and coverage of them. If regulatory approval for the digital therapeutic is sought and received from the FDA, insurance companies may be more likely to reimburse patients for the costs associated with therapy. Regulatory approval, however, may also be associated with some disadvantages, including that it is a slow and expensive process. The slow-moving nature of regulatory approval is in contrast to the rapidly evolving nature of technology. By the time an app receives FDA approval, it may have undergone several updates since conception. These updates can range anywhere from the addition of new services or features to simple bug fixes and updates to the software to make it compatible with newer operating systems. To ensure patients are able to afford to utilize digital therapeutics, FDA approval may be necessary; however, the process for approval in this field should be performed in such a way that it does not limit the evolution and progression of the technology. In addition to the potential cumbersome regulatory review process, regulatory approval of a digital therapeutic could lead to prescription-only status. In doing so, the company may inadvertently hinder patient access. Although this would allow for an increased ability to bill insurance companies for the therapeutic product, restricting access to prescription-only status may inhibit widespread adoption if there is a lack of prescriber awareness of how to write prescriptions for such apps. For example, if a doctor writes a prescription for a drug product, the doctor knows that the patient can take that prescription to the pharmacy to have it filled. If apps have prescription-only status, there will need to be a process for the verification of prescriptions issued to patients in order for the patient to download and utilize the app. Given the newness of the technology, many prescribers may be unaware of how this process will work.[9]

In a survey conducted by Personal Connected Health Alliance, the majority of physicians surveyed said they would use digital therapeutics in combination with existing drug therapy for their patients, indicating an openness to the addition of digital therapeutics into a patient's treatment plan, but not necessarily a willingness to try replacing traditional prescription medicines with such applications.

In addition, payors will need to determine whether they will cover digital therapeutics and, further, which benefit digital therapeutics will fall under - pharmacy, medical or an

alternative benefit. With a lack of data available evaluating the efficacy of digital therapeutics, some payors may delay coverage of technology until more information becomes available. For those plans that do elect to cover digital therapeutics, they will also need to determine the logistics of how these apps would be covered, including the billing process. Unlike traditional medications or medical services, there is no established way to bill the payor for use of an app, so such methods will need to be developed and clearly defined.

Another challenge facing the industry is that digital therapeutics require a higher level of engagement, from both the patient and the doctor, compared to alternative treatments. With traditional drug products, the patient must remember to take the medication as prescribed in order for it to work; however, with apps, patients must remember to input information, as needed, and follow directions from the app in order to achieve the therapeutic benefit. Without full engagement, the patient is unlikely to achieve the desired effect. For apps that require patient input of certain information, such as weight, blood pressure, or blood glucose, the efficacy of the app will also be dependent on the accuracy of the information being entered by the patient. Educating the patient on the proper use of the app, as well as the correct way to measure the necessary parameters, will be essential to the patient's success with the therapy.

When caring for patients, protecting their privacy is of the utmost importance. The use of digital therapeutics may present unique security and privacy challenges, given the significant exchange of patient information that occurs through the app. Ensuring these apps are compatible with both the Health Insurance Portability and Accountability Act and Health Information Technology standards is key to protecting patient information. These apps operate through personal devices such as cellphones; thus, the ability to control the flow of this information may be more difficult. In addition to the challenge of protecting patient information, sponsors of digital therapeutics may also have a difficult time convincing patients that these apps are secure enough to trust with their health information. Patients will be understandably wary of how well their information will be protected, and a breach of privacy early on could greatly hinder the implementation of this form of therapy.

As previously mentioned, the line between digital therapeutics and wellness apps is not clearly defined, which may lead to some confusion among patients.[1,2] Regulatory review and subsequent approval by the FDA may help to distinguish between the two and may make it more clear to both physicians and patients which apps have sufficient data demonstrating their efficacy. Without a regulatory review process to evaluate potential products as well as distinguish between digital therapeutics and wellness apps, patients may not find successful apps that match their clinical needs.

The future opportunities for digital therapeutics that can enhance or potentially replace pharmacotherapy are virtually endless.

What are the future opportunities in this field?

While many challenges and questions remain unanswered regarding the adoption of digital therapeutics into clinical practice, the future opportunities for digital therapeutics that can enhance or potentially replace pharmacotherapy are virtually endless. Perhaps the biggest opportunity relates to the amount of data that could be collected and studied. In traditional clinical trials, data collection is a burdensome process that requires significant effort on the part of the study investigators, as well as study participants who may be required to travel to the clinic for the data collection. As a result, the cost associated with clinical trials may also limit the scope of the study in terms of patient enrollment and study duration, among other factors. Given the digital nature of data collection that could occur using a digital therapeutic, data collection can occur remotely, allowing for extended periods of data collection. Instead of studying the long-term effects of a cholesterol-lowering medication over a period of a couple of years, for example, imagine the potential to continue collecting and analyzing the effects of that medication on a large patient population over 10 years.

Furthermore, the data that may be collected from patients engaging with a digital therapeutic platform is more likely to represent the "real world" use of the therapeutic, whether it is the app itself or a medication being used in conjunction with the app, compared to what is observed in clinical trials. This allows researchers to get a better understanding of how the app or the medication in question might work in patients outside of the context of a clinical trial.

Despite the unanswered questions, digital therapeutics represent an exciting multimodal treatment approach that is sure to increase patient engagement.

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For adult patients with relapsed or refractory CLL or SLL after at least 2 prior therapies

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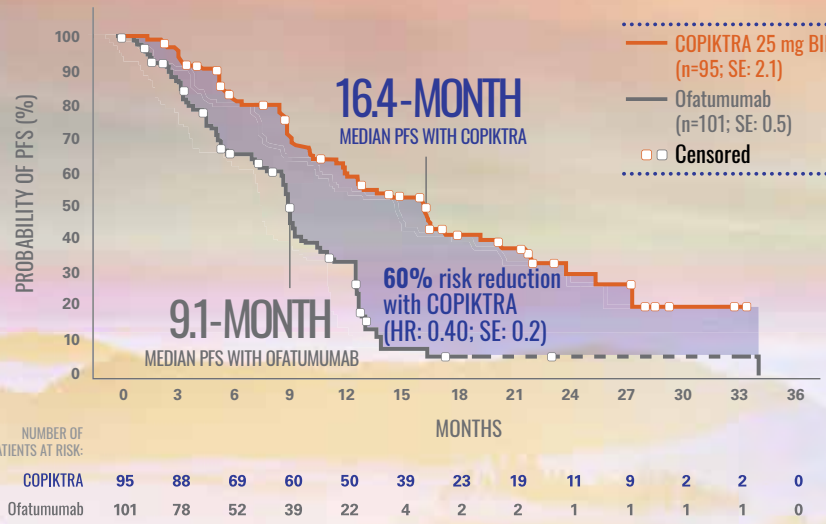
The first and only oral dual PI3K-δ and PI3K-γ inhibitor[1]

Patients achieved a >7 month median PFS advantage with oral COPIKTRA vs IV ofatumumab in the pivotal phase 3 DUO trial[1,2]*



NUMBER OF PATIENTS AT RISK:													
COPIKTRA	95	88	69	60	50	39	23	19	11	9	2	2	0
Ofatumumab	101	78	52	39	22	4	2	2	1	1	1	1	0

- Efficacy was based on a subanalysis of patients with at least 2 prior lines of therapy, where the risk:benefit ratio appeared greater in this more heavily pretreated population (n=196)[1]
- Safety was based on the comprehensive overall study population (N=319)[1]

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*Kaplan-Meier estimate.
CLL, chronic lymphocytic leukemia; δ, delta; γ, gamma; HR, hazard ratio; IV, intravenous; PI3K, phosphoinositide 3-kinase; PFS, progression-free survival; SE, standard error; SLL, small lymphocytic lymphoma.

IMPORTANT SAFETY INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS

- **Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected.**
- **Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA.**
- **Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA.**
- **Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA.**

WARNINGS AND PRECAUTIONS

Infections: Serious, including fatal (18/442; 4%), infections occurred in 31% of patients receiving COPIKTRA 25 mg BID (N=442). The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Treat infections prior to initiation of COPIKTRA. Advise patients to report new or worsening signs and symptoms of infection. For grade 3 or higher infection, withhold COPIKTRA until infection is resolved. Resume COPIKTRA at the same or reduced dose. Serious, including fatal, *Pneumocystis jirovecii* pneumonia (PJP) occurred in 1% of patients taking COPIKTRA. Provide prophylaxis for PJP during treatment with COPIKTRA and following completion of treatment with COPIKTRA until the absolute CD4+ T cell count is greater than 200 cells/μL. Withhold COPIKTRA in patients with suspected PJP of any grade, and permanently discontinue if PJP is confirmed. Cytomegalovirus (CMV) reactivation/infection occurred in 1% of patients taking COPIKTRA. Consider prophylactic antivirals during COPIKTRA treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold COPIKTRA until infection or viremia resolves. If COPIKTRA is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly.

Diarrhea or Colitis: Serious, including fatal (1/442; <1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg BID (N=442). Median time to onset of any grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month). Advise patients to report any new or worsening diarrhea. For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e., up to

IMPORTANT SAFETY INFORMATION (cont'd)

6 stools per day over baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents, continue COPIKTRA at the current dose, and monitor the patient at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g., budesonide). Monitor the patient at least weekly. Upon resolution of the diarrhea, consider restarting COPIKTRA at a reduced dose. For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs, or with severe diarrhea (Grade 3) (i.e., >6 stools per day over baseline), withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g., budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart COPIKTRA at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue COPIKTRA. Discontinue COPIKTRA for life-threatening diarrhea or colitis.

Cutaneous Reactions: Serious, including fatal (2/442; <1%), cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg BID (N=442). Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). Median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75th percentile: 6 months) with a median event duration of 1 month (range: 1 day to 37 months, 75th percentile: 2 months). Presenting features for the serious events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Advise patients to report new or worsening cutaneous reactions. Review all concomitant medications and discontinue any medications potentially contributing to the event. For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue COPIKTRA at the current dose, initiate supportive care with emollients, antihistamines (for pruritus), or topical steroids, and monitor the patient closely. Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or antihistamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart COPIKTRA at a reduced dose. Discontinue COPIKTRA if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous reactions, discontinue COPIKTRA. In patients with SJS, TEN, or DRESS of any grade, discontinue COPIKTRA.

Pneumonitis: Serious, including fatal (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg BID (N=442). Median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months. Withhold COPIKTRA in patients with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation, and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on COPIKTRA at the previous dose once the infection, pulmonary signs and symptoms resolve. For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids and resume COPIKTRA at a reduced dose upon resolution. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue COPIKTRA. For severe or life-threatening non-infectious pneumonitis, discontinue COPIKTRA and treat with systemic steroids.

Hepatotoxicity: Grade 3 and 4 ALT and/or AST elevation developed in 8% and 2%, respectively, of patients receiving COPIKTRA 25 mg BID (N=442). Two percent of patients had both an ALT or AST > 3 X ULN and total bilirubin > 2 X ULN. Median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with a median event duration of 1 month (range: 1 day to 16 months). Monitor hepatic function during treatment with COPIKTRA. For Grade 2 ALT/AST elevation (> 3 to 5 X ULN), maintain COPIKTRA dose and monitor at least weekly until return to < 3 X ULN. For Grade 3 ALT/AST elevation (> 5 to 20 X ULN), withhold COPIKTRA and monitor at least weekly until return to < 3 X ULN. Resume COPIKTRA at the same dose (first occurrence) or at a reduced dose for subsequent occurrences. For grade 4 ALT/AST elevation (> 20 X ULN), discontinue COPIKTRA.

Neutropenia: Grade 3 or 4 neutropenia occurred in 42% of patients receiving COPIKTRA 25 mg BID (N=442), with Grade 4 neutropenia occurring in 24% of all patients. Median time to onset of grade ≥3 neutropenia was 2 months. Monitor neutrophil counts at least every 2 weeks for the first 2 months of COPIKTRA therapy, and at least weekly in patients with neutrophil counts < 1.0 Gi/L (Grade 3-4). Withhold COPIKTRA in patients presenting with neutrophil counts < 0.5 Gi/L (Grade 4). Monitor until ANC is > 0.5 Gi/L, then resume COPIKTRA at same dose for the first occurrence or at a reduced dose for subsequent occurrences.

Embryo-Fetal Toxicity: Based on findings in animals and its mechanism of action, COPIKTRA can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Conduct pregnancy testing before initiating COPIKTRA treatment. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose.

ADVERSE REACTIONS

B-cell Malignancies Summary

Fatal adverse reactions within 30 days of the last dose occurred in 8% (36/442) of patients treated with COPIKTRA 25 mg BID. Serious adverse reactions were reported in 289 patients (65%). The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%) most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The most common adverse reactions (reported in ≥20% of patients) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain and anemia.

CLL/SLL

Fatal adverse reactions within 30 days of the last dose occurred in 12% (19/158) of patients treated with COPIKTRA and in 4% (7/155) of patients treated with ofatumumab. Serious adverse reactions were reported in 73% (115/158) of patients treated with COPIKTRA and most often involved infection (38%; 60/158) and diarrhea or colitis (23%; 36/158). COPIKTRA was discontinued in 57 patients (36%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 46 patients (29%), most often due to diarrhea or colitis and rash. The most common adverse reactions with COPIKTRA (≥20% of patients) were diarrhea or colitis, neutropenia, pyrexia, upper respiratory tract infection, pneumonia, rash, fatigue, nausea, anemia and cough.

DRUG INTERACTIONS

CYP3A Inducers: Coadministration with a strong CYP3A inducer may reduce COPIKTRA efficacy. Avoid coadministration with strong CYP3A4 inducers.

CYP3A Inhibitors: Coadministration with a strong CYP3A inhibitor may increase the risk of COPIKTRA toxicities. Reduce COPIKTRA dose to 15 mg BID when coadministered with a strong CYP3A4 inhibitor.

CYP3A Substrates: Coadministration of COPIKTRA with sensitive CYP3A4 substrates may increase the risk of toxicities of these drugs. Consider reducing the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities of the coadministered sensitive CYP3A substrate.

INDICATIONS AND USAGE

COPIKTRA™ (duvelisib) is indicated for: The treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

Please see brief summary of full Prescribing Information on the following pages.

REFERENCES: 1. COPIKTRA Prescribing Information, Verastem, Inc. **2.** Data on file, Verastem Oncology.

PM-US-DUV-18-0074 Printed in USA | November 2018

Verastem Oncology

COPIKTRA (duvelisib) Capsules, for oral use
BRIEF SUMMARY OF PRESCRIBING INFORMATION - CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

WARNING: FATAL AND SERIOUS TOXICITIES: INFECTIONS, DIARRHEA OR COLITIS, CUTANEOUS REACTIONS, and PNEUMONITIS

- Fatal and/or serious infections occurred in 31% of COPIKTRA-treated patients. Monitor for signs and symptoms of infection. Withhold COPIKTRA if infection is suspected *[see Warnings and Precautions (5.1)]*.
- Fatal and/or serious diarrhea or colitis occurred in 18% of COPIKTRA-treated patients. Monitor for the development of severe diarrhea or colitis. Withhold COPIKTRA *[see Warnings and Precautions (5.2)]*.
- Fatal and/or serious cutaneous reactions occurred in 5% of COPIKTRA-treated patients. Withhold COPIKTRA *[see Warnings and Precautions (5.3)]*.
- Fatal and/or serious pneumonitis occurred in 5% of COPIKTRA-treated patients. Monitor for pulmonary symptoms and interstitial infiltrates. Withhold COPIKTRA *[see Warnings and Precautions (5.4)]*.

1. INDICATIONS AND USAGE

1.1 Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)
COPIKTRA is indicated for the treatment of adult patients with relapsed or refractory CLL or SLL after at least two prior therapies.

3 DOSAGE FORMS AND STRENGTHS

Strength	Description
25 mg	White to off-white opaque and Swedish orange opaque capsule printed in black ink with "duv 25 mg"
15 mg	Pink opaque capsule printed in black ink with "duv 15 mg"

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS

5.1 Infections
Serious, including fatal (18/442; 4%), infections occurred in 31% of patients receiving COPIKTRA 25 mg BID (N = 442). The most common serious infections were pneumonia, sepsis, and lower respiratory infections. Median time to onset of any grade infection was 3 months (range: 1 day to 32 months), with 75% of cases occurring within 6 months. Treat infections prior to initiation of COPIKTRA. Advise patients to report any new or worsening signs and symptoms of infection. For grade 3 or higher infection, withhold COPIKTRA until infection has resolved. Resume COPIKTRA at the same or reduced dose *[see Dosage and Administration (2.3)]*. Serious, including fatal, *Pneumocystis jirovecii* pneumonia (PJP) occurred in 1% of patients taking COPIKTRA. Provide prophylaxis for PJP during treatment with COPIKTRA. Following completion of COPIKTRA treatment, continue PJP prophylaxis until the absolute CD4+ T cell count is greater than 200 cells/μL. Withhold COPIKTRA in patients with suspected PJP of any grade, and permanently discontinue if PJP is confirmed. CMV reactivation/ infection occurred in 1% of patients taking COPIKTRA. Consider prophylactic antivirals during COPIKTRA treatment to prevent CMV infection including CMV reactivation. For clinical CMV infection or viremia, withhold COPIKTRA until infection or viremia resolves. If COPIKTRA is resumed, administer the same or reduced dose and monitor patients for CMV reactivation by PCR or antigen test at least monthly *[see Dosage and Administration (2.3)]*.

5.2 Diarrhea or Colitis
Serious, including fatal (1/442; <1%), diarrhea or colitis occurred in 18% of patients receiving COPIKTRA 25 mg BID (N = 442). The median time to onset of any grade diarrhea or colitis was 4 months (range: 1 day to 33 months), with 75% of cases occurring by 8 months. The median event duration was 0.5 months (range: 1 day to 29 months; 75th percentile: 1 month). Advise patients to report any new or worsening diarrhea. For non-infectious diarrhea or colitis, follow the guidelines. For patients presenting with mild or moderate diarrhea (Grade 1-2) (i.e. up to 6 stools per day over baseline) or asymptomatic (Grade 1) colitis, initiate supportive care with antidiarrheal agents as appropriate, continue COPIKTRA at the current dose, and monitor the patient at least weekly until the event resolves. If the diarrhea is unresponsive to antidiarrheal therapy, withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide). Monitor the patient at least weekly. Upon resolution of the diarrhea, consider restarting COPIKTRA at a reduced dose. For patients presenting with abdominal pain, stool with mucus or blood, change in bowel habits, peritoneal signs or with severe diarrhea (Grade 3) (i.e. > 6 stools per day over baseline) withhold COPIKTRA and initiate supportive therapy with enteric acting steroids (e.g. budesonide) or systemic steroids. A diagnostic work-up to determine etiology, including colonoscopy, should be performed. Monitor at least weekly. Upon resolution of the diarrhea or colitis, restart COPIKTRA at a reduced dose. For recurrent Grade 3 diarrhea or recurrent colitis of any grade, discontinue COPIKTRA. Discontinue COPIKTRA for life-threatening diarrhea or colitis *[see Dosage and Administration (2.3)]*.

5.3 Cutaneous Reactions
Serious, including fatal (2/442; <1%), cutaneous reactions occurred in 5% of patients receiving COPIKTRA 25 mg BID (N = 442). Fatal cases included drug reaction with eosinophilia and systemic symptoms (DRESS) and toxic epidermal necrolysis (TEN). Median time to onset of any grade cutaneous reaction was 3 months (range: 1 day to 29 months, 75th percentile: 6 months), with a median event duration of 1 month (range: 1 day to 37 months, 75th percentile: 2 months). Presenting features for the serious events were primarily described as pruritic, erythematous, or maculo-papular. Less common presenting features include exanthem, desquamation, erythroderma, skin exfoliation, keratinocyte necrosis, and papular rash. Advise patients to report any new or worsening cutaneous reactions. Review all concomitant medications and discontinue any medications potentially contributing to the event. For patients presenting with mild or moderate (Grade 1-2) cutaneous reactions, continue COPIKTRA at the current dose, initiate supportive care with emollients, anti-histamines (for pruritus), or topical steroids, and monitor the patient closely. Withhold COPIKTRA for severe (Grade 3) cutaneous reaction until resolution. Initiate supportive care with steroids (topical or systemic) or anti-histamines (for pruritus). Monitor at least weekly until resolved. Upon resolution of the event, restart COPIKTRA at a reduced dose. Discontinue COPIKTRA if severe cutaneous reaction does not improve, worsens, or recurs. For life-threatening cutaneous reactions, discontinue COPIKTRA. In patients with SJS, TEN, or DRESS of any grade, discontinue COPIKTRA *[see Dosage and Administration (2.3)]*.

5.4 Pneumonitis
Serious, including fatal (1/442; <1%), pneumonitis without an apparent infectious cause occurred in 5% of patients receiving COPIKTRA 25 mg BID (N = 442). Median time to onset of any grade pneumonitis was 4 months (range: 9 days to 27 months), with 75% of cases occurring within 9 months. The median event duration was 1 month, with 75% of cases resolving by 2 months. Withhold COPIKTRA in patients who present with new or progressive pulmonary signs and symptoms such as cough, dyspnea, hypoxia, interstitial infiltrates on a radiologic exam, or a decline by more than 5% in oxygen saturation and evaluate for etiology. If the pneumonitis is infectious, patients may be restarted on COPIKTRA at the previous dose once the infection, pulmonary signs and symptoms resolve. For moderate non-infectious pneumonitis (Grade 2), treat with systemic corticosteroids, and resume COPIKTRA at a reduced dose upon resolution. If non-infectious pneumonitis recurs or does not respond to steroid therapy, discontinue COPIKTRA. For severe or life-threatening non-infectious pneumonitis, discontinue COPIKTRA and treat with systemic steroids *[see Dosage and Administration (2.3)]*.

5.5 Hepatotoxicity
Grade 3 and 4 ALT and/or AST elevation developed in 8% and 2%, respectively, in patients receiving COPIKTRA 25 mg BID (N=442). Two percent of patients had both an ALT or AST greater than 3 x ULN and total bilirubin greater than 2 x ULN. Median time to onset of any grade transaminase elevation was 2 months (range: 3 days to 26 months), with a median event duration of 1 month (range: 1 day to 16 months). Monitor hepatic function during treatment with COPIKTRA. For Grade 2 ALT/AST elevation (greater than 3 to 5 × ULN), maintain COPIKTRA dose and monitor at least weekly until return to less than 3 × ULN. For Grade 3 ALT/AST elevation (greater than 5 to 20 × ULN), withhold COPIKTRA and monitor at least weekly until return to less than 3 × ULN. Resume COPIKTRA at the same dose (first occurrence) or at a reduced dose for subsequent occurrence. For grade 4 ALT/AST elevation (greater than 20 × ULN) discontinue COPIKTRA *[see Dosage and Administration (2.3)]*.

5.6 Neutropenia
Grade 3 or 4 neutropenia occurred in 42% of patients receiving COPIKTRA 25 mg BID (N = 442), with Grade 4 neutropenia occurring in 24% of all patients. The median time to onset of Grade ≥ 3 neutropenia was 2 months (range: 3 days to 31 months), with 75% of cases occurring within 4 months. Monitor neutrophil counts at least every 2 weeks for the first 2 months of COPIKTRA therapy, and at least weekly in patients with neutrophil counts < 1.0 Gi/L (Grade 3-4). Withhold COPIKTRA in patients presenting with neutrophil counts < 0.5 Gi/L (Grade 4). Monitor until ANC is > 0.5 Gi/L, resume COPIKTRA at same dose for the first occurrence or a reduced dose for subsequent occurrence *[see Dosage and Administration (2.3)]*.

5.7 Embryo-Fetal Toxicity
Based on findings in animals and its mechanism of action, COPIKTRA can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment and for at least 1 month after the last dose *[see Use in Specific Populations (8.1, 8.3), Clinical Pharmacology (12.1, 12.3)]*.

6.1 Clinical Trial Experience

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

Summary of Clinical Trial Experience in B-cell Malignancies

The data described below reflect exposure to COPIKTRA in two single-arm, open-label clinical trials, one open-label extension clinical trial, and one randomized, open-label, actively controlled clinical trial totaling 442 patients with previously treated hematologic malignancies primarily including CLL/SLL (69%) and FL (22%). Patients were treated with COPIKTRA 25mg BID until unacceptable toxicity or progressive disease. The median duration of exposure was 9 months (range 0.1 to 53 months), with 36% (160/442) of patients having at least 12 months of exposure. For the 442 patients, the median age was 67 years (range 30 to 90 years), 65% were male, 92% were White, and 93% had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1. Patients had a median of 2 prior therapies. The trials required hepatic transaminases at least ≤ 3 times upper limit of normal (ULN), total bilirubin ≤1.5 times ULN, and serum creatinine ≤ 1.5 times ULN. Patients were excluded for prior exposure to a PI3K inhibitor within 4 weeks. Fatal adverse reactions within 30 days of the last dose occurred in 36 patients (8%) treated with COPIKTRA 25mg BID. Serious adverse reactions were reported in 289 (65%) patients. The most frequent serious adverse reactions that occurred were infection (31%), diarrhea or colitis (18%), pneumonia (17%), rash (5%), and pneumonitis (5%). Adverse reactions resulted in treatment discontinuation in 156 patients (35%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 104 patients (24%) due to adverse reactions, most often due to diarrhea or colitis and transaminase elevation. The median time to first dose modification or discontinuation was 4 months (range 0.1 to 27 months), with 75% of patients having their first dose modification or discontinuation within 7 months.

Common Adverse Reactions

Table 1 summarizes common adverse reactions in patients receiving COPIKTRA 25mg BID, and Table 2 summarizes the treatment-emergent laboratory abnormalities. The most common adverse reactions (reported in ≥ 20% of patients) were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia.

Table 1 Common Adverse Reactions (≥ 10% Incidence) in Patients with B-cell Malignancies Receiving COPIKTRA

Adverse Reactions	COPIKTRA 25 mg BID (N = 442)	
	Any Grade n (%)	Grade ≥ 3 n (%)
Blood and lymphatic system disorders		
Neutropenia†	151 (34)	132 (30)
Anemia†	90 (20)	48 (11)
Thrombocytopenia†	74 (17)	46 (10)
Gastrointestinal disorders		
Diarrhea or colitis†[a]	222 (50)	101 (23)
Nausea†	104 (24)	4 (< 1)
Abdominal pain	78 (18)	9 (2)
Vomiting	69 (16)	6 (1)
Mucositis	61 (14)	6 (1)
Constipation	57 (13)	1 (< 1)
General disorders and administration site conditions		
Fatigue†	126 (29)	22 (5)
Pyrexia	115 (26)	7 (2)
Hepatobiliary disorders		
Transaminase elevation†[b]	67 (15)	34 (8)
Infections and infestations		
Upper respiratory tract infection†	94 (21)	2 (< 1)
Pneumonia†[c]	91 (21)	67 (15)
Lower respiratory tract infection†	46 (10)	11 (3)
Metabolism and nutrition disorders		
Decreased appetite	63 (14)	2 (< 1)
Edema†	60 (14)	6 (1)
Hypokalemia†	45 (10)	17 (4)
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain†	90 (20)	6 (1)
Arthralgia	46 (10)	1 (< 1)
Nervous system disorders		
Headache†	55 (12)	1 (< 1)
Respiratory, thoracic and mediastinal disorders		
Cough†	111 (25)	2 (< 1)
Dyspnea†	52 (12)	8 (2)
Skin and subcutaneous tissue disorders		
Rash†[d]	136 (31)	41 (9)

†Grouped term for reactions with multiple preferred terms

[a]Diarrhea or colitis includes the preferred terms: colitis, enterocolitis, colitis microscopic, colitis ulcerative, diarrhea, diarrhea hemorrhagic

[b]Transaminase elevation includes the preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hypertransaminasemia, hepatocellular injury, hepatotoxicity

[c]Pneumonia includes the preferred terms: All preferred terms containing "pneumonia" except for "pneumonia aspiration"; bronchopneumonia, bronchopulmonary aspergillosis

[d]Rash includes the preferred terms: dermatitis (including allergic, exfoliative, perivascular), erythema (including multiforme), rash (including exfoliative, erythematous, follicular, generalized, macular & papular, pruritic, pustular), toxic epidermal necrolysis and toxic skin eruption, drug reaction with eosinophilia and systemic symptoms, drug eruption, Stevens-Johnson syndrome

Grade 4 adverse reactions occurring in ≥ 2% of recipients of COPIKTRA included neutropenia (18%), thrombocytopenia (6%), sepsis (3%), hypokalemia and increased lipase (2% each), and pneumonia and pneumonitis (2% each).

Table 2 Most Common New or Worsening Laboratory Abnormalities (≥ 20% Any Grade) in Patients with B-cell Malignancies Receiving COPIKTRA

Laboratory Parameter[a]	COPIKTRA 25 mg BID (N = 442)	
	Any Grade n (%)[b]	Grade ≥ 3 n (%)[b]
Hematology abnormalities		
Neutropenia	276 (63)	184 (42)
Anemia	198 (45)	66 (15)
Thrombocytopenia	170 (39)	65 (15)
Lymphocytosis	132 (30)	92 (21)
Leukopenia	129 (29)	34 (8)
Lymphopenia	90 (21)	39 (9)
Chemistry abnormalities		
ALT increased	177 (40)	34 (8)
AST increased	163 (37)	24 (6)
Lipase increased	133 (36)	58 (16)
Hypophosphatemia	136 (31)	23 (5)
ALP increased	128 (29)	7 (2)
Serum amylase increased	101 (28)	16 (4)
Hyponatremia	116 (27)	30 (7)
Hyperkalemia	114 (26)	14 (3)
Hypoalbuminemia	111 (25)	7 (2)
Creatinine increased	106 (24)	7 (2)
Hypocalcemia	100 (23)	12 (3)

[a]Includes laboratory abnormalities that are new or worsening in grade or with worsening from baseline unknown.

[b]Percentages are based on number of patients with at least one post-baseline assessment; not all patients were evaluable.

Grade 4 laboratory abnormalities developing in ≥ 2% of patients included neutropenia (24%), thrombocytopenia (7%), lipase increase (4%), lymphocytopenia (3%), and leukopenia (2%).

Summary of Clinical Trial Experience in CLL/SLL

Study 1

The safety data below reflects exposure in a randomized, open-label, actively controlled clinical trial for adult patients with CLL or SLL who received at least one prior therapy. Of 313 patients treated, 158 received COPIKTRA monotherapy and 155 received ofatumumab. The 442-patient safety analysis above includes patients from Study 1. COPIKTRA was administered at 25 mg BID in 28-day treatment cycles until unacceptable toxicity or progressive disease. The comparator group received 12 doses of ofatumumab with an initial dose of 300 mg intravenous (IV) on Day 1

followed a week later by 7 weekly doses of 2000 mg IV, followed 4 weeks later by 2000 mg IV every 4 weeks for 4 doses. In the total study population, the median age was 69 years (range: 39 to 90 years), 60% were male, 92% were White, and 91% had an ECOG performance status of 0 to 1. Patients had a median of 2 prior therapies, with 61% of patients having received 2 or more prior therapies. The trial required a hemoglobin ≥ 8 g/dL and platelets ≥ 10,000 µL with or without transfusion support, hepatic transaminases ≤ 3 times upper limit of normal (ULN), total bilirubin ≤ 1.5 times ULN, and serum creatinine ≤ 2 times ULN. The trial excluded patients with prior autologous transplant within 6 months or allogeneic transplant, prior exposure to a PI3K inhibitor or a Bruton's tyrosine kinase (BTK) inhibitor, and uncontrolled autoimmune hemolytic anemia or idiopathic thrombocytopenic purpura. During randomized treatment, the median duration of exposure to COPIKTRA was 11.6 months with 72% (114/158) exposed for ≥ 6 months and 49% (77/158) exposed for ≥ 1 year. The median duration of exposure to ofatumumab was 5.3 months, with 77% (120/155) receiving at least 10 of 12 doses. Fatal adverse reactions within 30 days of the last dose occurred in 12% (19/158) of patients treated with COPIKTRA and in 4% (7/155) of patients treated with ofatumumab. Serious adverse reactions were reported in 73% (115/158) of patients treated with COPIKTRA and most often involved infection (38% of patients; 60/158) and diarrhea or colitis (23% of patients; 36/158). COPIKTRA was discontinued in 57 patients (36%), most often due to diarrhea or colitis, infection, and rash. COPIKTRA was dose reduced in 46 patients (29%) due to adverse reactions, most often due to diarrhea or colitis and rash.

Common Adverse Reactions

Table 3 summarizes selected adverse reactions in Study 1, and Table 4 summarizes treatment-emergent laboratory abnormalities. The most common adverse reactions with COPIKTRA (reported in ≥ 20% of patients) were diarrhea or colitis, neutropenia, pyrexia, upper respiratory tract infection, pneumonia, rash, fatigue, nausea, anemia and cough.

Table 3. Common Nonhematologic Adverse Reactions (≥ 10% Incidence) in Patients with CLL/SLL Receiving COPIKTRA (Study 1)

Adverse Reactions	COPIKTRA N = 158		Ofatumumab N = 155	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Gastrointestinal disorders				
Diarrhea or colitis[†a]	57	25	14	2
Nausea[†]	23	0	11	0
Constipation	17	<1	8	0
Abdominal pain	16	3	7	0
Vomiting	15	0	7	0
General disorders and administration site conditions				
Pyrexia	29	3	10	<1
Fatigue[†]	25	4	23	4
Hepatobiliary disorders				
Transaminase elevation[†d]	11	6	4	<1
Infections and infestations				
Upper respiratory tract infection[†]	28	0	16	<1
Pneumonia[†b]	27	22	8	3
Lower respiratory tract infection[†]	18	4	10	1
Investigations				
Weight decreased	11	0	2	0
Metabolism and nutrition disorders				
Decreased appetite	13	0	3	<1
Edema[†]	11	1	5	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[†]	17	1	12	<1
Respiratory, thoracic and mediastinal disorders				
Cough[†]	23	1	16	0
Dyspnea	12	3	7	0
Skin and subcutaneous tissue disorders				
Rash[†c]	27	11	15	<1

Grades were obtained per CTCAE version 4.03.

[†]Grouped term for reactions with multiple preferred terms

[a]Diarrhea or colitis includes the preferred terms: colitis, enterocolitis, colitis microscopic, colitis ulcerative, diarrhea

[b]Pneumonia includes the preferred terms: All preferred term containing "pneumonia" except for "pneumonia aspiration"; bronchopneumonia, bronchopulmonary aspergillosis

[c]Rash includes the preferred terms: dermatitis (including allergic, exfoliative, perivascular), erythema (including multiforme), rash (including exfoliative, erythematous, follicular, generalized, macular & papular, pruritic, pustular), toxic skin eruption, drug eruption

[d]Transaminase elevation includes the preferred terms: alanine aminotransferase increased, aspartate aminotransferase increased, transaminases increased, hepatotoxicity

Table 4. Most Common New or Worsening Laboratory Abnormalities (≥ 20% Any Grade) in Patients with CLL/SLL Receiving COPIKTRA (Study 1)

Laboratory Parameter	COPIKTRA N = 158		Ofatumumab N = 155	
	Any Grade (%)	Grade ≥ 3 (%)	Any Grade (%)	Grade ≥ 3 (%)
Hematology abnormalities				
Neutropenia	67	49	52	37
Anemia	55	20	36	7
Thrombocytopenia	43	16	34	8
Lymphocytosis	30	22	11	6
Chemistry abnormalities				
ALT increased	42	7	12	0
Lipase increased	37	12	15	3
AST increased	36	3	14	1
Phosphate decreased	34	3	20	3
Hyperkalemia	31	4	24	1
Hyponatremia	31	7	18	3
Amylase increased	31	5	10	1
Hypoalbuminemia	31	2	15	1
Creatinine increased	29	1	31	0
Alkaline phosphatase increased	27	0	14	0
Hypocalcemia	25	1	17	1
Hypokalemia	20	8	8	0

Grades were obtained per CTCAE version 4.03.

Grade 4 laboratory abnormalities that developed in ≥ 2% of COPIKTRA treated patients included neutropenia (32%), thrombocytopenia (6%), lymphopenia (3%), and hypokalemia (2%).

The data above are not an adequate basis for comparison of rates between the study drug and the active control.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on COPIKTRA

CYP3A Inducers: Co-administration with a strong CYP3A inducer decreases duvelisib area under the curve (AUC) *[see Clinical Pharmacology (12.3)]*, which may reduce COPIKTRA efficacy. Avoid co-administration of COPIKTRA with strong CYP3A4 inducers.

CYP3A Inhibitors: Co-administration with a strong CYP3A inhibitor increases duvelisib AUC *[see Clinical Pharmacology (12.3)]*, which may increase the risk of COPIKTRA toxicities. Reduce COPIKTRA dose to 15 mg BID when co-administered with a strong CYP3A4 inhibitor *[see Dosage and Administration (2.4)]*.

7.2 Effects of COPIKTRA on Other Drugs

CYP3A Substrates: Co-administration with COPIKTRA increases AUC of a sensitive CYP3A4 substrate *[see Clinical Pharmacology (12.3)]* which may increase the risk of toxicities of these drugs. Consider reducing the dose of the sensitive CYP3A4 substrate and monitor for signs of toxicities of the co-administered sensitive CYP3A substrate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary: Based on findings from animal studies and the mechanism of action, COPIKTRA can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available data in pregnant women to inform the drug-associated risk. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary: There are no data on the presence of duvelisib and/or its metabolites in human milk, the effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from duvelisib in a breastfed child, advise lactating women not to breastfeed while taking COPIKTRA and for at least 1 month after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing: COPIKTRA can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Conduct pregnancy testing before initiation of COPIKTRA treatment.

Contraception

Females Based on animal studies, COPIKTRA can cause fetal harm when administered to a pregnant woman. Advise females of reproductive potential to use effective contraception during treatment with COPIKTRA and for at least 1 month after the last dose.

Males Advise male patients with female partners of reproductive potential to use effective contraception during treatment with COPIKTRA and for at least 1 month after the last dose.

Infertility Based on testicular findings in animals, male fertility may be impaired by treatment with COPIKTRA *[see Nonclinical Toxicology (13.1)]*. There are no data on the effect of COPIKTRA on human fertility.

8.4 Pediatric Use

Safety and effectiveness of COPIKTRA have not been established in pediatric patients. Pediatric studies have not been conducted.

8.5 Geriatric Use

Clinical trials of COPIKTRA included 270 (61%) patients that were 65 years of age and older and 104 (24%) that were 75 years of age and older. No major differences in efficacy or safety were observed between patients less than 65 years of age and patients 65 years of age and older.

PM-US-DUV-18-0056

Clinical Connections Spotlight:

Hemlibra® and Hemophilia

Hemophilia, historically referred to as the "Royal disease," since it affected the royal houses of England, Germany, Russia, and Spain in the 19th and 20th centuries, is an X-linked recessive bleeding disorder leading to spontaneous bleeding and hemorrhaging following trauma or surgery. It is characterized by a deficiency of Factor VIII, or FVIII (hemophilia A) or Factor IX (hemophilia B).

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In the United States, hemophilia has a prevalence of roughly 20,000 people, mostly males, with hemophilia A being four times more common than hemophilia B.[1] Clinical manifestations include bleeding into different locations within the body, including joints (hemarthrosis), muscles, and soft tissues. Long-term sequelae can include arthritis, chronic pain, muscle atrophy, and loss of mobility. The development of inhibitors, occurring in approximately 30% of patients with severe FVIII deficiency[2], represents a significant complication. Inhibitors can compromise treatment efficacy of factor replacement therapy, place patients at higher risk of experiencing untreatable and potentially fatal bleeds, and may require extremely high factor doses to overcome inhibitors.[3] Considering these challenges, hemophilia is a complex and costly condition.

In December 2018, Magellan Rx Management hosted a *Clinical Connections* national webinar on hemophilia and Hemlibra®. A distinguished panel of experts, including Dr. Miguel Escobar, Medical Director of Gulf States Hemophilia and Thrombophilia Center in Houston and Dr. Michael Tarantino, Medical Director and President of The Bleeding and Clotting Disorders Institute in Peoria, Ill., explored hemophilia with a focus on the latest agent on the market: emicizumab (Hemlibra®).

During the webinar, the proliferation of treatment options for hemophilia, with 18 new agents approved since 2010 and 37 unique products available in total, was highlighted. Treatment options include recombinant products, such as the newer extended half-life agents. The first humanized monoclonal antibody garnered U.S. Food and Drug Administration (FDA) approval for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with or without FVIII inhibitors. This approval is notable for myriad reasons. Emicizumab is administered subcutaneously, which differs from typical infused-factor replacement therapy, requires less-frequent

The experts drove home the message that the ultimate treatment goal for patients with hemophilia is to maintain a normal life with minimal or zero bleeds with a safe drug.

injections (weekly, biweekly, and every four-week dosing), and is efficacious in patients with or without inhibitors. The Key Opinion Leaders (KOLs) noted that while the pivotal HAVEN trials found significant reductions in the number of treated bleeds, there are potential safety concerns, as evidenced by the black box warning of microangiopathy and thrombosis. Moreover, there have been seven reported deaths in patients on emicizumab therapy. While not directly related to emicizumab therapy, these deaths warrant caution. Hence, the KOLs emphasized the importance of long-term, vigilant safety surveillance for emicizumab in the real world.

Drs. Escobar and Tarantino discussed the clinical approach to therapy both in patients with and without inhibitors. The experts drove home the message that the ultimate treatment goal for patients with hemophilia is to maintain a normal life with minimal or zero bleeds with a safe drug. In the era of personalized medicine, the panel recommended evaluating each patient for appropriate therapy to ensure that the product characteristics are a good fit for the patient. One of the factors noted to impact emicizumab selection was cost, a key consideration of payer members of integrated care teams.

Other selection considerations for emicizumab included difficult venous access and breakthrough bleeding, despite aggressive factor prophylaxis.

The panel delved into the future of hemophilia with the advent of gene therapy and the imminence of gene editing in the coming years. Almost three decades after the approval of the first FVIII product, new technology is advancing at a high pace. The panel expressed that in an era of accelerated technology, patient safety is paramount.

Magellan Rx Management's *Clinical Connections* is a dynamic platform to connect payers, experts, and KOLs to dialogue on agents and trends with substantial clinical, financial, and management impact to the pharmacy and medical healthcare ecosphere. The goal of *Clinical Connections* is not only to educate and inform but also to provide thought leadership and timely expertise on these most relevant and complex topics to payers. Clinical implications to best practices, management and billing strategies, logistical considerations, and the role of key stakeholders are among the rich topics of conversation in *Clinical Connections*.

To access the Clinical Connections webinar highlighted in this article, please visit: *https://www1.magellanrx.com/magellan-rx/events/webinars.aspx*

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NUPLAZID® (pimavanserin) for Parkinson's Disease Psychosis

Parkinson's disease (PD) is a neurodegenerative disorder that affects nearly 1 million Americans and more than 10 million people worldwide.[1,2] While the incidence increases with age, it is estimated that 4% of people with Parkinson's disease are diagnosed before age 50.[2] Approximately 50% of patients with Parkinson's disease will develop Parkinson's disease psychosis (PDP), which, on average, is diagnosed 10 years following the initial diagnosis of Parkinson's disease.[3] The symptoms of PDP have been identified as some of the most disturbing features of PD to the patient and caregiver and represent a leading cause of hospitalizations and long-term care placement among this patient population.[4-6]

The symptoms of PDP can be overlooked given its challenging recognition, and sometimes the symptoms go unaddressed. Prior to the U.S. Food and Drug Administration (FDA) approval of a treatment for PDP-associated symptoms, treatment required trial and error with use of off-label therapies, many of which have accompanying side effects limiting their use, thus highlighting the need for an effective treatment. To address this unmet need, pimavanserin, the first and only FDA-approved therapy for this condition, was developed for the treatment of hallucinations and delusions associated with PDP. Following a review of the safety data for pimavanserin, the FDA issued a statement in September 2018 stating it found no new or unexpected safety risks associated with pimavanserin and reaffirmed the conclusion that the drug's benefits outweigh its risk for patients living with PDP-associated symptoms.[7]

In July 2016, a panel of experts, including neurologists, psychiatrists, geropsychiatrists, geriatricians, and managed care pharmacy representatives convened to discuss opinions, ideas, and information regarding the optimal management of PDP.[8] Some of the key findings from this panel included the following:[8]

1. Removal of medications for PDP that worsen motor symptoms of Parkinson's disease is suggested.
2. Pimavanserin should be considered a first-line treatment for patients with an established diagnosis of PDP.
3. Initial authorization of pimavanserin should be for six months to demonstrate clinical response.
4. Continued authorization of pimavanserin should be for one year, and requests for continuation of therapy should be accompanied by physician attestation of response to treatment.
5. Pimavanserin treatment should be continued for a minimum of six weeks to assess efficacy.
6. For patients deemed to be nonresponders to pimavanserin, consideration should then be given to its discontinuation and selection of other therapy.

Since the initial product launch, a new 34-mg capsule formulation and 10-mg tablet strength of pimavanserin have been approved for the treatment of hallucinations and delusions associated with PDP.

Since the initial product launch, a new 34-mg capsule formulation and 10-mg tablet strength of pimavanserin have been approved for the treatment of hallucinations and delusions associated with PDP. The capsule will deliver a single dosing unit to reduce pill burden for patients. The 10-mg tablet was approved to accommodate patients requiring dose adjustments when used in combination with strong CYP3A4 inhibitors. The 17-mg tablet strength that previously provided the 34-mg dose and dose adjustments has been removed from the labeling. The 34-mg capsule and 10-mg tablet became available in August 2018.

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Migraine Management:

Gaps in Care and Therapeutic Advances

Migraine headaches affect approximately 38 million individuals in the United States and range in severity and duration from acute and mild to chronic and debilitating.[1] Migraines account for approximately $14 billion in both direct and indirect expenditures each year.[2] A significant proportion of those costs is related to frequent migraine headaches caused by poor adherence to acute and prophylactic medications, leading to more frequent emergency room and urgent care visits.[1]

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A 2016 study highlighted that the mean costs per patient associated with managing headaches were markedly higher in those suffering from chronic migraine when compared to acute migraine ($8,243 versus $2,649, respectively).[1]

Current Consensus Guidelines for Migraine Treatment

The differences in patient presentation require an individualized approach to therapy, which is primarily accomplished through trial and error. Of course, some of the agents used are preferable, as they may offer fewer adverse effects compared to other agents. Consensus treatment guidelines currently recommend utilizing acetaminophen, non steroidal anti-inflammatory drugs (NSAIDs) or over-the-counter (OTC) combination products, such as acetaminophen/aspirin/caffeine as first-line treatment options. It is important to note that the caffeine present in some OTC products may not be appropriate for certain individuals, such as those who are pregnant, and caffeine-containing products may be associated with withdrawal headaches.[3]

If the patient does not achieve an adequate response with any of the available OTC options, second-line treatment options may include butalbital/acetaminophen/caffeine (Fioricet®), and butalbital/aspirin/caffeine (Fiorinal®); this category previously included isometheptene/dichloralphenazone/acetaminophen (Midrin®), which is no longer available as of October 12, 2017.[3] Although the guidelines recommend the use of the butalbital-containing combination products, these products are often avoided in clinical practice due to butalbital being associated with an increased risk of rebound withdrawal headaches and overuse headaches.[3] The butalbital-containing products are also not FDA approved for the acute treatment of migraine.

For patients who fail to respond to the first-and second-line therapies outlined above, treatment with either a triptan or an ergot may be indicated.[3] In clinical practice, triptans are generally

preferred due to the more favorable side effect profile; however, triptans are contraindicated in numerous cardiac diseases, which may limit their use.[3] The pharmacokinetic profiles and available dosage forms of the FDA-approved triptans vary greatly, and the selection of a preferred agent is often based on individual patient factors, including the health plan's formulary.

Current treatments for migraine target acute treatment of episodes once they occur but do not resolve the underlying cause of migraine to prevent subsequent episodes.

It is important to note that failure to respond to one triptan does not constitute a class failure, so trials with multiple triptans may be necessary to find the most effective agent for an individual patient.[3] For migraine sufferers who benefit from triptans, adherence with dosage recommendations my become a challenge, as patient demand for the triptan may exceed the FDA-approved dosage and prescription drug benefit quantity limits. In terms of the ergots, common side effects of ergotamine tartrate/caffeine (Cafergot®) and dihydroergotamine (Migranal®) are nausea and vomiting, which may limit their use in some patients who are unable to tolerate them. Both the nasal spray and injectable formulations of dihydroergotamine are associated with nausea and vomiting that often requires pretreatment with an antiemetic.[3] The ergots are also contraindicated in heart disease, liver disease, kidney disease, and pregnancy. For patients receiving ergots, pretreatment with antiemetics is commonly indicated to reduce the increased risk of nausea and vomiting. The preferred antiemetics are metoclopramide and prochlorperazine. Chlorpromazine may be considered an alternative antiemetic treatment.[3]

Opioids are currently considered to be the last-line option for the acute treatment of migraine due to their lack of migraine-specific activity.[3] Perhaps the most significant issue with the use of opioids in acute migraine treatment is the development of tolerance, dependence, and a high risk of rebound headache. Despite guidelines recommending use of opioids as a last line option, these medications are commonly used as abortive therapies.[3] For patients who suffer from severe migraines, guidelines recommend that treatment be initiated with a triptan or ergot as first-line therapy, and an opioid may be considered if they fail to respond.[3]

Current Gaps in Migraine Treatment

Despite being considered last line treatment options, opioids have historically been overused in acute migraine.[1] Due to the likelihood of rebound headaches with this drug class, frequent use may lead to greater healthcare spending due to repeated use of abortive therapies, as well as more numerous Emergency-department visits.[1] Although increased spending is most directly correlated with opioid therapy, higher levels of spending have been tied to acute therapy in general. Those who use more acute medications are most likely to be in the upper tier of spending among migraine sufferers. This may be partially due to the fact that most acute treatments, such as the triptans, are associated with an increased risk of rebound headaches with overuse. As the patient experiences more migraines, their use of abortive therapy increases; as their use of abortive therapy increases, they may experience more rebound headaches.[1]

Current treatments for migraine target acute treatment of episodes once they occur but do not resolve the underlying cause of migraine to prevent subsequent episodes. Additionally, their side effect profiles and propensity to cause rebound headaches may limit their usefulness. Over time, focus of migraine management has shifted toward prophylaxis.

Migraine Prophylaxis

Both patients who experience more than two migraine attacks per month and those who do not experience clinical success with the therapies recommended for acute treatment may benefit from prophylactic treatment; beta-blockers are considered first-line.[4] Propranolol is generally preferred because there is more data supporting its use; however, metoprolol and timolol are considered appropriate alternatives.[4] Patients who do not achieve adequate migraine control with beta blockers may try divalproex or topiramate as alternative prophylactic options.[4]

For patients who fail first-line prophylactic therapies, tricyclic antidepressants or venlafaxine should be considered.[4] Of the tricyclic antidepressants, amitriptyline has the most robust data supporting its use.[4] Angiotensin receptor blockers (ARBs) and calcium channel blockers are considered last-line prophylactic options according to guidelines.[4] Consensus guidelines note that selective serotonin reuptake inhibitors (SSRIs) are ineffective for migraine prophylaxis; however, fluoxetine has some conflicting evidence, and further study is needed to determine its efficacy.[4]

Onabotulinum toxin A (Botox®) is FDA-approved for the treatment of chronic migraines, or migraines that occur on at least 15 days per month, lasting at least four hours per day.[5] Clinical trials suggest that

onabotulinum toxin A may not be effective in the prevention of acute migraines; however, there is some evidence for its use in chronic daily headaches.[5]

Lastly, although the triptans are indicated as abortive therapy, frovatriptan (Frova®) has demonstrated efficacy in the prevention of menstrual migraine and is recommended in this setting by consensus guidelines.[4]

New Treatment Approaches

Calcitonin gene-related peptide (CGRP) inhibitors are a new class of monoclonal antibodies that target CGRP.[6] CGRP is a vasoactive neuropeptide located in the trigeminovascular system that is involved in pain signaling and the inflammatory response associated with migraines.[6] Through antagonism of this neuropeptide, it is thought that the pain and inflammation associated with migraine can be prevented, leading to fewer migraines overall.[6] In May 2018, the FDA approved the first CGRP inhibitor, erenumab-aooe (Aimovig™). Erenumab-aooe is available as a once-monthly subcutaneous (SC) injection for self-administration and came to market at an estimated annual cost of $6,900, which was less expensive than the price initially predicted by industry analysts.[7] Following the approval of erenumab-aooe, fremanezumab-vfrm (Ajovy®) and galcanezumab-gnlm (Emgality®) were both approved in September 2018 with the same annual cost as erenumab-aooe.[8-10] Of the three approved CGRP inhibitors, the mechanisms of action differ slightly in that erenumab-aooe binds and antagonizes the CGRP receptor directly, while fremanzeumab-vfrm and galcanezumab-gnlm bind to the CGRP ligand to prevent the receptor from binding. Both fremanzeumab-vfrm and galcanezumab-gnlm were approved as once-monthly subcutaneous injections; however, fremanezumab-vfrm also has an approved regimen for every-three-month dosing. The CGRP inhibitors have demonstrated a favorable safety profile when compared with traditional prophylactic therapies, with the most common adverse event reported being injection-site reactions.[8-10]

In a study comparing the efficacy of erenumab-aooe 70 mg or 140 mg SC once monthly to placebo, treatment with erenumab-aooe was associated with a statistically significant reduction in mean migraine days per month (3.2-to 3.7-day reduction with erenumab-aooe vs 1.8-day reduction with placebo).[8] Furthermore, treatment with erenumab-aooe reduced the interference of migraines with daily activities.[8]

The CGRP inhibitors have demonstrated a favorable safety profile when compared with traditional prophylactic therapies, with the most common adverse event reported being injection-site reactions.

In clinical trials, fremanezumab-vfrm 225 mg once monthly and 675 mg every three months was compared to placebo.[9] Treatment with fremanezumab-vfrm resulted in a 3.7-day reduction in mean migraine days in the once-monthly dosing group, a 3.4-day reduction in the every-three-month dosing group, and a 2.2-day reduction in the placebo group.[9] In another clinical trial that evaluated treatment with fremanezumab-vfrm in patients who experienced at least 13 migraines per month at baseline, patients had 4.3 fewer migraine days with once-monthly dosing, 4.6 fewer migraine days with every-three-month dosing, and 2.5 fewer migraine days with placebo.[9] This data suggests that the efficacy of fremanezumab-vfrm may be more pronounced in patients who suffer from more frequent migraines.

Galcanezumab-gnlm, at once-monthly doses of 120 mg and 240 mg, was compared to placebo in patients who had between 4 and 14 migraine days per month at baseline. Treatment with galcanezumab-gnlm 120 mg and 240 mg resulted in statistically significant reductions of 4.7 and 4.6 migraine days, respectively, compared to a reduction of 2.8 days with placebo.[10] In addition, a significantly greater proportion of patients treated with galcanezumab-gnlm experienced reductions in migraine days of 50%, 75%, and 100% from baseline.[10]

Based on the available clinical trial data, the CGRP inhibitors were effective in reducing migraine days per month in patients with chronic migraine. Clinical trials suggest that the CGRP inhibitors were generally well tolerated, with a low incidence of adverse events. Of note, while the CGRP inhibitors may offer potential advantages in terms of side effects when compared to traditional prophylactic therapies, there is no direct evidence to establish that CGRP inhibitors are more efficacious than other prophylactic therapies, and clinical treatment guidelines have not yet been updated to include recommendations for CGRPs as of this date. CGRPs are estimated to cost approximately $6,000 more per patient per year compared to older agents.[11] A fourth CGRP inhibitor, eptinezumab, is currently being developed as an intravenous infusion administered every three months, and it is expected to reach the market in mid-to-late 2019.[12]

In addition to the treatment advancements being made in migraine prevention, there have also been significant advancements in the treatment of acute migraine. Lasmiditan is an investigational 5-HT1F agonist

that is currently being reviewed by the FDA for the acute treatment of migraine.[12] In clinical trials, lasmiditan was associated with a statistically significant reduction in headache symptoms compared to placebo. In addition, lasmiditan worked quickly, with one-third of patients treated with lasmiditan achieving headache freedom at two hours.[12] Lasmiditan may offer some advantages compared to other abortive therapies; while triptans and ergots are not recommended for patients with cardiovascular disease, lasmiditan was not associated with any cardiac safety signals, which suggests that it may be an important treatment option in these patients.[12]

Current Challenges

According to consensus guidelines, the majority of the traditional prophylactic treatment options have tolerability issues, such as the impact of beta blockers on exercise tolerance or the anticholinergic side effects associated with tricyclic antidepressants.[3,4] It is critical for patients to have an effective prophylactic regimen, as this prevents overuse of acute therapy, which may contribute to rebound headaches. The CGRP antagonists have the potential to bridge gaps in therapy for some individuals who do not achieve clinical success with traditional prophylactic agents. Despite the relatively high cost associated with them, there are patient populations who may derive clinical benefit from the CGRP inhibitors. Healthcare utilization costs were not reported in the clinical trials. However, some researchers theorized a potential reduction in migraine days would result in a proportional reduction in migraine-related healthcare expenditures due to reduction in the use of acute treatments and emergency room visits.[6-11]

It is critical for patients to have an effective prophylactic regimen, as this prevents overuse of acute therapy, which may contribute to rebound headaches.

Payor Considerations

The Institute for Clinical and Economic Review (ICER) conducted a review of erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm prior to their FDA approval. ICER utilized an annual cost projection of $8,500 per patient to determine the incremental cost-effectiveness ratios for each agent.[11] Based on their analysis, erenumab-aooe had an incremental cost of $147,000 per quality adjusted life year (QALY) compared to onabotulinum toxin A, while fremanezumab-vfrm had a cost of $315,000 per QALY compared to fremanezumab-vfrm.[11] It is important to note that this analysis was conducted based on an annual cost of $8,500, which is higher than the actual cost of $6,900.[7] Despite the clinical efficacy that CGRP inhibitors may offer, the ICER report suggests that they are likely outside of the willingness-to-pay thresholds for many payers.[11] In response to the analysis, manufacturers of CGRPs recommended a more patient-centered approach, taking into consideration the perspective of the patient along with assessing these products through the lens of the payor. Much of the financial burden of migraines stems from lost productivity affecting both the patient and their employer. In addition, it was suggested to consider erenumab-aooe in only treatment-experienced patients rather than those who are treatment-naïve, as they are the patient population with higher costs and fewer treatment options.[11]

In an effort to mitigate the high cost of new specialty drugs, the general management approach has been to utilize quantity limits, step therapy, and prior authorization.[13] By requiring quantity limits, payors can prevent overuse of abortive therapies that are associated with rebound headaches and can encourage patients with high utilization of abortive therapies to seek appropriate prophylactic therapy if they have not already done so. The FDA approval of three CGRP inhibitors within a short period of time may present an additional opportunity for payors to carefully compare products and select a preferred agent. Given that there has historically been a trend toward poor medication adherence with prophylactic therapy, payors may also consider implementing strategies to drive adherence, which may include seeking value-based agreements focused on achievement of certain adherence goals.[13]

Given that there has historically been a trend toward poor medication adherence with prophylactic therapy, payors may also consider implementing strategies to drive adherence, which may include seeking value-based agreements focused on achievement of certain adherence goals.

Future Directions

Although the management approaches discussed above are all important tools to help manage rising costs, the current environment has highlighted the need for finding new and innovative ways to improve the efficient use of healthcare resources. As an example, Magellan Rx Management and Amgen have entered into an innovative agreement to understand the unmet needs of individuals living with migraine. This initiative focuses on finding opportunities to identify treatment gaps, improve migraine diagnosis and management, and reduce the burden of migraine and healthcare resource utilization. To accomplish this, Magellan Method, Magellan Rx's innovation division, is working with its customers to gain real-world insights around migraine management, including the cost of migraine, gaps in treatment and opportunities to improve care. These insights will be utilized to help inform the development of educational materials for employers, payers and patients around the burden of migraines. The ultimate goal of the effort is for both Amgen and Magellan to support improvements in patient outcomes and the utilization of treatment resources. Ensuring the proper utilization of pharmacotherapy could lead to reductions in healthcare spending and improvements in patient outcomes.[14] In addition to the direct and indirect healthcare costs, the initiative seeks to address the $11 billion that employers in the United States lose each year due to lost productivity associated with migraines. This collaboration stemmed from the desire of both partners to move past volume-based models and focus more on value-based models to provide more effective care.[14]

Given the challenges associated with high-cost specialty drugs indicated for such a large patient population, it will be imperative for payors to consider innovative management strategies to control the accelerated growth in medication expenditures, while ensuring that effective clinical innovations are available to the patients who need them most. Programs that focus on promoting patient and provider education, as well as medication adherence, may play an important role in achieving clinical success.

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Indication

Chronic Migraine

BOTOX® for injection is indicated for the prophylaxis of headaches in adult patients with Chronic Migraine (≥ 15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in 7 placebo-controlled studies.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity, but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat Cervical Dystonia and spasticity and at lower doses.

CONTRAINDICATIONS

BOTOX® is contraindicated in the presence of infection at the proposed injection site(s) and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, Units of biological activity of BOTOX® cannot be compared to nor converted into Units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

See Boxed Warning.

No definitive serious adverse event reports of distant spread of toxin effect associated with BOTOX® for Chronic Migraine at the labeled dose have been reported.

Serious Adverse Reactions With Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received BOTOX® injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of BOTOX® to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of BOTOX®. The safety and effectiveness of BOTOX® for unapproved uses have not been established.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft-tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

BOTOX®
onabotulinumtoxinA injection

Mindful. Meticulous. Methodical.

That's Chronic Migraine treatment with an expert's touch

With BOTOX®, you give patients proven headache prevention:

- Established PREEMPT* procedure remains in the hands of healthcare professionals[1]
- 8 to 9 fewer headache and migraine/probable migraine days per month from baseline at week 24 (vs 6 to 7 with placebo)[2,3]
- 2 million treatments given to over 500,000 unique Chronic Migraine patients since FDA approval in 2010[4]

*__PREEMPT__ = **P**hase 3 **RE**search **E**valuating **M**igraine **P**rophylaxis **T**herapy. 155 Units in 31 injection sites across 7 head and neck muscle areas. Each injection should contain 5 Units (0.1 mL) of reconstituted BOTOX®. The recommended re-treatment schedule is every 12 weeks.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Increased Risk of Clinically Significant Effects With Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis (ALS), or neuromuscular junction disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia, and respiratory compromise from therapeutic doses of BOTOX® (see *Warnings and Precautions*).

Dysphagia and Breathing Difficulties

Treatment with BOTOX® and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing (see *Boxed Warning*).

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS

Adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: *Boxed Warning*, *Contraindications*, and *Warnings and Precautions*.

Chronic Migraine

The most frequently reported adverse reactions following injection of BOTOX® for Chronic Migraine include neck pain (9%), headache (5%), eyelid ptosis (4%), migraine (4%), muscular weakness (4%), musculoskeletal stiffness (4%), bronchitis (3%), injection-site pain (3%), musculoskeletal pain (3%), myalgia (3%), facial paresis (2%), hypertension (2%), and muscle spasms (2%).

Postmarketing Experience

Adverse reactions that have been identified during postapproval use of BOTOX® are discussed in greater detail in Postmarketing Experience (Section 6.3 of the Prescribing Information).

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Co-administration of BOTOX® or other agents interfering with neuromuscular transmission (eg, aminoglycosides, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin and also by administration of a muscle relaxant before or after administration of BOTOX®.

Please see brief summary of full Prescribing Information, including Boxed Warning, on the following pages.

References: 1. BOTOX® Prescribing Information, May 2018. **2.** Data on file, Allergan; PREEMPT 1 Final Report. **3.** Data on file, Allergan; PREEMPT 2 Final Report. **4.** Data on file, Allergan; Total Chronic Migraine Treatments.

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Allergan

BOTOX® (onabotulinumtoxinA)

WARNING: DISTANT SPREAD OF TOXIN EFFECT

Postmarketing reports indicate that the effects of BOTOX and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and spasticity and at lower doses. *[See Warnings and Precautions.]*

INDICATIONS AND USAGE

Chronic Migraine

BOTOX is indicated for the prophylaxis of headaches in adult patients with chronic migraine (≥15 days per month with headache lasting 4 hours a day or longer).

Important Limitations

Safety and effectiveness have not been established for the prophylaxis of episodic migraine (14 headache days or fewer per month) in seven placebo-controlled studies.

CONTRAINDICATIONS

Known Hypersensitivity to Botulinum Toxin

BOTOX is contraindicated in patients who are hypersensitive to any botulinum toxin preparation or to any of the components in the formulation *[see Warnings and Precautions]*.

Infection at the Injection Site(s)

BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products

The potency Units of **BOTOX** are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of **BOTOX** cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method *[see Description]*.

Spread of Toxin Effect

Postmarketing safety data from **BOTOX** and other approved botulinum toxins suggest that botulinum toxin effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and there have been reports of death related to spread of toxin effects. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, and particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, symptoms consistent with spread of toxin effect have been reported at doses comparable to or lower than doses used to treat cervical dystonia and spasticity. Patients or caregivers should be advised to seek immediate medical care if swallowing, speech or respiratory disorders occur.

No definitive serious adverse event reports of distant spread of toxin effect associated with **BOTOX** for Chronic Migraine at the labeled dose have been reported.

Serious Adverse Reactions with Unapproved Use

Serious adverse reactions, including excessive weakness, dysphagia, and aspiration pneumonia, with some adverse reactions associated with fatal outcomes, have been reported in patients who received **BOTOX** injections for unapproved uses. In these cases, the adverse reactions were not necessarily related to distant spread of toxin, but may have resulted from the administration of **BOTOX** to the site of injection and/or adjacent structures. In several of the cases, patients had pre-existing dysphagia or other significant disabilities. There is insufficient information to identify factors associated with an increased risk for adverse reactions associated with the unapproved uses of **BOTOX**. The safety and effectiveness of **BOTOX** for unapproved uses have not been established.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, soft tissue edema, and dyspnea. If such a reaction occurs, further injection of **BOTOX** should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Increased Risk of Clinically Significant Effects With Pre-Existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis or neuromuscular junction disorders (e.g., myasthenia gravis or Lambert-Eaton syndrome) should be monitored when given botulinum toxin. Patients with known or unrecognized neuromuscular disorders or neuromuscular junction disorders may be at increased risk of clinically significant effects including generalized muscle weakness, diplopia, ptosis, dysphonia, dysarthria, severe dysphagia and respiratory compromise from therapeutic doses of **BOTOX** *[see Warnings and Precautions]*.

Dysphagia and Breathing Difficulties

Treatment with **BOTOX** and other botulinum toxin products can result in swallowing or breathing difficulties. Patients with pre-existing swallowing or breathing difficulties may be more susceptible to these complications. In most cases, this is a consequence of weakening of muscles in the area of injection that are involved in breathing or oropharyngeal muscles that control swallowing or breathing *[see Warnings and Precautions]*.

Deaths as a complication of severe dysphagia have been reported after treatment with botulinum toxin. Dysphagia may persist for several months, and require use of a feeding tube to maintain adequate nutrition and hydration. Aspiration may result from severe dysphagia and is a particular risk when treating patients in whom swallowing or respiratory function is already compromised.

Treatment with botulinum toxins may weaken neck muscles that serve as accessory muscles of ventilation. This may result in a critical loss of breathing capacity in patients with respiratory disorders who may have become dependent upon these accessory muscles. There have been postmarketing reports of serious breathing difficulties, including respiratory failure.

Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle for the treatment of cervical dystonia have been reported to be at greater risk for dysphagia. Limiting the dose injected into the sternocleidomastoid muscle may reduce the occurrence of dysphagia. Injections into the levator scapulae may be associated with an increased risk of upper respiratory infection and dysphagia.

Patients treated with botulinum toxin may require immediate medical attention should they develop problems with swallowing, speech or respiratory disorders. These reactions can occur within hours to weeks after injection with botulinum toxin *[see Warnings and Precautions]*.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually exists, the risk of transmission would also be considered extremely remote. No cases of transmission of viral diseases, CJD, or vCJD have ever been identified for licensed albumin or albumin contained in other licensed products.

ADVERSE REACTIONS

The following adverse reactions to **BOTOX** (onabotulinumtoxinA) for injection are discussed in greater detail in other sections of the labeling:

- Spread of Toxin Effects *[see Warnings and Precautions]*
- Serious Adverse Reactions With Unapproved Use *[see Warnings and Precautions]*
- Hypersensitivity Reactions *[see Contraindications and Warnings and Precautions]*
- Increased Risk of Clinically Significant Effects With Pre-Existing Neuromuscular Disorders *[see Warnings and Precautions]*
- Dysphagia and Breathing Difficulties *[see Warnings and Precautions]*

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, the 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 clinical practice.

BOTOX and **BOTOX Cosmetic** contain the same active ingredient in the same formulation, but with different labeled Indications and Usage. Therefore, adverse reactions observed with the use of **BOTOX Cosmetic** also have the potential to be observed with the use of **BOTOX**.

In general, adverse reactions occur within the first week following injection of **BOTOX** and while generally transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenderness, swelling, erythema, and/or bleeding/bruising may be associated with the injection. Symptoms associated with flu-like symptoms (e.g., nausea, fever, myalgia) have been reported after treatment. Needle-related pain and/or anxiety may result in vasovagal responses (including syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin. However, weakness of nearby muscles may also occur due to spread of toxin *[see Warnings and Precautions]*.

Chronic Migraine

In double-blind, placebo-controlled Chronic Migraine efficacy trials (Study 1 and Study 2), the discontinuation rate was 12% in the **BOTOX** treated group and 10% in the placebo-treated group. Discontinuations due to an adverse event were 4% in the **BOTOX** group and 1% in the placebo group. The most frequent adverse events leading to discontinuation in the **BOTOX** group were neck pain, headache, worsening migraine, muscular weakness and eyelid ptosis.

The most frequently reported adverse reactions following injection of **BOTOX** for chronic migraine appear in the table below.

Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Frequent than in Placebo-treated Patients in Two Chronic Migraine Double-blind, Placebo-controlled Clinical Trials

Adverse Reactions by System Organ Class	BOTOX 155 Units-195 Units (N=687)	Placebo (N=692)
Nervous system disorders		
Headache	32 (5%)	22 (3%)
Migraine	26 (4%)	18 (3%)
Facial paresis	15 (2%)	0 (0%)
Eye disorders		
Eyelid ptosis	25 (4%)	2 (<1%)
Infections and Infestations		
Bronchitis	17 (3%)	11 (2%)
Musculoskeletal and connective tissue disorders		
Neck pain	60 (9%)	19 (3%)
Musculoskeletal stiffness	25 (4%)	6 (1%)
Muscular weakness	24 (4%)	2 (<1%)
Myalgia	21 (3%)	6 (1%)
Musculoskeletal pain	18 (3%)	10 (1%)
Muscle spasms	13 (2%)	6 (1%)
General disorders and administration site conditions		
Injection site pain	23 (3%)	14 (2%)
Vascular Disorders		
Hypertension	11 (2%)	7 (1%)

Other adverse reactions that occurred more frequently in the **BOTOX** (onabotulinumtoxinA) group compared to the placebo group at a frequency less than 1% and potentially **BOTOX** related include: vertigo, dry eye, eyelid edema, dysphagia, eye infection, and jaw pain. Severe worsening of migraine requiring hospitalization occurred in approximately 1% of **BOTOX** treated patients in Study 1 and Study 2, usually within the first week after treatment, compared to 0.3% of placebo-treated patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to onabotulinumtoxinA in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In a long term, open-label study evaluating 326 Cervical Dystonia patients treated for an average of 9 treatment sessions with the current formulation of **BOTOX**, 4 (1.2%) patients had positive antibody tests. All 4 of these patients responded to **BOTOX** therapy at the time of the positive antibody test. However, 3 of these patients developed clinical resistance after subsequent treatment, while the fourth patient continued to respond to **BOTOX** therapy for the remainder of the study.

One patient among the 445 hyperhidrosis patients (0.2%), two patients among the 380 adult upper limb spasticity patients (0.5%) and no patients among 406 migraine patients with analyzed specimens developed the presence of neutralizing antibodies.

In overactive bladder patients with analyzed specimens from the two phase 3 studies and the open-label extension study, neutralizing antibodies developed in 0 of 954 patients (0.0%) while receiving **BOTOX** 100 Unit doses and 3 of 260 patients (1.2%) after subsequently receiving at least one 150 Unit dose. Response to subsequent **BOTOX** treatment was not different following seroconversion in these three patients.

In detrusor overactivity associated with neurologic condition patients with analyzed specimens in the drug development program (including the open-label extension study), neutralizing antibodies developed in 3 of 300 patients (1.0%) after receiving only **BOTOX** 200 Unit doses and 5 of 258 patients (1.9%) after receiving at least one 300 Unit dose. Following development of neutralizing antibodies in these 8 patients, 4 continued to experience clinical benefit, 2 did not experience clinical benefit, and the effect on the response to **BOTOX** in the remaining 2 patients is not known.

The data reflect the patients whose test results were considered positive for neutralizing activity to **BOTOX** in a mouse protection assay or negative based on a screening ELISA assay or mouse protection assay.

Formation of neutralizing antibodies to botulinum toxin type A may reduce the effectiveness of **BOTOX** treatment by inactivating the biological activity of the toxin. The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that **BOTOX** injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of **BOTOX**. 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 drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry eye; hyperhidrosis; hypoacusis; hypoaesthesia; localized muscle twitching; malaise; paresthesia; peripheral neuropathy; radiculopathy; erythema multiforme, dermatitis psoriasiform, and psoriasiform eruption; strabismus; tinnitus; and visual disturbances.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin *[see Warnings and Precautions]*.

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of **BOTOX** and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Anticholinergic Drugs

Use of anticholinergic drugs after administration of **BOTOX** may potentiate systemic anticholinergic effects.

Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of **BOTOX**.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no studies or adequate data from postmarketing surveillance on the developmental risk associated with use of **BOTOX** in pregnant women. In animal studies, administration of **BOTOX** during pregnancy resulted in adverse effects on fetal growth (decreased fetal weight and skeletal ossification) at clinically relevant doses, which were associated with maternal toxicity *[see Data]*.

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

Data

Animal Data

When **BOTOX** (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately equal to the human dose of 400 Units, on a body weight basis (Units/kg).

When **BOTOX** was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the human dose of 400 Units, based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 2 times the human dose of 400 Units, based on Units/kg.

Lactation

Risk Summary

There are no data on the presence of **BOTOX** in human or animal milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **BOTOX** and any potential adverse effects on the breastfed infant from **BOTOX** or from the underlying maternal conditions.

Pediatric Use

Prophylaxis of Headaches in Chronic Migraine

Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use

Of the 2145 patients in placebo-controlled clinical studies of **BOTOX** for the treatment of spasticity, 33.5% were 65 or older, and 7.7% were 75 years of age or older. No overall differences in safety were observed between elderly patients and younger patients.

In clinical studies of **BOTOX** across other indications, no overall differences in safety were observed between elderly patients and younger patients, with the exception of Overactive Bladder. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

OVERDOSAGE

Excessive doses of **BOTOX** for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection *[see Boxed Warning and Warnings and Precautions]*. These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care could involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raised against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 30 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a8.htm.

Revised: 05/2018

Manufactured by: Allergan Pharmaceuticals Ireland
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BCM70211_v3 06/18

BOTOX®
onabotulinumtoxinA injection

Allergan

Pharmacogenetics in Managed Care:

Opportunities and Barriers to Adoption

The National Institutes of Health (NIH) defines precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person," and this approach is growing in relevance and popularity in the healthcare industry.[1]

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One of the most promising areas of study within precision medicine is the growing understanding and clinical application of information regarding how an individual's genetic makeup can affect his or her response to medications, known as pharmacogenetics (PGx). Over the past couple of decades, advances in PGx have started to bring precision medicine to the forefront of the rapidly changing healthcare system in ways that are yet to be fully realized. The impact can be widespread, as demonstrated by the example of several commonly prescribed medications whose effects can be negatively affected by a small change in an individual's DNA makeup (Table 1). Going forward, advances in research and technology could play a large role in how healthcare is personalized for individual patients and may begin to influence the way healthcare is delivered to future patient populations.

What advances in PGx have been made?

Although PGx seems to be a novel idea, the concept is not new. Evidence that a person's genes affect the way they respond to a particular medication dates back to 1957.[2] Since then, it has become increasingly apparent that an individual's genetic makeup contributes to many aspects of their response to medications. This may include factors such as pharmacokinetics, pharmacodynamics, metabolism and excretion. Currently, the FDA recognizes over 200 medications that are affected by PGx.[3]

Along with advances in PGx expertise, the cost of genetic testing has plummeted in recent years, making these insights far more accessible. In the early 1990s, Congress set aside $3 billion dollars to fund the Human Genome Project. It took nearly a decade to complete the sequencing of the human genome.[4] Today, a consumer can purchase an at-home genetic testing kit for less than $200 dollars and receive direct-to-consumer results within weeks.[5] Although these newer tests do not test a full genome, most use a validated method called genotyping that looks specifically at portions of a person's DNA to identify clinically relevant aspects of a person's genome, including sections that can affect response to medications. Controversy exists regarding interpretation of at-home results with-

out health-professional guidance and privacy concerns of the data.

With advances and increasing utilization of precision medicine technologies, including PGx testing, stakeholders need to understand PGx-associated research standards.[6] The following assessments are key to understanding the role of PGx:

Analytic Validity:
How well the test predicts the presence or absence of a particular gene or genetic change.

Clinical Validity:
How well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.

While PGx has made significant progress within the research world, and communities are increasingly comfortable with the idea of sharing a person's individual genetic code, there appears to be a hesitation in utilizing PGx within the broader healthcare industry.

Clinical Utility:
Whether the test can provide information about diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer and providers.

There have been advances in the development of evidence to provide insight on both analytical and clinical validity research associated with PGx.[7] However, despite an increase in research that assesses clinical utility of PGx,

TABLE 1. COMMONLY PRESCRIBED MEDICATIONS WITH POTENTIALLY SIGNIFICANT PGX CONCERN[3, 15]

Drug	Level of Concern	Gene Mutation
Allopurinol	High	HLA-B
Amitriptyline	High	CYP2D6
Aripiprazole	High	CYP2D6
Atomoxetine	Moderate	CYP2D6
Atorvastatin	Moderate	SLCO1B1
Carbamazepine	Major	HLA-A
Celecoxib	Moderate	CYP2C9
Citalopram	Major	CYP2C19
Clopidogrel	Major	CYP2C19
Escitalopram	Major	CYP2C19
Metoprolol	Moderate	CYP2D6
Nortriptyline	Major	CYP2D6
Omeprazole	Moderate	CYP2C19
Paroxetine	Major	CYP2D6
Risperidone	Moderate	CYP2D6
Rosuvastatin	Moderate	SLCO1B1
Sertraline	Moderate	CYP2C19
Simvastatin	Moderate	SLCO1B1
Sulfonylureas (class)	Major	G6PD
Tamsulosin	Moderate	CYP2D6
Tramadol	Major	CYP2D6
Warfarin	Moderate	VKORC1

data is somewhat limited. A significant challenge to producing evidence of clinical utility is the need for assessment of larger sample sizes to prove that a PGx result truly results in a uniform clinical outcome.

Until this new approach to evaluating PGx research becomes more familiar to clinical stakeholders and decision-makers, these research standards can be loosely compared to more traditional pharmaceutical Phase I, II, and III clinical trials. As the body of knowledge demonstrating clinical utility grows, it is anticipated the application of PGx to effect meaningful clinical outcomes will have the opportunity to grow. Additionally, the challenge for payors will be how to include PGx in value assessments.

Why has broader acceptance of PGx been limited?

With the increase in availability of genetic testing and the sharp decrease in the price of the tests, one can predict that it is only a matter of time before PGx becomes the linchpin of precision medication technologies. As at-home genetic testing kits become increasingly available, these tests are no longer seen as science fiction by the general population. Furthermore, pharmaceutical manufacturers have begun to collaborate with leaders within the genetic testing space to begin conceptually testing novel treatments using large genetic databases. Although this collaboration has caused some concern, it may be a sign of precision medicine making strides into mainstream medication discovery.[9]

While PGx has made significant progress within the research world, and communities are increasingly comfortable with the idea of sharing a person's individual genetic code, there appears to be a hesitation in utilizing PGx within the broader healthcare industry. This hesitation is nuanced, as in the world of specialty medications, particularly in the oncology sector, the use of genetic testing has become fairly commonplace. Acceptance has been driven by the growing body of knowledge and familiarity with the fact that certain oncology agents are effective only within specific genetic settings. However, outside the oncology space, using PGx as a precision medicine tool to optimize therapy has been slow to gain traction. From a clinical perspective, this slow adoption appears to stem from several population concerns, including the following:

Patient Perception

Although at-home kits have become popular, many people remain concerned about having their genetic code made available. Some individuals find comfort in understanding their genes but fear sharing this information with anyone, including members of the healthcare system. Others prefer not to know, ascribing to the view that, "ignorance is bliss."

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Physician Acceptance

Physicians often rely on evidence-based medicine to deliver optimal care to their patients. As mentioned above, there is a lack of evidence of clinical utility that is substantial enough to warrant large-scale changes in clinical guidelines. Additionally, many classically trained physicians are unfamiliar with PGx and how it may relate to their patient population. Furthermore, when available, most electronic medical record (EMR) systems do not utilize PGx results. As a result, it is nearly impossible for most physicians to operationalize their patient's PGx information, even if available.

Pharmacist Utilization

Many Doctorate of Pharmacy (PharmD) programs now offer classes dedicated to the subject of PGx. In fact, all ACPE-accredited PharmD programs must provide some level of PGx education.[10] However, most pharmacy based interfaces do not incorporate PGx data. Pharmacists have limited insight, even when patients have PGx data available. Furthermore, community pharmacists face multiple, competing obligations when engaging with patients. As a result, even if PGx results were available, conducting a review is not likely to be a priority the pharmacist has time to undertake.

Have there been any applicable PGx studies in managed care settings?

The increased completion of retrospective, generally smaller, clinical utility (Phase III-like) trials has resulted in a handful of "real world"-population based prospective clinical trials.

One of the first real-world managed care trials was performed with a traditional Medicare Medication Therapy Management (MTM)-eligible population for a small Part D plan. The trial did not identify participants based on PGx risk factors; rather it was offered to beneficiaries who met Centers for Medicare & Medicaid Services (CMS) MTM eligibility criteria. The results were mixed, as use of PGx did not increase the overall number of identified clinical adverse outcomes. However, the severity of the interactions identified, along with the physician acceptance of the resulting clinical recommendations, were slightly higher when PGx was involved. Qualitatively, the authors reported significant hesitation

amongst the identified patient population – and a level of uncertainty from prescribers themselves when contacted.[11]

Another recent, unpublished, trial using randomly selected employees of a large healthcare corporation showed similar results. In 2017, 115 employees had PGx testing and their current and past medications were analyzed. Of those tested, 45 (40%) employees were found to have at least one medication that was a cause of concern. Further follow-up indicated that in those members, 27% (n=12) reported a current or past adverse drug reaction potentially due to a drug-gene interaction. In a sub-analysis, those employees who were considered high utilizers of prescription drug therapies, or recipients of polypharmacy, had the highest risk of potential drug-gene reactions.[12]

Although these types of prospective clinical trials showing clinical utility are promising, many stakeholders are disappointed by the lack data showing cost-effectiveness of these data. In spite of increasing clinical outcome support, there have been no landmark trials demonstrating the economic benefit of PGx outside of the specialty-oncology setting.

What are the barriers to PGx utilization in the managed care industry?

In addition to a lack of cost-effectiveness trials, there are other significant barriers within managed care that have delayed the uptake of PGx as a widely adopted tool. Because the managed care industry is largely driven by clinical, economic, and technological advances, there is a need for multiple systems and processes to align before the true benefit of PGx testing can be realized.

For example, one of the benefits of PGx testing is that a test does not need to be repeated. Unlike most lab tests that are analyzing changing variables (e.g., Hemoglobin A1c, Prothrombin Time and International Normalized Ratio ((PT/INR)), and others), a person's genetic makeup remains static. When tests are done correctly, retesting is unnecessary. The issue with avoiding unnecessary retesting arises when there is a need to share the results among stakeholders. Currently, there are limited options for sharing clinical information with stakeholders, including patients, physicians, pharmacists, and payors. This is a data-management and systems concern. Due to limitations on sharing of PGx results, there are significant delays in identifying a means to collaborate on strategies to implement an effective precision-medicine-management program based on PGx results.

Because the managed care industry is largely driven by clinical, economic, and technological advances, there is a need for multiple systems and processes to align before the true benefit of PGx testing can be realized.

Additional concern arises when considering the humanistic impact of the outcome of a PGx test. Although a true PGx analysis will only analyze portions of the genome that affect medications, some consumer-level tests may evaluate multiple other genetic traits. The manner in which the availability of this additional information is best managed remains unclear. For example, patients undergoing testing may be unprepared to discover negative genetic traits, such as being a carrier for the BrCA gene, or for a condition such as cystic fibrosis. An important part of a broader conversation in preparing for widespread PGx testing is consideration of the potential need to provide appropriate additional patient support, as needed. The scope and strategy for offering this support remains unclear. For example, it might include policies allowing for genetic counselors or preparing healthcare providers such as MTM pharmacists and nurse case managers to support patients and potentially establish mechanisms for triage to further support those patients experiencing negative effects from genetic test results.

Further complicating the issue are remaining regulatory concerns. In 2008, Congress passed the Genetic Information Nondiscrimination Act (GINA), which provided protections to individuals who had their genetic information tested. This was an advancement, as it provided protections against discrimination by employers or insurers because of a gene mutation that could result in an increased risk of having a disorder. Despite these protections, there are continued concerns, as GINA does not protect patients from all discrimination. For example, GINA does not apply to small companies (fewer than 15 employees), members of the U.S. military, or those receiving benefits from the Department of Veterans Affairs (VA). Additionally, GINA does not offer protections against genetic discrimination in life insurance.[13]

Finally, the frequent lack of coordination between the medical and pharmacy benefit adds complexity and the potential for misalignment of incentives to cover PGx testing. PGx offers a means of minimizing adverse drug reactions and preventing resultant undesired medical events. The prescription drug benefit serves as a platform for taking action based on PGx results. The medical benefit realizes savings due to improved medical outcomes, due to the prevention of drug-gene interactions. Unfortunately, the lack of alignment of financial incentives inherent in many health insurance benefit designs might lead to discrepant clinical and financial objectives. The segment of the payer organization incurring expenses related to testing may not be able to realize the financial benefits of the test. Such misalignment may delay broader uptake of PGx testing.

Are there solutions to these barriers, and what could the future hold for PGx?

In 2017, the Academy of Managed Care Pharmacy held a "Partnership Forum" to discuss what was necessary to remove many of these barriers.[14] The forum discussion identified several barriers that need to be addressed before PGx becomes a viable tool. Many of the items necessary to remove barriers included forming workgroups utilizing multiple stakeholders to address hurdles such as:

Evaluation of Evidence

1. Multiple stakeholders must create working groups to define how to standardize definitions and create guidance for how to appropriately study and disseminate results.
2. Develop "Value Assessment" frameworks to support the clinical utility of the tests.

Test Collection/Dissemination

1. Create rules to achieve interoperability between healthcare networks and allow for the current clinical decision software (e.g. EMRs) to interpret PGx data.

Implement Novel Benefit Designs

1. Focus on long-term, preventative screening using PGx and create new utilization management policies promoting the use of PGx.

Improve Regulations

1. Broaden GINA to cover more individuals.
2. Create a process by which genetic information can be communicated with patients that allows them to easily understand, regardless of their health-literacy level.

Once these barriers are addressed, it is hoped that an increase in PGx utilization in the payor setting will occur and can have a profound impact. In addition to decreased healthcare utilization and improved clinical outcomes, PGx testing may decrease utilization management requirements for certain medications, resulting in fewer prior authorizations and/or step therapy requirements. Additionally, broader PGx testing could contribute to the possibility of creating truly customized formularies, based on a patient's individual genetic makeup. PGx has the potential to be an innovative component of treatment plans, assisting in addressing rising costs, as well as a component of value-based reimbursement solutions.

Within the managed care setting, PGx-guided precision medicine is currently limited by technical, economic, educational, and ethical limitations. These are barriers to PGx acceptance by patients, physicians, pharmacists, and payors. Although PGx is currently used in a handful of specialized settings, its use in a broader population remains limited. The speed by which PGx becomes more widely adopted depends on future clinical trials that demonstrate both clinical and economic outcomes. Progress in tackling the challenges surrounding PGx uptake will encourage payors to implement clinical processes around PGx and to begin to realize the full potential of precision medicine.

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INDICATIONS

Adult Ulcerative Colitis (UC)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for inducing and maintaining clinical response, inducing and maintaining clinical remission, improving endoscopic appearance of the mucosa, and achieving corticosteroid-free remission.

Adult Crohn's Disease (CD)
ENTYVIO (vedolizumab) is indicated in adult patients with moderately to severely active CD who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids for achieving clinical response, achieving clinical remission, and achieving corticosteroid-free remission.

IMPORTANT SAFETY INFORMATION

- ENTYVIO (vedolizumab) for injection is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients.
- Infusion-related reactions and hypersensitivity reactions including anaphylaxis have occurred. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment.
- Patients treated with ENTYVIO are at increased risk for developing infections. Serious infections have been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis, and cytomegaloviral colitis. ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding ENTYVIO in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice.

In UC & CD

FOR ADULTS WITH MODERATELY TO SEVERELY ACTIVE UC OR CD FOR WHOM OTHER THERAPIES HAVE NOT WORKED WELL ENOUGH

With...

Entyvio®
vedolizumab

Long-term focus—from the start:

GI-FOCUSED ACTION

Entyvio specifically binds to α4β7 integrin, blocking its interaction with MAdCAM-1, which is mainly expressed on gut endothelial cells[1]

WITH

REMISSION ACHIEVED

UC and CD patients achieved remission at 52 weeks vs placebo. Studies included bio-naïve and anti-TNFα–experienced patients[1,2]

AND

5-YEAR INTEGRATED SAFETY

A 5-year analysis, including an open-label continuation study, demonstrated consistent results with clinical trials across safety parameters[1,3]

Individual results may vary.

Begin the Change

IMPORTANT SAFETY INFORMATION *(continued)*

- Although no cases of PML have been observed in ENTYVIO clinical trials, JC virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death has occurred in patients treated with another integrin receptor antagonist. A risk of PML cannot be ruled out. Monitor patients for any new or worsening neurological signs or symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue ENTYVIO dosing permanently.
- There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury.
- Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines and may receive live vaccines if the benefits outweigh the risks.
- Most common adverse reactions (incidence ≥3% and ≥1% higher than placebo): nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

Please see brief summary of Prescribing Information on adjacent pages.

References: 1. Entyvio [prescribing information]. Deerfield, IL: Takeda Pharmaceuticals America, Inc. **2.** Data on file. Takeda Pharmaceuticals America, Inc. Deerfield, IL. **3.** Colombel JF, et al. *Gut*. 2017;66:839-851.

Printed in U.S.A./July 2018 USD/VED/17/0097(2)b

Learn how you can help your patients reach remission—visit EntyvioHCP.com

Takeda

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

ENTYVIO (vedolizumab) for injection, for intravenous use

INDICATIONS AND USAGE

Adult Ulcerative Colitis

ENTYVIO (vedolizumab) is indicated for:

- inducing and maintaining clinical response,
- inducing and maintaining clinical remission,
- improving the endoscopic appearance of the mucosa, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Adult Crohn's Disease

ENTYVIO (vedolizumab) is indicated for:

- achieving clinical response,
- achieving clinical remission, and
- achieving corticosteroid-free remission

in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

CONTRAINDICATIONS

ENTYVIO is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to ENTYVIO or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate) *[see Warnings and Precautions and Adverse Reactions]*.

WARNINGS AND PRECAUTIONS

Infusion-Related Reactions and Hypersensitivity Reactions

In UC Trials I and II and CD Trials I and III, hypersensitivity reactions occurred including a case of anaphylaxis (one out of 1434 patients [0.07%]) *[see Adverse Reactions]*. Allergic reactions including dyspnea, bronchospasm, urticaria, flushing, rash, and increased blood pressure and heart rate have also been observed. The majority were mild to moderate in severity as assessed by the investigator. Experience with other biologic medications suggests that hypersensitivity reactions and anaphylaxis to ENTYVIO may vary in their time of onset from during infusion or immediately post-infusion to occurring up to several hours post-infusion.

If anaphylaxis or other serious allergic reactions occur, discontinue administration of ENTYVIO immediately and initiate appropriate treatment (e.g., epinephrine and antihistamines).

Infections

Patients treated with ENTYVIO are at increased risk for developing infections *[see Adverse Reactions]*. The most commonly reported infections in clinical trials occurring at a rate greater on ENTYVIO than placebo involved the upper respiratory and nasal mucosa (e.g., nasopharyngitis, upper respiratory tract infection). Serious infections have also been reported in patients treated with ENTYVIO, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

ENTYVIO is not recommended in patients with active, severe infections until the infections are controlled. Consider withholding treatment in patients who develop a severe infection while on treatment with ENTYVIO. Exercise caution when considering the use of ENTYVIO in patients with a history of recurring severe infections. Consider screening for tuberculosis (TB) according to the local practice. For progressive multifocal leukoencephalopathy (PML), see *Warnings and Precautions*.

Progressive Multifocal Leukoencephalopathy

Another integrin receptor antagonist has been associated with progressive multifocal leukoencephalopathy (PML), a rare and often fatal opportunistic infection of the central nervous system (CNS). PML is caused by the John Cunningham (JC) virus and typically only occurs in patients who are immunocompromised.

In ENTYVIO clinical trials, patients were actively monitored for PML with frequent and regular screenings, and evaluations of any new, unexplained neurological symptoms, as necessary. While zero cases of PML were identified among patients with at least 24 months of exposure, a risk of PML cannot be ruled out. No claims of comparative safety to other integrin receptor antagonists can be made based on this data.

Monitor patients on ENTYVIO for any new onset, or worsening, of neurological signs and symptoms. Typical signs and symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. The progression of deficits usually leads to death or severe disability over weeks or months. If PML is suspected, withhold dosing with ENTYVIO and refer to a neurologist; if confirmed, discontinue dosing permanently.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO. In general, the combination of transaminase elevations and elevated bilirubin without evidence of obstruction is generally recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. ENTYVIO should be discontinued in patients with jaundice or other evidence of significant liver injury *[see Adverse Reactions]*.

Live and Oral Vaccines

Prior to initiating treatment with ENTYVIO, all patients should be brought up to date with all immunizations according to current immunization guidelines. Patients receiving ENTYVIO may receive non-live vaccines (e.g., influenza vaccine injection) and may receive live vaccines if the benefits outweigh the risks. There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO *[see Adverse Reactions]*.

ADVERSE REACTIONS

The following topics are also discussed in detail in the Warnings and Precautions section:

- Infusion-Related Reactions and Hypersensitivity Reactions *[see Warnings and Precautions]*
- Infections *[see Warnings and Precautions]*
- Progressive Multifocal Leukoencephalopathy *[see Warnings and Precautions]*
- Liver Injury *[see Warnings and Precautions]*

Clinical Trials Experience

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

The data described below reflect exposure to ENTYVIO in 3,326 patients and healthy volunteers in clinical trials, including 1,396 exposed for greater than one year, and 835 exposed for greater than two years.

The safety data described in *Table 2* are derived from four controlled Phase 3 trials (UC Trials I and II, and CD Trials I and III); data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

In these trials, 1,434 patients received ENTYVIO 300 mg for up to 52 weeks, and 297 patients received placebo for up to 52 weeks. Of these, 769 patients had ulcerative colitis and 962 patients had Crohn's disease. Patients were exposed for a mean duration of 259 days (UC Trials I and II) and 247 days (CD Trials I and III).

Adverse reactions were reported in 52% of patients treated with ENTYVIO and 45% of patients treated with placebo (UC Trials I and II: 49% with ENTYVIO and 37% with placebo; CD Trials I and III: 55% with ENTYVIO and 47% with placebo). Serious adverse reactions were reported in 7% of patients treated with ENTYVIO compared to 4% of patients treated with placebo (UC Trials I and II: 8% with ENTYVIO and 7% with placebo; CD Trials I and III: 12% with ENTYVIO and 9%, with placebo).

The most common adverse reactions (reported by ≥3% of patients treated with ENTYVIO in the UC Trials I and II and CD Trials I and III combined group and ≥1% higher than in combined placebo group) were nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain and pain in extremities (*Table 2*).

Table 2. Adverse Reactions in ≥3% of ENTYVIO-treated Patients and ≥1% Higher than in Placebo (UC Trials I and II* and CD Trials I and III*)

Adverse Reaction	ENTYVIO† (N=1434)	Placebo‡ (N=297)
Nasopharyngitis	13%	7%
Headache	12%	11%
Arthralgia	12%	10%
Nausea	9%	8%
Pyrexia	9%	7%
Upper respiratory tract infection	7%	6%
Fatigue	6%	3%
Cough	5%	3%
Bronchitis	4%	3%
Influenza	4%	2%
Back pain	4%	3%
Rash	3%	2%
Pruritus	3%	1%
Sinusitis	3%	1%
Oropharyngeal pain	3%	1%
Pain in extremities	3%	1%

*Data from patients receiving open-label ENTYVIO treatment at Weeks 0 and 2 (prior to entry into UC Trial II and CD Trial III) and from Weeks 6 to 52 (non-responders at Week 6 of UC Trial I and CD Trial I) are included.

†Patients who received ENTYVIO for up to 52 weeks.

‡Patients who received placebo for up to 52 weeks.

Safety data for patients (n=279) in UC Trials I and II and CD Trials I and III who received ENTYVIO at Weeks 0 and 2 and were then randomized to placebo at Week 6 for up to 52 weeks, and for patients (n=416) in CD Trial II, a 10 week Crohn's disease trial, are similar to those listed in *Table 2*.

Infusion-Related Reactions and Hypersensitivity Reactions

Serious infusion-related reactions and hypersensitivity reactions including anaphylaxis have been reported following ENTYVIO administration in clinical trials *[see Warnings and Precautions]*. In UC Trials I and II and Crohn's Trials I and III, one case of anaphylaxis [one out of 1434 patients treated with ENTYVIO (0.07%)] was reported by a Crohn's disease patient during the second infusion (symptoms reported were dyspnea, bronchospasm, urticaria, flushing, rash and increased blood pressure and heart rate) and was managed with discontinuation of infusion and treatment with antihistamine and intravenous hydrocortisone.

In UC Trials I and II and CD Trials I and III, 4% of patients treated with ENTYVIO and 3% of patients treated with placebo experienced an infusion-related reaction (IRR). The most frequently observed IRR in the patients treated with ENTYVIO (reported more than twice) were nausea, headache, pruritus, dizziness, fatigue, infusion-related reaction, pyrexia, urticaria and vomiting (each of these adverse reactions occurred in <1% in all patients treated with ENTYVIO) and no individual adverse reaction reported occurred at a rate above 1%. These reactions generally occurred within the first two hours after the infusion and resolved with no treatment or following antihistamine and/or IV hydrocortisone treatment. Less than 1% of patients treated with ENTYVIO had IRRs assessed by the investigator as severe, and IRRs requiring discontinuation of study treatment occurred in <1%.

In clinical trials, for patients with mild IRRs or hypersensitivity reactions, physicians were allowed to pretreat with standard medical treatment (e.g., antihistamine, hydrocortisone and/or acetaminophen) prior to next infusion.

Infections

In UC Trials I and II and CD Trials I and III, the rate of infections was 0.85 per patient-year in the patients treated with ENTYVIO and 0.7 per patient-year in the patients treated with placebo *[see Warnings and Precautions]*. The infections consisted primarily of nasopharyngitis, upper respiratory tract infection, sinusitis, and urinary tract infection. Two percent of patients discontinued ENTYVIO due to infections.

In UC Trials I and II and CD Trials I and III, the rate of serious infections was 0.07 per patient-year in patients treated with ENTYVIO and 0.06 per patient-year in patients treated with placebo. Serious infections were more common in Crohn's disease patients than ulcerative colitis patients, and anal abscesses were the most frequently reported serious adverse reaction in Crohn's disease patients. Over 48 months, there was no increase in the rate of serious infections.

In controlled- and open-label long-term extension trials in adults treated with ENTYVIO, serious infections have been reported, including anal abscess, sepsis (some fatal), tuberculosis, salmonella sepsis, Listeria meningitis, giardiasis and cytomegaloviral colitis.

In UC Trials I and II and CD Trials I and III, sepsis, including bacterial sepsis and septic shock, was reported in four of 1434 (0.3%) patients treated with ENTYVIO and in two of 297 patients treated with placebo (0.7%). During these trials, two Crohn's disease patients treated with ENTYVIO died due to reported sepsis or septic shock; both of these patients had significant comorbidities and a complicated hospital course that contributed to the deaths. In an open label long-term extension trial, additional cases of sepsis (some fatal), including bacterial sepsis and septic shock, were reported. The rate of sepsis in patients with ulcerative colitis or Crohn's disease receiving ENTYVIO was two per 1000 patient-years.

In clinical trials, all patients were screened for tuberculosis. One case of latent, pulmonary tuberculosis was diagnosed during the controlled trials with ENTYVIO. Additional cases of pulmonary tuberculosis were diagnosed during the open-label trial. All of these observed cases occurred outside the United States, and none of the patients had extrapulmonary manifestations.

Liver Injury

There have been reports of elevations of transaminase and/or bilirubin in patients receiving ENTYVIO *[see Warnings and Precautions]*. In UC Trials I and II and CD Trials I and III, three patients reported serious adverse reactions of hepatitis, manifested as elevated transaminases with or without elevated bilirubin and symptoms consistent with hepatitis (e.g., malaise, nausea, vomiting, abdominal pain, anorexia). These adverse reactions occurred following two to five ENTYVIO doses; however, based on case report information it is unclear if the reactions indicated drug-induced or autoimmune etiology. All patients recovered following discontinuation of therapy with some requiring corticosteroid treatment. In controlled trials, the incidence of ALT and AST elevations ≥3 x ULN was <2% in patients treated with ENTYVIO and in patients treated with placebo. In the open-label trial, one additional case of serious hepatitis was observed.

Malignancies

In UC Trials I and II and CD Trials I and III, malignancies (excluding dysplasia and basal cell carcinoma) were reported in six of 1434 (0.4%) patients treated with ENTYVIO, including colon cancer (n=2), transitional cell carcinoma (n=1), breast cancer (n=1), carcinoid tumor of the appendix (n=1) and squamous cell carcinoma (n=1). Malignancy was reported in one of 297 (0.3%) patients treated with placebo (squamous cell carcinoma).

Malignancies (excluding dysplasia and basal cell carcinoma) observed during the ongoing open-label long-term extension trial included B-cell lymphoma, breast cancer, colon cancer, malignant hepatic neoplasm, malignant lung neoplasm, malignant melanoma, lung cancer of primary neuroendocrine carcinoma, renal cancer and squamous cell carcinoma. Overall, the number of malignancies in the clinical trials was small; however, long-term exposure was limited.

Live and Oral Vaccines

There are no data on the secondary transmission of infection by live vaccines in patients receiving ENTYVIO.

In a placebo-controlled study of healthy volunteers, 61 subjects were given a single ENTYVIO 750 mg dose (2.5 times the recommended dose), and 62 subjects received placebo followed by intramuscular vaccination with Hepatitis B surface antigen and oral cholera vaccine. After intramuscular vaccination with three doses of recombinant Hepatitis B surface antigen, those treated with ENTYVIO did not have lower rates of protective immunity to Hepatitis B virus. However, those exposed to ENTYVIO did have lower seroconversion rates and anti-cholera titers relative to placebo after receiving the two doses of a killed, oral cholera vaccine. The impact on other oral vaccines and on nasal vaccines in patients is unknown.

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to vedolizumab in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

In UC Trials I and II and CD Trials I and III, in patients who received ENTYVIO, the frequency of antibodies detected in patients was 13% at 24 weeks after the last dose of study drug (greater than five half-lives after last dose). During treatment, 56 of 1434 (4%) of patients treated with ENTYVIO had detectable anti-vedolizumab antibody at any time during the 52 weeks of continuous treatment. Nine of 56 patients were persistently positive (at two or more study visits) for anti-vedolizumab antibody and 33 of 56 patients developed neutralizing antibodies to vedolizumab. Among eight of these nine subjects

with persistently positive anti-vedolizumab antibody and available vedolizumab concentration data, six had undetectable and two had reduced vedolizumab concentrations. None of the nine subjects with persistently positive anti-vedolizumab antibody achieved clinical remission at Weeks 6 or 52 in the controlled trials.

DRUG INTERACTIONS

Natalizumab

Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO with natalizumab.

TNF Blockers

Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO with TNF blockers.

Live Vaccines

Live vaccines may be administered concurrently with ENTYVIO only if the benefits outweigh the risks *[see Warnings and Precautions]*.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ENTYVIO during pregnancy. Information about the registry can be obtained by calling 1-877-TAKEDA7 (1-877-825-3327).

Pregnancy Category B:

Risk Summary

There are no studies with ENTYVIO in pregnant women. No fetal harm was observed in animal reproduction studies with intravenous administration of vedolizumab to rabbits and monkeys at dose levels 20 times the recommended human dosage. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the benefits to the mother outweigh the risk to the unborn child.

Clinical Considerations

Any adverse pregnancy effect from ENTYVIO would likely be greater during the second and third trimesters of pregnancy. Monoclonal antibodies are transported across the placenta in a linear fashion as pregnancy progresses, with the largest amount transferred during the third trimester.

Animal Data

A reproduction study has been performed in pregnant rabbits at single intravenous doses up to 100 mg/kg administered on gestation Day 7 (about 20 times the recommended human dosage) and has revealed no evidence of impaired fertility or harm to the fetus due to vedolizumab. A pre- and post-natal development study in monkeys showed no evidence of any adverse effect on pre- and post-natal development at intravenous doses up to 100 mg/kg (about 20 times the recommended human dosage).

Nursing Mothers

It is unknown whether vedolizumab is present in human milk. Vedolizumab was detected in the milk of lactating monkeys. Exercise caution when administering vedolizumab to a nursing woman.

Pediatric Use

Safety and effectiveness of ENTYVIO in pediatric patients have not been established.

Geriatric Use

Clinical trials of ENTYVIO did not include sufficient numbers of subjects aged 65 and over (46 Crohn's and ulcerative colitis patients aged 65 and over were treated with ENTYVIO during controlled Phase 3 trials) to determine whether they respond differently from younger subjects. However, no overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

Manufactured by:
Takeda Pharmaceuticals America, Inc.
Deerfield, IL 60015

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For more information, go to www.ENTYVIO.com or call 1-877-825-3327

Revised: February 2018

VMB245 R2_Brf. L-BZV-0218-4

Rare Disease Management:

Pipeline and Managed Care Implications

Defining Rare Disease

According to the Orphan Drug Act of 1983, an orphan drug is defined as a drug intended to treat, diagnose, or prevent a rare disease.[1] A rare disease is defined as one that affects fewer than 200,000 individuals in the United States, or one that affects more than 200,000 individuals but the drug sponsors would not be expected to recover the cost of developing the new drug.

Jeff Januska, PharmD
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Magellan Rx Management

Current estimates suggest that there are 7,000 known rare diseases that affect a total of approximately 30 million Americans.[1,2] In context, approximately 10% of the U.S. population has been diagnosed with a rare disease.[3]

According to the National Institutes of Health (NIH), about 50% of individuals affected by rare diseases are children. Furthermore, rare diseases are the cause of 35% of deaths in the first year of life, and approximately 30% of children diagnosed with a rare disease will die before their fifth birthday.[3]

Current Challenges

One of the most significant challenges associated with the management of rare disease is the diagnosis.[2] Rare diseases are, by definition, very uncommon, so most doctors have never seen them. In addition, many rare diseases lack diagnostic criteria to aid in the identification and early diagnosis of disease. As a result, patients may undergo a battery of tests and incorrect diagnoses, moving from provider to provider before they receive the correct diagnosis.[2] Of the known rare diseases, approximately 80% are genetic. With the advent and successful completion of the Human Genome Project in 2003, the understanding of the interplay between our genetic composition and disease has dramatically increased, thus allowing for significant advances in the diagnosis of rare diseases.[2,4]

Once a patient is correctly diagnosed with a rare disease, they often face another significant challenge: the scarcity of viable treatment options. Despite the significant progress in the field, only about 5% of known rare diseases have a Food and Drug Administration (FDA)-approved treatment option. Patients are often left with ineffective treatment options and supportive care.[1,3]

Current Trends in Drug Development

The overarching goal of the Orphan Drug Act was to incentivize drug manufacturers to develop treatments for rare diseases by offering tax credits and seven years of marketing exclusivity for new therapies.[3,5] The success of the Orphan Drug Act is indisputable, with more than 600 drugs for rare diseases receiving approval since the inception of the program.[3] Trends in drug development suggest a shifting focus

of the pharmaceutical industry to rare diseases. In the past 10 years, more than 230 new orphan drugs were approved by the FDA. In addition, in 2015 alone, almost half (47%) of all novel drug approvals were for rare disease indications.[3,5] Of these approvals, eight medications were first-in-class treatments that represented a new approach for treating disease, five of these medications were for pediatric indications, and eleven were for oncology indications.[3]

There are currently over 560 medications in development for the treatment of rare diseases. Of these, more than 230 medications are being studied in rare cancers, including rare blood cancers, representing approximately 40% of the rare disease pipeline.[3] In addition to oncology indications, other rare diseases with potential treatments in the pipeline including blood disorders, such as sickle cell anemia or beta thalassemia; genetic disorders, such as cystic fibrosis and spinal muscular atrophy; and neurological disorders, such as amyotrophic lateral sclerosis and seizure disorder.[3]

In the past 10 years, more than 230 new orphan drugs were approved by the FDA. In addition, in 2015 alone, almost half (47%) of all novel drug approvals were for rare disease indications.

Recent FDA Approvals

As of December 3, the FDA has approved 70 new treatment options for orphan indications in 2018.[6,7] These new approvals include previously approved agents with new indications that qualify under the Orphan Drug Act or a new agent with multiple approved orphan indications. Of the 59 novel agents approved in 2018, 33 agents had been awarded the Orphan Drug designation by the FDA (see Table 1).[7] Of the 33 novel orphan drugs approved, 13 were approved for oncology indications, four were approved for infectious diseases, two were approved for rare seizure disorders in children, and two were approved for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis.[7]

Given the lack of effective treatment options for many previously neglected orphan diseases, if and when a new treatment option came to market, payors were largely obligated to cover the medication in the absence of alternatives. The increasing focus of the pharmaceutical industry on bringing drugs to market under the Orphan Drug Act, in some cases, is giving patients, payors and clinicians treatment options in disease states that previously had none, as well as multiple treatment options for some conditions. As a result, payors may find themselves with similar tools at their disposal as they would in other, non-orphan disease states, such as selecting a preferred product. Examples of such scenarios include the following:

1 Onpattro™ (patisiran)

Patisiran is a ribonucleic acid interference (RNAi) therapeutic agent that is now approved for the treatment of polyneuropathy of hereditary transthyretin amyloidosis, which is an autosomal-dominant, progressive, and life-threatening disease that occurs as a result of mutations in the gene encoding transthyretin.[8] In patients with this disease, mutant and wild-type transthyretin deposit as amyloid within the peripheral nerves, as well as the heart and gastrointestinal tract. As a result, patients may experience polyneuropathy and cardiomyopathy.[8]

RNAi is a method of controlling gene expression that uses small interfering RNAs bound to the RNA-induced silencing complex to ultimately cleave target messenger RNA (mRNA).[8] Utilizing this technology, patisiran is designed to inhibit hepatic synthesis of transthyretin by controlling gene expression. In the Phase III APOLLO trial, patients with hereditary transthyretin amyloidosis with polyneuropathy were randomized to treatment with patisiran, given intravenously every three weeks, or placebo.[8] At 18 months, patients treated with patisiran experienced a significantly lower change from baseline in the modified Neuropathy Impairment Score+7 (mNIS+7) score compared to placebo, which indicates a benefit in terms of polyneuropathy (least-squares mean change in mNIS+7 from baseline, -6.0±1.7 with patisiran vs 28.0±2.6 with placebo; P<0.001).[8] Of the patients treated with patisiran, 74% had a less than 10-point increase from baseline in mNIS+7 from baseline to 18 months, compared to 14% of patients in the placebo group. Furthermore, 56% of patients in the patisiran group had an improvement in mNIS+7 at 18 months, compared to 4% of patients in the placebo group. In terms of safety, patisiran had a similar incidence of adverse events, including serious adverse events, compared to placebo.[8]

2 Tegsedi™ (inotersen)

Inotersen received FDA approval for the same indication as patisiran; however, it has a different mechanism of action in that it is an antisense oligonucleotide that complements exactly the mRNA that

TABLE 1. ORPHAN DRUGS FDA APPROVED IN 2018[6,7*]

Brand (Generic) Name	FDA-Approved Indication	Date of Approval
Lutathera® (lutetium Lu 177 dotatate)	Treatment of GEP-NETs	1/26/2018
Trogarzo™ (ibalizumab-uiyk)	Treatment of HIV-1 infection in treatment-experienced adults with documented multi-ART class resistance and evidence of HIV-1 replication despite ongoing ART	3/6/2018
Crysvita® (burosumab-twza)	Treatment of X-linked hypophosphatemia (also known as vitamin D-resistant rickets)	4/17/2018
Palynziq™ (pegvaliase-pqpz)	Treatment of hyperphenylalaninemia	5/24/2018
Moxidectin	Treatment of onchocerciasis volvulus in children and adults	6/13/2018
Epidiolex® (cannabidiol)	Treatment of LGS and Dravet syndrome	6/25/2018
Braftovi™ (encorafenib)	Treatment of stage IIB-IV melanoma positive for BRAF mutation (in combination with binimetinib)	6/27/2018
Mektovi® (binimetinib)	Treatment of stage IIB-IV melanoma positive for BRAF mutation (in combination with encorafenib)	6/27/2018
Tpoxx® (tecovirimat)	Treatment of smallpox	7/13/2018
Krintafel® (tafenoquine)	Treatment of malaria	7/20/2018
Omegaven® (fish oil triglycerides)	Treatment of parenteral nutrition-associated liver disease	7/27/2018
Poteligeo® (mogamulizumab-kpkc)	Treatment of patients with cutaneous T-cell lymphoma	8/8/2018
Galafold™ (migalastat)	Treatment of Fabry disease	8/10/2018
Onpattro™ (patisiran)	Treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis	8/10/2018
Diacomit® (stiripentol)	Treatment of Dravet syndrome	8/20/2018
Oxervate™ (cenegermin-bkbj)	Treatment of neurotrophic keratitis	8/22/2018
Takhzyro™ (lanadelumab-flyo)	Treatment of angioedema	8/23/2018
Lumoxiti™ (moxetumomab pasudotox-tdfk)	Treatment of hairy cell leukemia	9/13/2018
Copiktra™ (duvelisib)	Treatment of CLL and SLL	9/24/2018
Vizimpro® (dacomitinib)	Treatment of NSCLC with EGFR, HER2, HER4, or DDR2 mutations	9/27/2018
Revcovi™ (elapegademase-lvlr)	Treatment of adenosine deaminase deficiency in patients with SCID	10/5/0218
Tegsedi™ (inotersen)	Treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis	10/5/2018
Lorbrena® (lorlatinib)	Treatment of ALK-positive or ROS1-positive NSCLC	11/2/2018
Gamifant™ (emapalumab-lzsg)	Treatment of hemophagocytic lymphohistiocytosis	11/20/2018
Daurismo™ (glasdegib)	Treatment of AML	11/21/2018
Vitrakvi® (larotrectinib)	Treatment of solid tumors with NTRK-fusion proteins	11/26/2018
Firdapse® (amifampridine phosphate)	Treatment of Lambert-Eaton Myasthenic syndrome	11/28/2018
Xospata® (gilteritinib)	Treatment of AML	11/28/2018
Nplate® (romiplostim)	Treatment of thrombocytopenia	12/14/2018
Envarsus Xr® (tacrolimus)	Prophylaxis of organ rejection in kidney-transplant patients	12/19/2018
Keytruda® (pembrolizumab)	Treatment of recurrent locally advanced metastatic MCC	12/19/2018
Elzonris® (tagraxofusp-erzs)	Treatment of blastic plasmacytoid dendritic cell neoplasm	12/21/2018
Ultomiris™ (ravulizumab-cwvz)	Treatment of PNH	12/21/2018

*Current as of Jan. 2, 2019
Abbreviations: ALK=anaplastic lymphoma kinase, AML=acute myeloid leukemia, ART=antiretroviral therapy, CLL=chronic lymphocytic leukemia, GEP-NET=gastroenteropancreatic neuroendocrine tumor, HIV-1=human immunodeficiency virus-1, LGS=Lennox-Gastaut syndrome, MCC=Merkel cell carcinoma, NSCLC=non-small cell lung cancer, NTRK=neurotrophic receptor tyrosine kinase, PNH=paroxysmal nocturnal hemoglobinuria, SCID=severe combined immunodeficiency, SLL=small lymphocytic lymphoma

The increasing focus of the pharmaceutical industry on bringing orphan drugs to market under the Orphan Drug Act, in some cases, is giving payors and clinicians treatment options in disease states that previously had none, as well as multiple treatment options for some conditions.

encodes for transthyretin.[7,9] Inotersen works by binding the mRNA, resulting in the degradation of transthyretin by RNAase. In the Phase III NEURO-TTR trial, patients were randomized to treatment with inotersen, given as a once-weekly subcutaneous injection, or placebo. At 15 months, patients treated with inotersen had a mean improvement in mNIS+7 of 19.7 points compared to patients treated with placebo (P<0.001).[9] In addition, a statistically significant benefit with inotersen was observed as early as within eight months of treatment. Inotersen was associated with an increased risk of thrombocytopenia and glomerulonephritis compared to placebo, resulting in a Black Box Warning for glomerulonephritis and the FDA requirement for a Risk Evaluation and Mitigation Strategy (REMS) program.[9-11]

Prior to the FDA approval of patisiran and inotersen, treatment options were very limited and included orthotopic liver transplantation and transthyretin tetramer stabilizers (i.e., tafamidis or diflunisal); however, many patients continued to have disease progression despite these treatment approaches.[8-11] With the approval of two high-cost, novel agents for the treatment of such a rare and difficult-to-treat disease, payors and clinicians alike are eager to identify potential advantages or disadvantages with each agent. Although both agents came to market with an annual cost of $450,000 per patient, according to BioPharm Insight, some experts have predicted that patisiran may ultimately claim market superiority.[11,12] Three experts interviewed by BioPharm Insight suggested that patisiran may have a better safety and efficacy profile; however, it was noted that the pivotal trials for each agent may have been too different to support that claim.[12] Given the similarities between the two products, there may be opportunities for payors to select a preferred agent, a management strategy that has not been widely utilized in the orphan disease arena in the past.

The mean cost per patient per year for an orphan drug was $147,308 in 2017, which is four times the mean cost for non-orphan drugs, at $30,708 per patient per year.

Rare Disease Pipeline

Sickle cell disease is another orphan disease that is receiving a lot of attention within the pharmaceutical industry. Historically, the treatment options for sickle cell disease have been very limited beyond palliative treatment. In 2017, the FDA approved Endari® (L-glutamine) for the prevention of complications related to sickle cell disease, making it the first therapeutic agent to be approved for sickle cell disease in 20 years.[13] In the pivotal Phase III trial, patients treated with L-glutamine had 25% fewer hospital visits for sickle cell crisis, were hospitalized 33% less often, were discharged from the hospital 4.5 days sooner, and were 65% less likely to have acute chest syndrome compared to patients who received placebo.[13] Despite the apparent efficacy of L-glutamine in clinical trials, clinicians are concerned with real-world adherence to the therapy, given that approximately one-third of patients in the clinical trial dropped out. The good news for patients is that there are several more agents in the pharmaceutical pipeline that are being studied for sickle cell disease, including rivipansel and crizanlizumab.[13]

Rivipansel is a small molecule that works by preventing the sickle erythrocytes from adhering to the vascular endothelium by inhibiting the adhesion molecules, P-selectin and E-selectin.[14] In a Phase II trial, treatment with rivipansel reduced the duration of vaso-occlusive crisis by 63 hours compared to placebo. The safety profile of rivipansel was similar to the placebo group, with the most common treatment-emergent adverse events being gastrointestinal symptoms and rash.

Crizanlizumab is a monoclonal antibody that targets P-selectin to inhibit cell-cell adhesions.[15] In the Phase IIb SUSTAIN trial, treatment with crizanlizumab was associated with a 45% reduction in the annual rate of painful vaso-occlusive crises compared to placebo. Crizanlizumab was generally well tolerated with a low incidence of

adverse events.[15] The manufacturer plans to submit a Biologics License Application (BLA) to the FDA in 2019.[16]

Future Trends in Rare Diseases and Managed Care Implications

There is no doubt that the advances being made in orphan diseases are bringing life-sustaining and lifesaving treatments to patients who have historically had few, if any, options. When it comes to rare diseases, however, the proverbial elephant in the room is the high cost of treatment. According to a report from EvaluatePharma, the mean cost per patient per year for an orphan drug was $147,308 in 2017, which is four times the mean cost for non-orphan drugs, at $30,708 per patient per year.[5] As high-cost gene therapies come to market over the next few years, this mean cost is expected to continue to increase. According to a survey issued by the Pharmacy Benefit Management Institute, 55% of payors said that the cost of therapy was their primary concern, and 71% felt that the current drug prices are not sustainable.[5]

Perhaps one of the most impactful ways that payors are currently addressing the influx of high-cost orphan drugs is by tightly managing access to these medications with clinical programs. Given that orphan drugs are intended to treat very rare diseases, the patient population being targeted is very specific. Prior authorization remains an important tool for restricting access to orphan drugs to those patients who are most likely to benefit from their use. In addition, monitoring programs may be considered to ensure that patients are adhering to the medications and achieving the best clinical outcomes possible.

Given the significant unmet need for effective treatments, as well as the high cost of developing orphan drugs, value-based payment models should be considered to ensure that lifesaving treatments are available to those who need them. The development of payment models, such as the amortized payment model and the pay-for-performance payment model, has introduced new options for the management of orphan drug utilization. Due to several challenges associated with the use of these models, neither model has been widely adopted or used at this point. As the market for high-cost orphan drugs continues to expand, payors and manufacturers alike will be challenged to find a way to make these lifesaving therapies available to the patients who need them.

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PIPELINE DRUG LIST*

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
metoclopramide (Gimoti®)	Evoke Pharma, Inc.	Diabetic gastroparesis	Intranasal	Submitted	4/1/2019
rizatriptan benzoate (Rizaport®)	IntelGenx Technologies Corp.	Migraine and other headaches	SL; oral transmucosal	Submitted	4/1/2019
sumatriptan (DFN-02)	Dr. Reddy's Laboratories	Migraine and other headaches	Intranasal	Submitted	4/2/2019
RI-002	ADMA Biologics, Inc.	Primary immunodeficiencies	IV	Submitted	4/2/2019
selinexor (KPT-330)	Karyopharm Therapeutics	MM	Oral	Orphan drug; priority review; fast-track	4/5/2019
dolutegravir and lamivudine (Tivicay®/Epivir®)	GlaxoSmithKline plc.	HIV/AIDS	Oral	Submitted	4/18/2019
risankizumab	AbbVie, Inc.	Psoriasis	IV; SQ	Submitted	4/25/2019
bupivacaine and meloxicam (HTX-011)	Heron Therapeutics, Inc.	Postsurgical pain	Instillation	Priority Review; fast-track; breakthrough therapy	4/30/2019
fosfomycin (Contepo®)	Nabriva Therapeutics plc.	Urinary tract and reproductive tract infections	IV	Fast-track	4/30/2019
biosimilar trastuzumab	Pfizer Inc.	Breast cancer	IV	Submitted	April 2019
amisulpride (Barhemsys®)	Acacia Pharma Group plc.	Emesis	IV	Resubmitted after CRL	5/3/2019
quizartinib	Daiichi Sankyo Co., Ltd.	AML	Oral	Fast-track; orphan drug; breakthrough therapy; priority review	5/24/2019
loxicodegol (NKTR-181)	Nektar Therapeutics	Chronic low-back pain	Oral	Fast-track	5/28/2019
biosimilar adalimumab	Samsung Bioepis Co., Ltd	RA; psoriasis; PA; Crohn's disease; UC; axial spondyloarthritis; hidradenitis suppurativa; uveitis; juvenile RA	SQ	Submitted	May 2019

*The U.S. Food and Drug Administration did not accept new applications for non emergency drugs or medical devices requiring a user-fee payment for a multi-week period during the partial government shutdown, which began December 22. As a result, these are tentative dates.

PIPELINE DRUG LIST* CONT.

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
onasemnogene abeparvovec-xxxx (Zolgensma®)	Novartis AG	Spinal muscular atrophy	IV	Fast-track; orphan drug; breakthrough therapy	May 2019
mannitol (Bronchitol®)	Pharmaxis Ltd.	CF	Inhaled	Fast-track; orphan drug	6/20/2019
bremelanotide	AMAG PHARMACEUTICALS, INC.	Female sexual arosal disorder	SQ	Submitted	6/21/2019
celiprolol hydrochloride (Edsivo®)	Acer Therapeutics, Inc.	Metabolic – general	Oral	Orphan drug	6/25/2019
tiopronin reformulation	Retrophin, Inc.	Cystinuria	Oral	Submitted	6/28/2019
biosimilar bevacizumab	Pfizer Inc.	NSCLC	IV	Submitted	June 2019
biosimilar rituximab	Pfizer Inc.	Indolent NHL	IV	Submitted	Q2 2019
afamelanotide (Scenesse®)	Clinuvel Pharmaceuticals, Ltd.	Porphyria	Intradermal	Fast-track; orphan drug	7/8/2019
apremilast (Otezla®)	Celgene Corporation	Behçet's Syndrome	Oral	Orphan drug	7/19/2019
riluzole (BHV-0223)	Biohaven Pharmaceutical Holding Company	ALS	SL; oral transmucosal	Orphan drug	7/19/2019
ferric maltol (Feraccru®)	Shield Therapeutics plc.	Anemia	Oral	Submitted	7/26/2019
tafamidis meglumine (Vyndaqel®)	Pfizer Inc.	Transthyretin Amyloid Cardiomyopathy	Oral	Fast-track; orphan drug; breakthrough therapy	July 2019
glucagon (AMG504-1)	Eli Lilly & Company	Hyperinsulinemia/ hypoglycemia	IM; intranasal	Submitted	April-July 2019
imvamune	Bavarian Nordic A/S	Smallpox vaccine	SQ	Submitted	June-July 2019
plasminogen (Ryplazim™)	Prometic Life Sciences, Inc.	Hypoplasminogenemia	IV	Fast-track; orphan drug	Q2-Q3 2019

Abbreviations: ALS = amyotrophic lateral sclerosis; AML = acute myeloid leukemia; CF = cystic fibrosis; IM = intramuscular; IV = intravenous; MM = multiple myeloma; NHL = non-Hodgkin's lymphoma; NSCLC = non-small-cell lung cancer; PA = psoriatic arthritis; RA = rheumatoid arthritis; SL = sublingual; SQ = subcutaneous; UC = ulcerative colitis

*The U.S. Food and Drug Administration did not accept new applications for non emergency drugs or medical devices requiring a user-fee payment for a multi-week period during the partial government shutdown, which began December 22. As a result, these are tentative dates.

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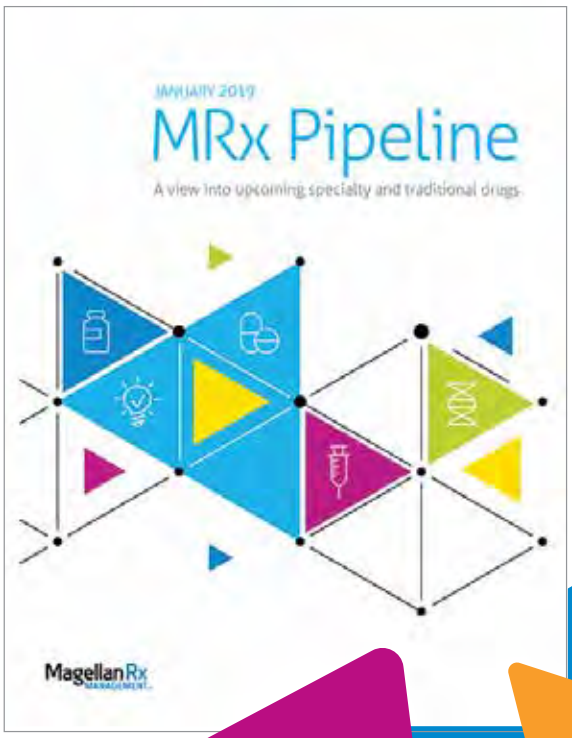

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