PD-1 and PD-L1 Inhibitors: Major Shift in Cancer Treatment Approaches

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Hemophilia: Treatment Landscape, Pipeline Agents, and Management Strategies

Newsstand: Opioid Overutilization Program, PCMH Model, and CMS White Paper

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Summer 2017

Migraine Treatment:

Clinical Considerations and Implications of New and Emerging Treatment Options

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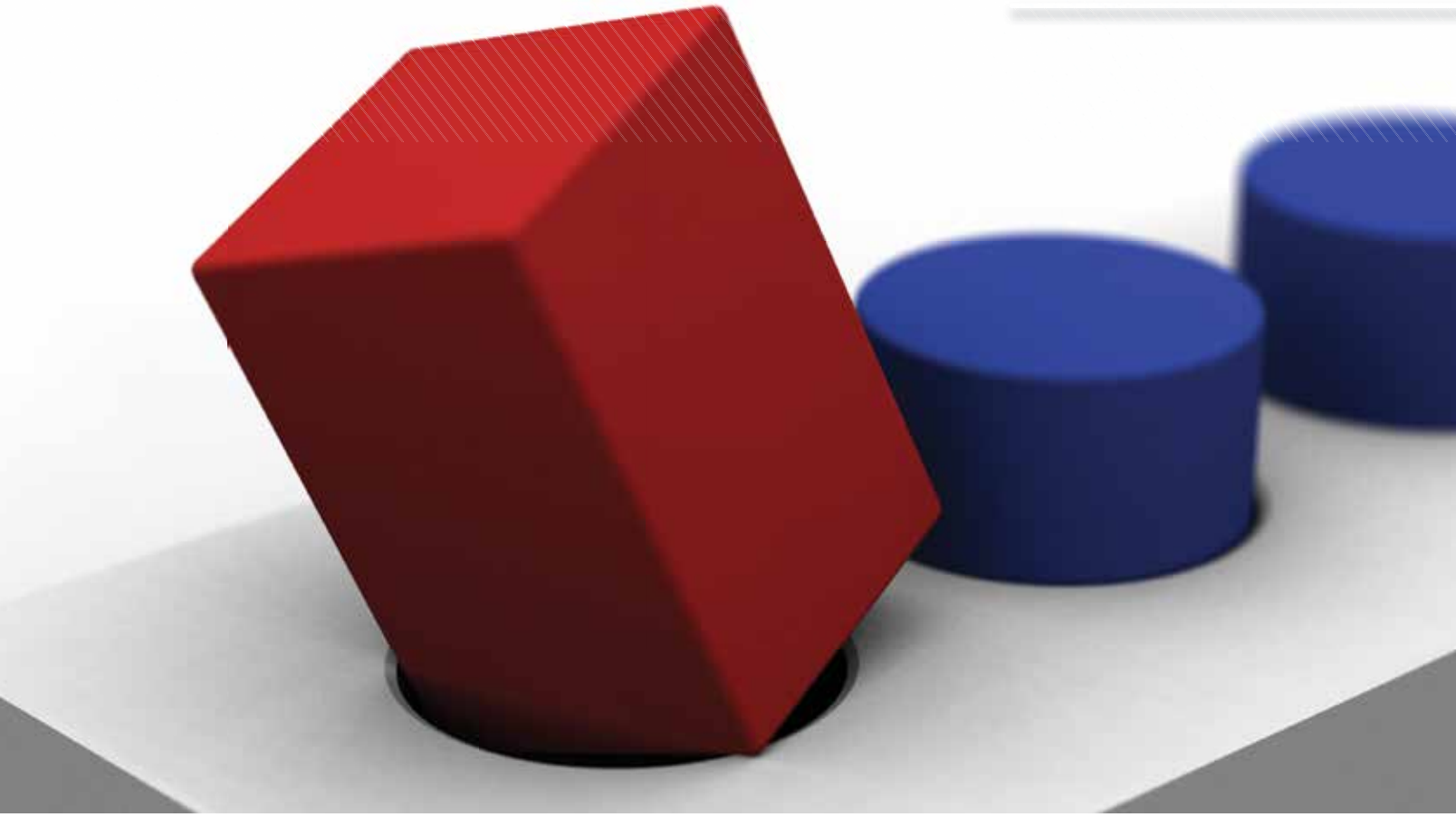

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15950 North 76th Street
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Tel: 401-344-1000
Fax: 401-619-5215
MagellanRxReport@magellanhealth.com
magellanrx.com

Publishing Staff

Todd C. Lord, PharmD, AE-C, CDOE
Themmi Evangelatos, PharmD, MSBA
Briana Santaniello, PharmD, MBA
Carolyn Farnum, BS

Advertising and Sales

Servi Barrientos
401-344-1020
sbarrientos@magellanhealth.com

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Features

Mostafa Kamal
Chief Executive Officer
Magellan Rx Management

Dear Managed Care Colleagues,

Welcome to our summer issue of the Magellan Rx™ Report! While it's hard to believe that we're already halfway through the year, it's not at all surprising that so much has happened in managed care pharmacy since the spring issue. In fact, it's this constantly evolving state of affairs that makes managed care such an exciting field to work in!

The Food and Drug Administration (FDA) got off to a fast start in 2017, with 18 new drug approvals in the first four months of the year alone. Fortunately, Magellan Rx Management was poised to prepare payors for these approvals with the quarterly MRx Pipeline that offers clinical insights and competitive intelligence on anticipated specialty and traditional drugs in the pipeline. Magellan Rx Management was also prepared to share with payors the member and payor impact of high-cost specialty drugs billed on the medical benefit in the seventh annual Medical Pharmacy Trend Report™. Here at Magellan Rx Management, we help our clients manage the fastest-growing, most complex areas of health, including special populations, complete pharmacy benefits, and other specialty areas of healthcare.

In this issue of the Magellan Rx™ Report, the cover story reviews the current treatment landscape for migraines and discusses treatments and devices in the pipeline that, if approved, have the potential to make a clinical impact as well as influence the pharmacy and/or medical budgets of managed care organizations.

A second article of focus provides a comprehensive update to the PD-1/PD-L1 article that was last featured in the spring 2016 issue of the Report. Updates since the 2016 article include the approvals of Tecentriq®, Bavencio®, and Imfinzi™ and new indications for Opdivo® and Keytruda®.

Another article of interest presents the benefits associated with computerized cognitive behavioral therapy (CCBT) — software applications that deliver short-term, goal-oriented, solution-focused care to individuals with behavioral health conditions — which has been validated and supported in numerous clinical outcomes studies. Despite the availability of and cost-savings opportunities associated with CCBT, many individuals do not have access to this service, making CCBT an under-explored opportunity to improve outcomes and reduce total healthcare costs for individuals with behavioral health conditions.

The final article discusses hemophilia, while addressing the different types of the disease; the economic, societal, and humanistic burden of the disease; treatment guidelines; product landscape; implications for managed care; and future directions, including pipeline agents and new strategies for 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.

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
Magellan Rx Management

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Managed Care Newsstand

Pharmacy Benefit Management Institute (PBMI) Recognizes Anthem's Opioid Overutilization Management Program

The U.S. Department of Health and Human Services reported that in 2014, six out of 10 drug overdose deaths were opioid-related and approximately 165,000 of those deaths were due to the overuse of prescription opioids. Several patient identification and treatment barriers have been identified as contributors to the opioid epidemic, especially the lack of patient-centric coordination of benefits to address opioid addiction comprehensively. To address these issues, Anthem designed the Opioid Overutilization Management Program, which originally started as an outreach program with prescriber-benefit coordination when determining the best treatment options for patients. Since 2013, the program has expanded into a case management program for Medicare beneficiaries and dual-eligible members with opioid-abuse potential. The primary objectives of the program are:

- Identification of members with potential opioid overuse
- Notification of prescribers and identification of a key decision-maker for the member
- Coordination of benefits such as referrals to behavioral health case management for members who have medical benefits
- Maintenance of data sharing with the Special Investigations Unit (SIU) and Medicare Drug Integrity Contractor (MEDIC) for potential fraud, waste, and abuse details
- Ensuring the Centers for Medicare & Medicaid Services (CMS) mandate is satisfied for plan-sponsored opioid retrospective drug utilization review (rDUR)
- Facilitation of reporting in the CMS quarterly Overutilization Monitoring System (OMS) report

From 2013 to 2016, the program identified 957 members eligible for case management and has maintained a point-of-sale (POS) restriction rate of 6%. There has also been a reduction of 55% in share of opioid overutilizers among all members using opioid prescription medications. Lastly, 56% of identified members on the OMS report did not reappear for 12 or more months, ultimately indicating overutilization had resolved.

Source:
Anthem PBMI Excellence Award Nomination for Case Management Strategies — Anthem's Opioid Overutilization Program. News release. March 8, 2017.

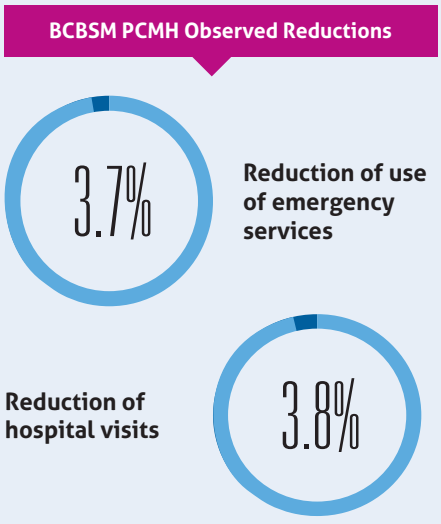
Blue Cross Blue Shield of Michigan's Patient-Centered Medical Home (PCMH) Model Reduces Hospital and Emergency Center Use and Associated Costs

With Blue Cross Blue Shield of Michigan's (BCBSM) PCMH model, primary care physicians lead care teams that "coordinate patients' healthcare, track patients' conditions and test results, and ensure that patients receive needed care at the appropriate time and in the most appropriate setting." Physician practices that have converted to the BCBSM PCMH model have reduced patients' use of emergency services by 3.7% and hospital visits by 3.8%. The reduction in use of emergency department services and hospital visits was three times greater (11.2% and 13.9%, respectively) for patients who had six specific chronic conditions (asthma, angina, diabetes, chronic obstructive pulmonary disease [COPD], high blood pressure, and congestive heart failure) and were being closely monitored. The reduction in hospital and emergency department visits has translated to a significant cost savings associated with the PCMH model. Specifically, reductions of 17.2% and 9.4% were observed in the hospital per-member-per-month (PMPM) cost and emergency department PMPM cost, respectively, for patients with the aforementioned six chronic conditions.

According to David Share, MD, MPH, senior vice president of Value Partnerships at BCBSM, "We worked with physicians statewide to determine what the qualities and characteristics of a PCMH practice should be. We are pleased to see the care management and care coordination characteristics are resulting in Blue Cross members needing fewer hospital stays and emergency visits."

This model is the largest designation of its kind nationally, with the involvement of 4,534 primary care physicians in 1,638 designated practices across Michigan, which translates to a Blue Cross-designated PCMH physician presence in 97.5% of the state.

Source:
Study Shows Blue Cross Patient-Centered Medical Home Model Reduces Hospital and Emergency Center Use. News release. April 24, 2017.



Centers for Medicare & Medicaid Services (CMS) Publishes White Paper Discussing Healthcare Payor Strategies to Reduce the Harms Associated with Opioids

In January 2017, CMS published a white paper titled "Healthcare Payer Strategies to Reduce the Harms of Opioids — The Healthcare Fraud Prevention Partnership's (HFPP) Commitment to the Management of Opioid Misuse and Opioid Use Disorder." HFPP is a voluntary, public-private partnership between the federal government, state agencies, law enforcement, private health insurance plans, employer organizations, and healthcare anti-fraud associations, which seeks to identify and reduce fraud, waste, and abuse. HFPP is well-positioned to examine the opioid crisis and play a monumental role in the development and implementation of key recommendations from a unique perspective due to its broad membership.

As of November 2016, HFPP partners, known as white paper partner champions, include 70 representatives from 7 federal agencies, 38 private payor organizations, 14 state Medicaid or healthcare agencies, and 11 insurance and healthcare anti-fraud associations. Some of the private plans that were integral to this partnership included Aetna, Anthem, AvMed, Florida Blue, EmblemHealth, Health Alliance Plan, Horizon Blue Cross Blue Shield of New Jersey, Independence Blue Cross, Moda Health, UnitedHealthcare, and Magellan Health. These partners have committed themselves to the creation of an HFPP white paper that describes the best practices for serious consideration by all payors and other relevant stakeholders to address and minimize opioid-related harm while ensuring access to medically necessary therapies.

Payors can assist in combatting the growing opioid crisis by identifying and sharing strategies such as reimbursement and coverage policies, conditions surrounding provider plan participation, and the dissemination of information to a variety of audiences to address the issues that lead to fraud, waste, and abuse in the healthcare system. These interventions are particularly favored by payors due to their existing relationships with providers, pharmacies, patients, employers, and law enforcement if fraud is identified. Payors have a large amount of healthcare information that can be used in the identification and intervention on behalf of patients at risk for associated opioid-related harm; this information can also be used to target fraud, waste, and abuse when providers prescribe opioids.

HFPP has identified five specific actions that should be considered for implementation by payors within their own organization as soon as possible:

1. **Train providers on the Centers for Disease Control and Prevention (CDC) Guideline for Prescribing Opioids for Chronic Pain.** This encourages payors to evaluate communication and incentive models in order for providers to become educated on and adhere to the guideline.

   For example, Anthem conducts provider outreach via various websites with information on prescription drug misuse, direction to CMS' Medicare Learning Network (MLN) Matters publications, and provider newsletters. These outreach forms also encourage the use of safe alternatives to opioids, non-opioid analgesics, and non-pharmacologic treatments.

2. **Promote access to medication-assisted treatment (MAT).** This is recommended as part of a complete treatment program through reimbursement policy, provider recruitment, and education for patients who misuse opioids or have opioid use disorder (OUD). MAT used in combination with behavioral therapy is more effective in treating OUD than behavioral therapy alone.

3. **Communicate the availability of naloxone.** HFPP supports reducing unnecessary barriers to the availability of naloxone. This promotion of naloxone availability for patients at risk of opioid abuse is intended to prevent the unintended consequences associated with the misuse or ineffective management of prescription opioids.

4. **Encourage the use of data to identify fraudulent, wasteful, or abusive practices associated with opioids in order to target corrective action.** The use of payor data is encouraged to identify patients at risk of opioid misuse and OUD, prevent nonmedical use of prescription opioids and drug diversion schemes, and appropriately act upon those findings. Data systems can be used to aid and direct investigative resources and appropriate interventions.

5. **Identify and disseminate effective practices across the healthcare sector.** Collaborative efforts should be made to develop effective strategies in the identification of patients at risk of opioid misuse or OUD, providers whose opioid prescribing patterns fail to comply with quality indicators, methods that are particularly effective at preventing or treating OUD, and ways to measure this effectiveness.

Through coordinated action with a large group of key stakeholders, payors — including members of the HFPP — have the opportunity to decrease prescription opioid misuse and OUD in the U.S. This crisis of opioid misuse and OUD creates substantial problems for payors, governmental agencies, employers, and law enforcement partners of the HFPP. The severe health consequences and costs of opioids have increased significantly over the past two decades, which is a trend that correlates to the increase of opioid prescriptions written and the number of people using them for nonmedical purposes.

Source:
Healthcare Payer Strategies to Reduce the Harms of Opioids — The Healthcare Fraud Prevention Partnership's (HFPP) Commitment to the Management of Opioid Misuse and Opioid Use Disorder. CMS news release. January 1, 2017.

Migraine Headache:

Clinical Considerations and Implications of New and Emerging Treatment Options

Prevalence and Epidemiology

Migraine is a common neurological disorder of intense, recurrent/chronic headache pain that can often be a cause of extreme disability in affected individuals. Roughly 28 million women in the U.S. are affected by migraine and the condition affects three times as many women as men (18% vs. 6% of the population, respectively).[1-3]

Avi Mamidi, PharmD, BCPS
Regional Clinical Pharmacy Coordinator
Sutter Health Office of Patient Experience

Around half of women who suffer from migraines have more than one attack each month, with one-quarter experiencing four or more monthly attacks.[3] While upward of 40 million people in the U.S. suffer from migraine, only around 500 certified headache specialists are available to manage this condition.[3]

The social effects of headache are substantial. Data suggest that headache disorders are the third leading cause of disability in the world in terms of disability-adjusted life years and account for one-fifth of work absences.[2,4] Migraines represent 0.5% of all ambulatory care visits, with 52.8% of all visits for migraine occurring in primary care settings, 23.2% in specialty outpatient settings, and 16.7% in emergency departments.[5] Overall, migraine affects about one out of every seven people in the U.S.[3,5]

Pathophysiology

While the pathophysiology of migraine is not completely understood, a generally accepted view is that the pathway begins with depolarization of meningeal perivascular trigeminal nerve endings, generally initiated by a wave of cortical spreading depression.[6] Central sensitization in trigeminal pathways results from elevated impulses via the first branch of the trigeminal nerve.[6] Activation of the trigeminovascular pathway in migraine may explain why pain is restricted to the head, most often affecting the periorbital area and intensifying with increases in intracranial pressure.[7] Early treatment of migraine is key, as central sensitization is associated with poor response to therapy and progression to chronic migraine.[6]

At this time, it remains unclear whether the brains of migraineurs are altered structurally as a consequence of migraine itself.[7] However, molecular, anatomic, and functional abnormalities that lead to sensitivity, homeostatic fluctuations, and decreased ability to adapt result in recurrent headaches.[7] Genetic predisposition has been suggested as the vast majority of migraine sufferers have a family history of migraine.[7]

Healthcare Burden

Every 10 seconds, someone in the U.S. presents to an emergency de-

partment complaining of head pain.[3] While most migraine sufferers experience one to two attacks per month, more than 4 million people suffer chronic daily migraine with at least 15 migraine days per month.[3] Additionally, more than 90% of sufferers are unable to work or function normally during their migraine.[3]

From an economic standpoint, healthcare and lost productivity costs associated with migraine are estimated to be as high as $36 billion annually in the U.S.[3] Additionally, healthcare costs are 70% higher in families with a migraine sufferer than in families without.[3] American employers lose more than $13 billion every year as a result of more than 100 million lost workdays due to employees with migraine.[3] Like those who suffer from other chronic diseases, migraine sufferers experience high medical costs, while receiving little social and economic support and limited access to effective healthcare.[8]

DIAGNOSIS

Compared to other chronic diseases, migraine continues to be a poorly understood disease that is often undiagnosed and undertreated.[3,9] Indeed, more than half of all migraine sufferers are never diagnosed, while the vast majority of diagnosed migraine sufferers do not seek medical care for their pain.[3] Moreover, while 25% of migraine sufferers would benefit from preventive treatment, only 12% of all sufferers receive it.[3]

A migraine diagnosis is made by (1) applying the International Classification of Headache Disorders third edition criteria and (2) excluding secondary headache disorders.[10] Migraine is defined as a headache lasting four to 72 hours and is often unilateral, pulsating, moderate to severe in pain, and worsened by physical activity.[10] It is accompanied by photophobia and phonophobia or nausea.[10] Chronic migraine occurs on 15 or more days in a given month, while episodic migraine occurs with or without aura fewer than 15 days per month.[10]

Differential diagnosis can be a challenge, since migraine is one of several headache types.[11] Primary headache disorders often have overlapping symptoms that can make accurate diagnosis and subsequent treatment very difficult.

Inability to differentiate symptoms between these types of headache is a significant challenge among providers who do not specialize in neurology or headaches, which can potentially lead to mismanagement.

Other types of frequent headache include:[10,11]

Cluster headache: severe unilateral headache lasting 15 to 180 minutes, occurring at least every two days and up to eight times a day. It is associated with ipsilateral autonomic symptoms and/or agitation.

Episodic cluster headache: cluster headache cycles occurring with at least one month of pain-free remission every 12 months.

Chronic cluster headache: cluster headache cycles occurring for at least one year without remission of at least one month.

Tension headache: often bilateral, non-pulsating, mild to moderate headache, not worsened by physical activity. Generally not associated with nausea or photophobia and phonophobia.

MANAGEMENT

Migraine treatment approaches are generally guided by several factors:[12]

- Severity of attacks
- Presence of nausea and/or vomiting
- Treatment setting (medical care facility vs. outpatient)
- Patient-specific factors (e.g. vascular risk factors, drug preference, costs, etc.)

Several guidelines are available to help guide the diagnosis and treatment of migraine.[13-16] Symptomatic treatment of migraine involves several potential options, including nonsteroidal anti-inflammatory drugs (NSAIDs), dopamine antagonists, corticosteroids, opioids, antiemetics, triptans, and various combinations of these classes.[10,16]

With regard to commonly used over-the-counter agents for migraine treatment, acetaminophen 1,000 mg is superior to placebo; however, aspirin 900 to 1,000 mg is more effective than acetaminophen, as are prescription-only diclofenac 50 mg and ibuprofen 400 mg.[17-21] For migraine-induced nausea and vomiting, there is no strong consensus on which antiemetic is most helpful. If migraine-induced nausea cannot be controlled with antiemetics, rectally administered analgesics may be useful.

Combination analgesics containing acetaminophen and codeine are frequently used for migraine, but opioid overuse for symptomatic migraine remains a widespread problem. This is in spite of guidelines that recommend nonopioid medications as first-line therapy.[22] With known risks of opioid

misuse and the potential for developing rebound headache, the use of opioids for migraine should be considered only if all other regimens have proven to be ineffective or are contraindicated.[22]

At this time, several triptans — selective agonists of serotonin 1B/1D receptors — are available for the treatment of migraine.[22] All currently available triptans have been shown to be effective in the treatment of migraine, and these agents are available in several formulations and routes of administration.[22] Oral formulations are most common; though sumatriptan, for example, has oral, intranasal powder, intranasal solution, and subcutaneous injection formulations.[23] Other triptans include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan, and additional formulations include rectal suppositories, patches, and needleless injections, which may be selected based on patient preferences. Generally, triptans are very effective in the symptomatic treatment of migraine. When the initial triptan choice proves to be ineffective, strategies such as dose increases, changing route of administration, or switching to another agent are all potential options.[22]

Although triptans are generally safe and well-tolerated, the most frequent side effects of triptans are nausea and tight or burning sensations in the head, neck, or chest. Potentially serious cardiovascular effects are rare, occurring in less than one in 1 million exposures.[24] However, triptans are contraindicated in patients with uncontrolled hypertension, transient ischemic attack or stroke, previous myocardial infarction, and peripheral vascular disease.[22] They are generally not recommended for use in pregnancy or breastfeeding, though epidemiological data have demonstrated no additional risk for significant fetal abnormalities.[25,26] Episodic migraine can also be managed with non-pharmacologic therapy, such as biofeedback and cognitive behavioral therapy.[27]

Preventive therapy for migraine includes lifestyle modification (e.g. diet, sleep hygiene, stress management) and Food and Drug Administration (FDA)-approved agents such as topiramate, divalproex sodium, tricyclic antidepressants, and beta blockers.[23,27] An alternative to currently approved treatments may be botulinum toxin, which, when injected into specific pericranial locations at three-month intervals, may offer effective prophylaxis with minimal side effects.[27] The evidence, however, has been inconsistent to date, with varying benefits observed.[28-30] Another potential preventive method is transcutaneous supraorbital neurostimulation (Cefaly®), which has been shown to be as effective as other preventive drug and non-drug anti-migraine treatments, with a favorable safety profile.[31]

"American employers lose more than $13 billion every year as a result of more than 100 million lost workdays due to employees with migraine."

Managed Care Implications

Migraine continues to represent a difficult clinical problem in the managed care environment, with a significant toll in terms of disability, treatment costs, and quality of life. As mentioned above, at this time there are several potential preventive methods, though there is no consensus about the optimal approach to prophylaxis in patients with frequent or intractable migraine. However, triptan-based abortive treatment has become the standard of care in patients with acute migraine.[13]

Although triptans are highly effective medications, they are also costly, with per-dose wholesale acquisition costs (WACs) ranging from approximately only $1 per tablet of generic sumatriptan to as high as $150 per injection of Zembrace™ SymTouch™. With proper use, triptans represent a cost-effective treatment strategy; however, triptan overuse is widespread and results in further elevated treatment costs, medication waste, and increased risk for toxicity.[30]

The costs of migraine assumed by managed care organizations (MCOs) can be substantial and exacerbated by inappropriate use of prescription medications, especially triptans and opioids, as well as over-the-counter medications.[6] Specifically, overuse of medication can lead to increased costs and poor patient outcomes through medication overuse headache and unnecessary visits for medical care. In the U.S., average total hospital costs are about $1,800 per visit, which can be substantially higher if imaging is ordered.[32] As alluded to previously, one factor correlated with escalating utilization of hospital services (including the emergency department) is opioid use. Data have shown that patients dependent on opioids used the emergency department almost 24 more times per year than those who were not.[33]

Clinicians who care for patients who experience migraines continue to face several challenges. For example, opioids are still used in over half of all emergency department visits for migraine despite recommendations against this practice due to concerns regarding tolerance, dependence, and addiction, as well as evidence suggesting their ineffectiveness in migraines and potential linkage to prolonged emergency department stays.[6,13,27,32] Additionally, discussing preventive care is an unmet need, with one-quarter of general practitioners not doing so.[34] Barriers to initiating abortive or preventive treatment in practice include perceived lack of effectiveness, patients' negative attitudes toward medication, medication side effects, previous unsuccessful therapy, and acceptable

quality of life with migraines.[34]

Additionally, few providers are familiar with International Classification of Headache Disorders diagnostic criteria. While treatment guidelines exist, they are not frequently used in practice.[35,36] Moreover, clinicians have reported "liking" to treat other medical conditions more than migraine.[37] When asked to rate the statement: "I like to treat patients with _____ disease or symptom" on a 1 to 5 scale (1 = strongly disagree; 5 = strongly agree), clinicians rated migraine at 3.2 compared to an overall mean of 4.4 for all diseases.[37]

The emergence of generic triptans and new formulations may prompt ongoing formulary reviews of the migraine category. To this point, efficacy parameters need to be specific to the migraine or headache category, including data across multiple endpoints. Financial considerations include relative cost of care, available therapeutic options, appropriate use in therapy, and potential for abuse or overutilization. In managed care, appropriate migraine treatment can reduce outpatient and emergency visits, as well as diagnostic scans and hospitalizations.[6] To address the unmet need for safe, clinically effective, and cost-effective treatment for this patient population, pharmaceutical and device manufacturers have made research and development efforts in this therapeutic area. These innovative treatment options are described below.

EMERGING AGENTS

Challenges to effective migraine treatment include incomplete therapeutic response, side effects, suboptimal adherence, and medication overuse.[6] Even with considerable progress in diagnosis and treatment in recent decades, the management of migraine and other headache disorders continues to depend on certain agents that are not primarily indicated for the condition. Moreover, patients with refractory migraine, in particular, have few effective treatment options. Investigational treatment options hold promise for addressing unmet patient needs and lowering disability caused by migraines.[38,39]

"At this time, four monoclonal antibodies targeting CGRP or its receptor are in phase III trials for migraine, while a small-molecule CGRP antagonist is being investigated for migraine prevention."

Triptans and Ergot Derivatives

As mentioned previously, several triptans are available in a variety of formulations and routes of administration, yet new formulations of these agents are being investigated as well. For example, inhaled zolmitriptan is also in development for the treatment of acute migraine and features an aerodynamic design that helps facilitate rapid and consistent delivery of the medication.[39]

Dihydroergotamine — available in intravenous, subcutaneous, intramuscular, and intranasal formulations — is indicated for acute migraine treatment with or without aura. Additionally, an orally inhaled formulation has an anticipated launch during 2017 in the U.S.[23,40]

Serotonin Receptor Agonist Therapy

Lasmiditan, a non-triptan serotonin 1F receptor agonist, has shown efficacy in treating acute migraine in the phase III SAMURAI study, while two other phase III studies (SPARTAN and GLADIATOR) are underway. In SAMURAI, freedom from migraine pain two hours after dosing was significantly higher with lasmiditan 100 mg and 200 mg compared to placebo (28.2%, 32.2%, and 15.3%, respectively).[41] By targeting the 1F receptor, which does not cause vasoconstriction, lasmiditan may avoid cardiovascular/cerebrovascular effects associated with other triptans which target 1B/1D receptors and work through vasoconstriction.[42,43]

Anti-CGRP Monoclonal Antibodies

A great deal of research has focused on calcitonin gene-related peptide (CGRP) and its role as a migraine trigger.[38,44,45] CGRP dilates cerebral and peripheral blood vessels and, as a result, inhibition of CGRP has become a novel area of treatment.[44,45] Early CGRP antagonists, the "-gepants," showed clinical efficacy but were associated with toxicity and adverse events. Monoclonal antibodies (mAbs) against CGRP or its receptor have gained significant interest in recent years. At this time, four mAbs targeting CGRP or its receptor (LY2951742, galcanezumab; ALD403, eptinezumab; TEV-48125, fremanezumab; and AMG334, erenumab) are in phase III trials for migraine, while the small-molecule CGRP antagonist MK-8031 (atogepant) is being investigated for migraine prevention.[39] Each of these agents has shown promise in early clinical trials.[11,46-51]

Of note, positive results from the phase III HALO study of fremanezumab (Teva Pharmaceutical Industries Ltd.) for the prevention of chronic migraine were recently announced.[49] Additionally, topline results from the HALO study in episodic migraine will be released in the near future.[49] The manufacturer has also announced its plans to submit a Biologics License Application (BLA) to the FDA for fremanezumab later this year.[49]

Neuromodulation

Neuromodulation techniques are increasingly used in neurology and include noninvasive treatments and implantable devices.[52] Methods such as transcutaneous supraorbital nerve stimulation

CONCLUSIONS

In managed care, the proactive approach to treatment is optimal and involves several foundational elements:[6]

- Regular use of diagnostic and treatment guidelines
- Employment of effective and individualized treatment that deters medication misuse
- Consideration of fast-acting medications to reduce rescue therapy when appropriate
- Education of patients on migraine triggers and warning signs
- Review of economic considerations and patient concerns whenever initiating treatment
- Referral of patients to specialists when necessary

have been found to be effective in episodic migraine prevention, while vagus nerve stimulation (VNS) has shown promise for treating acute migraine.[52,53] With these methods, the visual cortex is the target of choice; consequently, studies in migraine prevention and acute treatment of aura have been encouraging. Noninvasive methods are delivered by devices that patients can purchase and self-administer on an as-needed or scheduled basis.[50-53] Given that these non-pharmacological treatments are still under development, actual treatment costs are not yet known. Of note, treatment with non-invasive vagus nerve stimulation (nVNS) has demonstrated cost savings in one clinical trial in patients with chronic cluster headache; however, further studies are needed to demonstrate the potential for cost savings opportunities in the treatment of migraine.[53,54]

Implantable devices are placed using percutaneous or surgical procedures, and are powered either wirelessly or by surgically implanted batteries. As a result, the settings of these devices can be changed remotely. Therapeutic targets include the cerebral cortex, occipital nerves (including trigeminal nerve branches and vagus nerves), cranial nerves, and the trigeminal nucleus caudalis in the high cervical spinal cord.[53] An example is occipital nerve stimulation for chronic migraine, which has shown modest results but offers hope to highly disabled patients who failed all other treatments.[52] Moving forward, the use of neuromodulation will likely increase in migraine treatment as an alternative to medication or as add-on therapy, particularly because of its favorable safety profile.

Several therapeutic options for migraine are at the disposal of clinicians, and clinical considerations, such as efficacy, safety, tolerability, mechanism of action, formulation, and onset of analgesic effect, are among the most important factors when choosing therapy. By implementing individualized options backed by quality clinical trial evidence, it is possible to make a substantial difference in the lives of the majority of patients with migraine.

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PD-1 and PD-L1 Inhibitors:

A Major Shift in the Cancer Treatment Landscape

The Agency for Healthcare Research and Quality (AHRQ) estimated that in 2014, the direct medical costs associated with cancer in the U.S. were approaching $88 billion annually.[1] Furthermore, the cost of cancer care varies according to type of cancer.[1,2] In 2010, female breast cancer was thought to have the highest cost at $16.5 billion annually, followed by colorectal cancer ($14.1 billion), lymphoma ($12.1 billion), lung cancer ($12.1 billion), and prostate cancer ($11.8 billion).[3]

Robert Schoenhaus, PharmD
Director, Pharmacy Benefits Administration, Sharp HealthCare

Individuals who have a history of cancer also tend to utilize more healthcare resources related to both short-term and long-term side effects of cancer, its treatment, and monitoring for its recurrence.[4] It is anticipated that the economic burden will continue to grow as the population ages and medical advancements allow for greater survivorship.[4] Cancer also represents a significant societal burden, given the lost productivity of the individual diagnosed, the additional related healthcare costs that increase insurance premiums, and increased income taxes when care is covered by federally funded or state-funded plans.[5]

FDA-Approved Indications

In 2014, pembrolizumab (Keytruda®, Merck & Co.) became the first programmed death-1 (PD-1) inhibitor approved by the Food and Drug Administration (FDA), soon followed by nivolumab (Opdivo®, Bristol-Myers Squibb) in 2015.[6,7] The approval of these agents marked the beginning of what would become a significant shift in the treatment approach to a variety of cancers. PD-1 is an immune-inhibitory receptor that can be found on the surface of T cells as well as other various immune cells.[8] The PD-1 receptor interacts with programmed death-ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), both of which are expressed on the surface of various immune cells; however, PD-L1 can also be expressed on the surface of tumor cells as a mechanism to evade the host immune system by inhibiting T cell activation and cytokine production.[8] By blocking the interaction between the PD-1 receptor and the PD-L1 expressed on the cancer cell, PD-1 inhibitors allow the immune cells to recognize and attack the cancer cell.[8] It is important to note that the interaction between PD-1, PD-L1, and PD-L2 on immune cells is essential for maintaining a healthy immune system.[8-10]

In 2016, the FDA approved atezolizumab (Tecentriq®, Genentech), the

TABLE 1. FDA-APPROVED INDICATIONS FOR PD-1/PD-L1 INHIBITORS[6,7,11-13]

Indication	Keytruda®	Opdivo®	Tecentriq®	Bavencio®	Imfinzi™
• Melanoma	• Treatment of unresectable or metastatic melanoma	• Single-agent treatment of BRAF V600 wild-type unresectable or metastatic melanoma • Single-agent treatment of BRAF V600-positive unresectable or metastatic melanoma • In combination with ipilimumab: treatment of unresectable or metastatic melanoma	N/A	N/A	N/A
• HNSCC	• Second-line treatment of recurrent or metastatic HNSCC that progressed during/following platinum-containing chemotherapy	• Second-line treatment of recurrent or metastatic HNSCC that progressed following platinum-containing chemotherapy	N/A	N/A	N/A
• NSCLC	• In combination with pemetrexed plus carboplatin: first-line treatment of metastatic nonsquamous NSCLC regardless of PD-L1 expression and with no EGFR or ALK mutations • First-line treatment of metastatic NSCLC in patients whose tumors have high PD-L1 expression (TPS ≥50%) with no EGFR or ALK mutations • Second-line treatment of metastatic NSCLC in patients whose tumors express PD-L1 (TPS ≥1%) with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy for these mutations prior to receiving Keytruda®	• Second-line treatment of metastatic NSCLC with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy for these mutations prior to receiving Opdivo®	• Second-line treatment of metastatic NSCLC with disease progression on or after platinum-containing chemotherapy; patients with EGFR or ALK mutations should have disease progression on FDA-approved therapy for these mutations prior to receiving Tecentriq®	N/A	N/A
• RCC	N/A	• Second-line treatment of advanced RCC following prior anti-angiogenic therapy	N/A	N/A	N/A
• cHL	• Fourth-line (or later) treatment of refractory cHL in adult and pediatric patients following ≥3 prior lines of therapy	• Treatment of cHL in adult patients whose disease relapsed or progressed after autologous HSCT and brentuximab vedotin or ≥3 lines of systemic therapy that includes autologous HSCT	N/A	N/A	N/A
• Urothelial carcinoma	• First-line treatment of locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy • Second-line treatment of locally advanced or metastatic urothelial carcinoma that progressed during/following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy	• Second-line treatment of locally advanced or metastatic urothelial carcinoma that progressed during/following platinum-containing chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy	• First-line treatment of locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy • Second-line treatment of locally advanced or metastatic urothelial carcinoma that progressed during/following platinum-containing chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy	• Second-line treatment of locally advanced or metastatic urothelial carcinoma that progressed following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy	• Second-line treatment of locally advanced or metastatic urothelial carcinoma that has progressed during/following platinum-containing chemotherapy or within 12 months of neoadjuvant/adjuvant treatment with platinum-containing chemotherapy
• MCC	N/A	N/A	N/A	• Treatment of metastatic MCC in adult and pediatric patients ≥12 years of age	N/A
• MSI-H, dMMR solid tumors	• Second-line treatment of adult and pediatric patients with unresectable or metastatic MSI-H or dMMR solid tumors that have progressed after prior treatment and who have no satisfactory alternative treatment options • MSI-H or dMMR colorectal cancer following progression on a fluoropyrimidine, oxaliplatin, and irinotecan	N/A	N/A	N/A	N/A

Abbreviations: ALK = anaplastic lymphoma kinase, dMMR = mismatch repair deficient, EGFR = epidermal growth factor receptor, HSCT = hematopoietic stem cell transplantation, MSI-H = microsatellite instability-high, N/A = not applicable, TPS = tumor proportion score

first agent approved to specifically target PD-L1, followed by avelumab (Bavencio®, Pfizer) and durvalumab (Imfinzi™, AstraZeneca) in 2017.[11-13] The purported benefit of targeting the PD-L1 subtype is that the interaction between PD-1 and PD-L2 would remain intact.[8] Theoretically, this helps avoid autoimmune pneumonitis or nephritis, which may occur if interaction between PD-1 and PD-L2 expressed on normal cells within the lung and kidney is blocked.[8] Of note, clinical trials to date have not demonstrated significant differences in safety between the PD-1 and PD-L1 inhibitors; though, a meta-analysis has shown that both PD-1 and PD-L1 inhibitors are better tolerated compared to chemotherapy with favorable risk-to-benefit ratios.[8,14]

Following their initial approvals, the approved indications for the PD-1/PD-L1 inhibitors have continued to grow and now include melanoma (Keytruda® and Opdivo®), head and neck squamous cell carcinoma (HNSCC) (Keytruda® and Opdivo®), non-small cell lung cancer (NSCLC) (Keytruda®, Opdivo®, and Tecentriq®), renal cell carcinoma (RCC) (Opdivo®), classical Hodgkin's lymphoma (cHL) (Keytruda® and Opdivo®), and urothelial carcinoma (Keytruda®, Opdivo®, Tecentriq®, Bavencio®, and Imfinizi™). Bavencio® is the only PD-L1 inhibitor and first FDA-approved therapy for the treatment of adult and pediatric patients 12 years of age and older with metastatic Merkel cell carcinoma (MCC).[12] Keytruda® is currently the only PD-1 inhibitor that is FDA-approved for the treatment of adult and pediatric patients who have unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors.[6] The specific indications for which these agents are approved are listed in Table 1.[6-13]

PD-1/PD-L1 Inhibitor Pipeline

The role of PD-1/PD-L1 inhibitors continues to be explored across a wide variety of tumor types. Keytruda® recently received FDA approval for the treatment of locally advanced or metastatic urothelial carcinoma in patients who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy; locally advanced or metastatic urothelial carcinoma in patients who are not eligible for cisplatin-containing chemotherapy; and MSI-H cancer.[15,16] The approval of Keytruda® for the treatment of MSI-H and dMMR solid tumors represents the first FDA approval of a cancer treatment for any solid tumor with a specific genetic feature, rather than the typical approval of a treatment based on the location in the body in which the tumor is located.[17]

Table 2 provides a snapshot of some of the indications for which the PD-1 and PD-L1 inhibitors are currently being studied.[18,19]

The most recent PD-L1 agent to market, Imfinzi™, is being studied for the first-line treatment of urothelial carcinoma as monotherapy and in combination with tremelimumab, a cytotoxic T lymphocyte antigen 4 (CTLA-4) inhibitor.[20] The combination of Imfinzi™ and tremelimumab is also being investigated for its role in the treatment of NSCLC, HNSCC, gastric cancer, pancreatic cancer, hepatocellular carcinoma, and advanced solid tumors.[19]

Despite the clinical success of the PD-1/PD-L1 inhibitors, a large proportion of patients fail to respond to monotherapy.[21] Based on clinical data, it appears that higher levels of PD-L1 expression on tumor cells (TPS ≥50%) corresponds to greater efficacy of PD-1/PD-L1 inhibitor therapy; however, there are many challenges associated with using PD-L1 expression to guide treatment decisions, including that PD-L1 expression can vary based on the part of the tumor that is biopsied as well as the time at which it is biopsied.[22] Given the limitations of PD-1/PD-L1 inhibitor monotherapy, there is a great deal of interest in utilizing combinations of synergistic immunotherapies as well as the combination of immunotherapy with other antitumor treatment modalities to further improve survival.[23]

The combination of Opdivo® and ipilimumab (Yervoy®, Bristol-Myers Squibb), approved by the FDA in 2015 for the treatment of unresectable or metastatic melanoma, regardless of BRAF mutation status, is an example of combination treatment.[23] The mechanism of action of Yervoy®, CTLA-4 inhibition, complements that of Opdivo® (activated T-cell response) via enhanced T-cell activation and proliferation.[23] The end result is thought to be a more robust immune response directed at the tumor.[23]

The approval of this combination was based on the results of the phase III CheckMate-067 trial, which demonstrated statistically significant improvements in progression-free survival associated with Opdivo® and Yervoy® combination therapy or Opdivo® monotherapy compared to Yervoy® as monotherapy (P<0.0001 for both comparisons).[24] Although the trial was not designed to detect a difference between combination therapy and Opdivo® monotherapy, an exploratory analysis found that combination therapy resulted in reduced risk of progression by 24% compared to Opdivo® monotherapy (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.60 to 0.92).[24,25]

The combination of Opdivo® and Yervoy® is also being studied for the treatment of endometrial carcinoma, fallopian tube cancer, gastroesophageal cancer, gastrointestinal stromal tumor, glioblastoma, gliosarcoma, hepatocellular carcinoma, HER2-negative inflammatory breast cancer, HNSCC, Hodgkin's lymphoma, human immunodeficiency virus (HIV)-associated solid tumors, kidney cancer, malignant pleural MCC, multiple myeloma, gastric cancer, mesothelioma, myelodysplastic syndrome, nasopharyngeal carcinoma, NSCLC, pancreatic cancer, primary peritoneal cancer, prostate cancer, leukemia, RCC, sarcoma, uveal melanoma, squamous cell lung cancer, and ovarian cancer.[18] Yervoy® is also being studied in combination with Keytruda® for the treatment of melanoma, NSCLC, and RCC.[19]

TABLE 2. ADDITIONAL TUMOR TYPES/CONDITIONS IN WHICH PD-1/PD-L1 INHIBITORS ARE BEING STUDIED*[18,19]

Keytruda®	Opdivo®	Tecentriq®	Bavencio®	Imfinzi™
Bladder cancer	Bladder cancer	Bladder cancer	Bladder cancer	Bladder cancer
Breast cancer	Breast cancer	Breast cancer	Breast cancer	
Colorectal cancer	Colorectal cancer	Colorectal cancer	Colorectal cancer	
Hematologic malignancies	Hematologic malignancies	Hematologic malignancies		
			HNSCC	HNSCC
Leukemia, acute myeloid (AML)	Leukemia, acute myeloid (AML)	Leukemia, acute myeloid (AML)	Leukemia, acute myeloid (AML)	
	Leukemia, chronic lymphocytic (CLL)	Leukemia, chronic lymphocytic (CLL)		
	Leukemia, chronic myeloid (CML)	Leukemia, chronic myeloid (CML)		
		Lymphoma	Lymphoma	
	MCC		MCC	
Melanoma	Melanoma	Melanoma		Melanoma, metastatic or unresectable
Multiple myeloma	Multiple myeloma	Multiple myeloma		
	Myelodysplastic syndrome	Myelodysplastic syndrome		Myelodysplastic syndrome
Non-Hodgkin's lymphoma	Non-Hodgkin's lymphoma			
NSCLC	NSCLC	NSCLC	NSCLC	NSCLC
Ovarian cancer	Ovarian cancer	Ovarian cancer	Ovarian cancer	
Pancreatic cancer	Pancreatic cancer			Pancreatic cancer
Prostate cancer	Prostate cancer	Prostate cancer		
RCC	RCC	RCC	RCC	
Small cell lung cancer	Small cell lung cancer	Small cell lung cancer		
Solid tumors	Solid tumors	Solid tumors	Solid tumors	Solid tumors
Stomach cancer	Stomach cancer		Stomach cancer	

** = List is not all-inclusive and displays only some of the tumor types in which more than one of these therapies is being studied*

The second most recent PD-L1 agent to market, Bavencio®, is being studied in various combinations that include kinase inhibitors (e.g., axitinib [Inlyta®], crizotinib [Xalkori®]), EGFR antagonists (e.g., cetuximab [Erbitux®]), chemotherapy, and radiation.[18] These Bavencio®-based combination regimens are being studied for a variety of indications that include AML, fallopian tube cancer, glioblastoma, HNSCC, leiomyosarcoma, liposarcoma, NSCLC, ovarian cancer, primary peritoneal cancer, and RCC.[18]

Implications for Managed Care

Payors have historically managed the PD-1/PD-L1 inhibitors based on their specific FDA-approved indications for use, which previously differed slightly among the available agents. As the number of FDA-approved agents and approved indications continues to rapidly increase, there may be opportunities to seek supplemental rebates by selecting a preferred agent. Given that the PD-1/PD-L1 inhibitors do not carry the same indications, the best approach may be to select a preferred agent for each indication, carefully considering the clinical data available to ensure that a clinically appropriate therapy is available to patients for each indication.[6,7,11-13] The increasing use of PD-1/PD-L1 inhibitors in combination with a variety of immunotherapies and anti-tumor treatment approaches poses the largest financial challenge overall. The payor will be tasked with creating management strategies that ensure appropriate use of these combinations, while also controlling cost. This will require careful consideration to determine which patients are most likely to benefit from these therapies based on factors such as previous treatments and PD-L1 expression. Given the ever-changing treatment landscape, it will be important to keep close watch on new developments in the PD-1/PD-L1 arena.

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Seth D. Feuerstein, M.D., J.D.
Chief Innovation Officer and Chief Medical Officer, Medical and Digital Innovation, Magellan Healthcare

Brian Keenaghan, MS
Director of Innovation, Magellan Health

Behavioral health conditions are highly prevalent; research suggests approximately 26% of adults worldwide have behavioral health conditions.[4] In addition, the healthcare costs for individuals with behavioral health conditions are as much as two to three times higher compared to those without these conditions.[5] Unfortunately, patients with behavioral health conditions face difficulty in accessing behavioral healthcare due to factors such as state- and local-level policies, lack of insurance coverage or inadequate insurance coverage, limited or no available treatment providers, and lack of available treatment types.[6,7] Behavioral health conditions can be treated through counseling, cognitive behavioral therapy (CBT), pharmacotherapy, and other management strategies. Although prescription medications can be useful in certain individuals, the overprescribing of medications to treat behavioral health conditions has become a significant problem.[8] Fortunately, computerized cognitive behavioral therapy (CCBT) — software applications that deliver short-term, goal-oriented, solutions-focused care to individuals with behavioral health conditions — has been validated and supported in numerous clinical outcomes studies.[9,10] Despite the availability of and cost-savings opportunities associated with CCBT, many individuals do not have access to this service.[10-14] CCBT may represent an under-explored opportunity to improve outcomes and reduce the total healthcare costs for individuals with behavioral health conditions.

Current Treatment Approaches and Barriers to Behavioral Healthcare for Select Behavioral Health Conditions

Behavioral health conditions encompass a number of disorders including, but not limited to, anxiety, panic and phobia, depression and low mood, substance use and abuse, and obsessive compulsive disorder (OCD). There are also other conditions, such as insomnia and sleep problems, which are common symptoms of many behavioral health conditions, and thus will be included in this discussion. Treatment guidelines for the

"Across the nation, there is only one mental health provider for every 790 individuals, and there are more than 4,000 areas worldwide that are considered to be shortage areas for behavioral health professionals."

management of generalized anxiety disorder (GAD) and OCD are published by the Anxiety and Depression Association of America (ADAA); guidelines for major depressive disorder are published by the American Psychiatric Association (APA); guidelines for substance use disorder are published by the American Society of Addiction Medicine (ASAM); and guidelines for insomnia are published by the American Academy of Sleep Medicine (AASM). First-line recommendations for all of the aforementioned conditions involve CBT with or without the use of pharmacotherapy, and a combination of the two therapies has demonstrated the most successful outcomes for many behavioral health conditions.[15-19]

According to many studies, CBT may be as effective as pharmacotherapy, particularly among patients with depression, and is associated with fewer adverse effects and lower instances of relapse compared to pharmacotherapy.[8,20] Despite the benefits associated with CBT, this modality of care is not as widely used as pharmacotherapy for many patients with behavioral health conditions. In fact, between 2001 and 2010, there was a 22% increase in the use of psychotropic drugs by adults in the U.S.; in 2010, Americans spent more than $16 billion on antipsychotics and $11 billion on antidepressants, according to industry

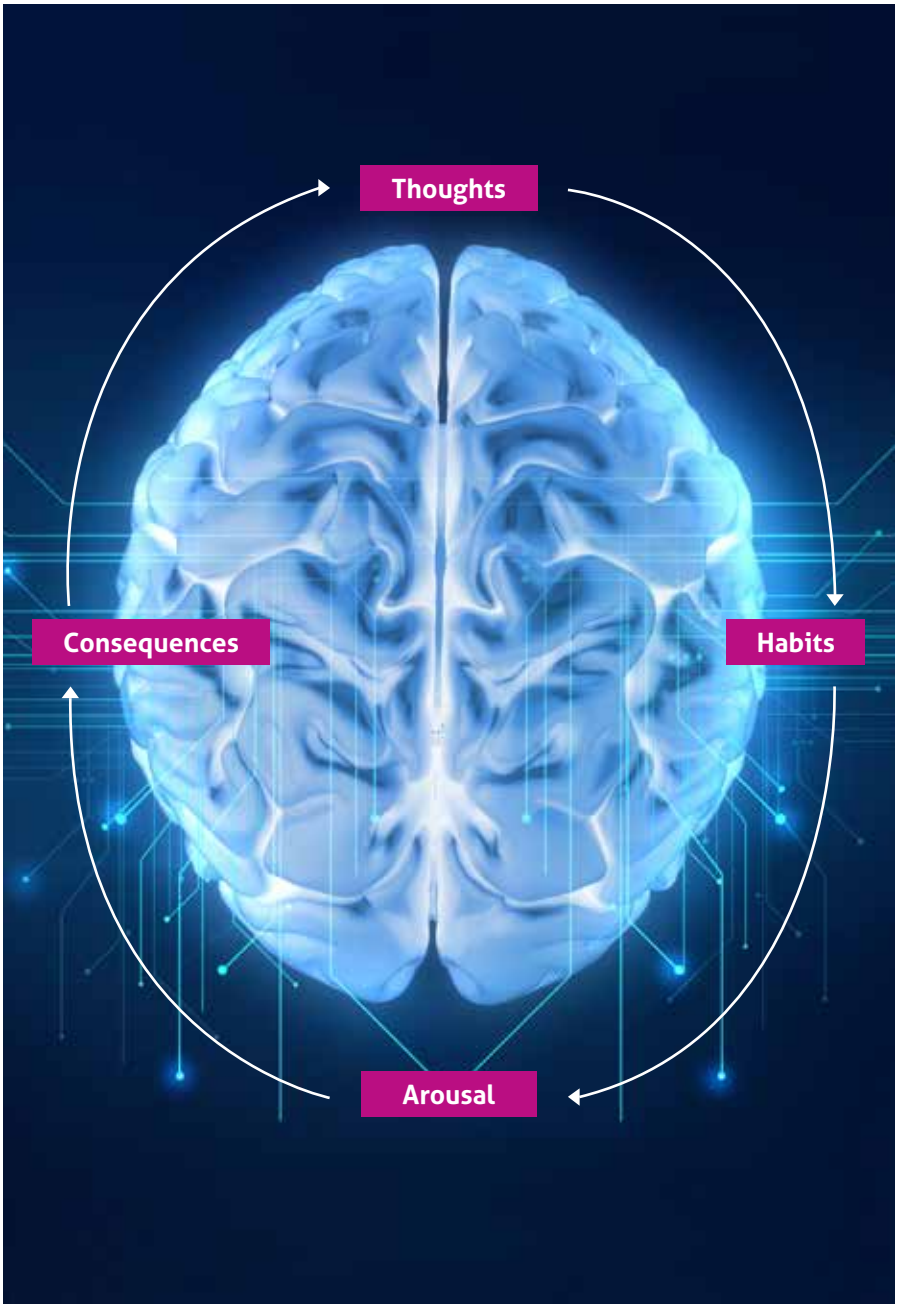
data.[8] In comparison, the number of patients receiving CBT is dwindling, according to a medical survey, which may be a result of lower psychotherapy reimbursement rates for clinicians and higher out-of-pocket costs to patients, among other reasons.[8,21]

Patient and provider barriers can prevent access to behavioral healthcare. At the patient level, behavioral healthcare is costly and poses a significant financial barrier to insured patients with insufficient finances to cover the costs associated with treatment, including copays, coinsurance, or out-of-pocket expenses for services that are not covered by insurance.[7] For the uninsured population, these treatment-associated costs can be even more daunting, as the entire cost of treatment is likely to be the responsibility of the patient.[7] Research has demonstrated that individuals with behavioral health conditions are two and a half to seven times more likely to face barriers to medical care, and half of adults who have an untreated need did not receive treatment because of these costs.[7] Potential barriers faced by patients include a lack of access to a primary care provider, inability to seek necessary medical care, lack of access to necessary prescription treatments, and delayed treatments because of costs.[7]

At the provider level, there are a number of barriers, the most notable of which is the shortage of qualified providers to care for patients with behavioral health conditions.[7] Across the nation, there is only one mental health provider for every 790 individuals, and there are more than 4,000 areas worldwide that are considered to be shortage areas for behavioral health professionals.[22,23] Whether as a result of a lack of access to a behavioral health specialist or an inability to receive treatment from a behavioral health specialist due to coverage limitations or financial reasons, many patients who seek treatment for their behavioral health conditions do so through their primary care provider in the form of pharmacotherapy. Of note, a 2009 study indicated that nearly 80% of prescriptions for antidepressants are written by physicians who are not psychiatrists; however, research has suggested that patients with depression who seek treatment prefer psychotherapy over pharmacotherapy.[8,24,25]

In addition to the above barriers, the stigma associated with mental illness can prevent patients from seeking treatment.[26] Despite the progress that has been made in addressing this issue, the stigmatization of mental illness continues to exist for various cultural, religious, and social reasons.[27,28] So long as stigmatization of behavioral health conditions persists, individuals will continue to suffer

PSYCHOSOCIAL INSOMNIA MODEL



from inadequate or negative treatment outcomes, and recovery will be hindered.[28,29] One strategy to increase access to and usage of behavioral health services is to present and offer such services in a manner that respects patients' cultural, religious, and social beliefs.[26] Another strategy is to offer these services in a private fashion in the comfort of the patient's home or location of choice through the assistance of CCBT software.

Bridging the Gap with CCBT and Implications for Managed Care

CCBT delivers CBT through interactive, digital sessions that can be completed by patients at their own pace, and at a location of their choice, at any time. CCBT helps identify unhelpful thinking, modify beliefs, and change behaviors, and helps patients learn to problem-solve.[10] Presently, a handful of companies offer CCBT, including, but not limited to, Magellan's Cobalt suite (including RESTORE™, FearFighter™, MoodCalmer™, SHADE™, and OCFighter™), Pear Therapeutics' reSET™, UPMC's Beating the Blues US™, Learn to Live, and Empower Interactive's Good Days Ahead.[9,30-33] These programs differ in terms of the conditions they are designed to manage, cost, length of programming, confidentiality, availability in on-demand format, device compatibility, data analytic capabilities, telehealth, chat, and call center services, and a user's ability to interact and/or interface with clinicians to notify them of routine care updates or emergencies, such as risk of harm to self or others.[9,30-33]

Collectively, insomnia, depression, anxiety, substance abuse, and OCD are present in more than a quarter of all adults and comprise more than 90% of behavioral health complaints.[34] Across all available CCBT platforms, there is wide variability in services offered for specific behavioral health conditions, with some platforms offering services for just one of these conditions, and only one platform that offers a full suite of CCBT software that covers all of these conditions. With regard to cost, patients may pay anywhere from approximately $100 to more than $1,000 for a predetermined number of sessions or a certain number of months of access. Prices vary depending on length of programming and whether the platform includes clinician-provided services or module-only access. For module-only access, many of these services are available 24 hours a day, seven days a week, with on-demand and mobile-application access options; for clinician-provided services, only certain CCBT platforms offer 24/7 access to care. Additionally, some platforms are accessible from desktop computers only, while others can be accessed on some or all devices, from desktop to mobile. Regardless of the platforms used, it is crucial that these platforms offer monitoring and notification of appropriate individuals (e.g. clinicians, emergency personnel, etc.) of risk of user self-harm or harm to others. Some programs achieve this through screening software, contracting with the National Suicide Prevention Lifeline or other crisis lines; others use different strategies.

"Other benefits of CCBT include more effective use of clinician time, reduced pharmacy spend, shortened wait lists, improved access to care, standardized care, and patient empowerment."

Available CCBT platforms also differ in the amount of outcomes data and evidence of success, ranging from limited evidence for use with some programs and robust, positive evidence for use in others.[22] As mentioned previously, certain CCBT platforms have been validated and supported in numerous clinical outcomes studies.[10,22] In addition, a 2014 systematic review and meta-analysis revealed that CCBT could potentially offer an effective and cost-effective alternative and complementary service to in-person therapy.[35] Of note, some CCBT programs are designed to serve as adjunctive therapy and can be administered by clinicians, whereas others do not require clinician administration and can be used directly and anonymously by patients as monotherapy; even still, some robust programs can be used in either fashion. Additionally, CCBT programs may offer patients a preferable alternative to pharmacological treatment, as research has suggested that approximately 75% of patients prefer psychological therapy over pharmacological therapy.[36]

Research suggests that many insurance policies provide coverage for CCBT, which falls under the mental health benefit; however, many patients are not accessing these services for a variety of reasons, which potentially include lack of awareness and understanding of program availability, how to access the services, and what the services provide.[37] Given the significant number of barriers to accessing behavioral health treatment and the potentially detrimental outcomes associated therewith, CCBT offers an innovative solution that helps narrow gaps in care. Other benefits of CCBT include more effective use of clinician time, reduced pharmacy spend, shortened wait lists, improved access to care, standardized care, and patient empowerment.[34] Various coverage considerations must be made by payors when determining what types of behavioral health services will be provided to members with these conditions; however, CCBT represents an attractive and relatively untapped opportunity for cost-savings and improved outcomes for patients and providers.

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RETINAL DISEASES CAN HAVE A BIG EFFECT ON VISION

See for yourself what it's like in **virtual reality**

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Doctor-recommended screening, diagnosis, and potential treatment are important for your members with Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME.* Otherwise, these members may be facing serious risk of vision loss, which may require ongoing resources.[1-3]

THERE'S EYLEA—A treatment option that can fit your plan

- **EYLEA has proven outcomes as demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in Patients with DME**[4]
- **With monthly and every-other-month dosing,† EYLEA offers flexible dosing options to help meet the needs of your providers and your members**[4]

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

*The FDA-approved indications for EYLEA are Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR) in Patients with DME.

†After an initial monthly dosing period for certain indications.

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

EYLEA® (aflibercept) Injection
For Intravitreal Injection

REGENERON

04/2017
US-LEA-13814

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA package insert for full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA is indicated for the treatment of:

- **Neovascular (Wet) Age-Related Macular Degeneration (AMD)**
- **Macular Edema Following Retinal Vein Occlusion (RVO)**
- **Diabetic Macular Edema (DME)**
- **Diabetic Retinopathy (DR) in Patients with DME**

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments. Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.7) and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure. Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.7)*].

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3)*]

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

A total of 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

Adverse Reactions	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%
Eye pain	9%	9%
Cataract	7%	7%
Vitreous detachment	6%	6%
Vitreous floaters	6%	7%
Intraocular pressure increased	5%	7%
Ocular hyperemia	4%	8%
Corneal epithelium defect	4%	5%
Detachment of the retinal pigment epithelium	3%	3%
Injection site pain	3%	3%
Foreign body sensation in eyes	3%	4%
Lacrimation increased	3%	1%
Vision blurred	2%	2%
Intraocular inflammation	2%	3%
Retinal pigment epithelium tear	2%	1%
Injection site hemorrhage	1%	2%
Eyelid edema	1%	2%
Corneal edema	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, and endophthalmitis.

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following BRVO in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

Adverse Reactions	CRVO		BRVO	
	EYLEA (N=218)	Control (N=142)	EYLEA (N=91)	Control (N=92)
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	EYLEA (N=578)	Control (N=287)	EYLEA (N=578)	Control (N=287)
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.

6.2 Immunogenicity. As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy. Pregnancy Category C. Aflibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg.

There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Females of reproductive potential should use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

8.3 Nursing Mothers. It is unknown whether aflibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

8.4 Pediatric Use. The safety and effectiveness of EYLEA in pediatric patients have not been established.

8.5 Geriatric Use. In the clinical studies, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [*see Warnings and Precautions (5.1)*].

Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

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REGENERON

Hemophilia:

Treatment Landscape, Agents in the Pipeline, and Management Strategies

Hemophilia is a rare X-linked congenital bleeding disorder that affects approximately one in 10,000 births, with an estimated total global incidence at 400,000 in 2010.[1] There are two subtypes: hemophilia A, which is caused by a deficiency in coagulation factor VIII; and hemophilia B, which is caused by a deficiency in coagulation factor IX.[1]

Kat Wolf Khachatourian, PharmD, MBA
Vice President, Pharmacy Services & Strategy, QualChoice Health Plan Services

These deficiencies in coagulation factors occur as a result of mutations in the clotting factor genes.[1] Hemophilia A is the more common subtype and accounts for approximately 80 to 85% of individuals with hemophilia.[1]

The severity of bleeding that occurs in individuals with hemophilia varies and is dependent on the clotting factor level.[1] The hemophilia treatment guidelines stratify patients into three clinical severity levels:[1]

1. Individuals with mild disease, defined as 5 to 40% of normal clotting factor, may only experience severe bleeding episodes with major trauma or surgery.
2. Individuals with moderate disease, defined as 1 to 5% of normal clotting factor, may experience spontaneous bleeding episodes periodically, as well as prolonged bleeding following a surgical procedure or minor trauma.
3. Lastly, the most severe individuals with <1% of normal clotting factor may experience spontaneous bleeding into their joints and muscles without trauma or provocation.[1] These bleeding episodes commonly affect weight-bearing joints and may lead to the development of hemophilic arthropathy, which may be associated with significant pain and disability.[2] Patients with the most severe form of the disease are also at risk for life-threatening bleeding, such as intracranial hemorrhage, and are more likely to develop inhibitors than patients with mild or moderate disease.[1]

Patients with hemophilia are typically managed with clotting factor concentrates, which treat active bleeds and prevent recurrent bleeds.[1]

Because hemophilia is a chronic condition, patients with hemophilia may require treatment with clotting factor concentrates throughout their lifetime. The cost to treat patients increases with the severity of disease due to an increased requirement for factor replacement. These blood products are associated with a significant cost that varies according to the individual's disease severity and how much clotting factor concentrate is required for treatment and maintenance.[1,3] Direct costs associated with hemophilia management include medication costs and significant medical costs due to office visits,

hospitalizations, medical procedures, and laboratory tests.[4] Some studies have estimated that the average healthcare costs for patients with hemophilia in the U.S. may be as high as $140,000 per patient per year.[5,6]

As mentioned previously, patients with the most severe form of disease are more likely to develop inhibitors than patients with mild or moderate disease; however, inhibitors can still develop in these patient groups as well.[1]

Risk factors for inhibitor development include the following:[4]

- Age
- Ethnicity
- Family history
- Genetic defects
- Types of factor products used
- Frequency and amount of treatment
- Presence of other immune disorders

The cost of managing patients who develop inhibitors, or antibodies that neutralize the clotting factor, may be significantly higher than patients without inhibitors. The development of inhibitors in patients with hemophilia has been associated with a twofold increased risk of hospitalization secondary to bleeding complications.[4] Although there are treatments available for patients who develop inhibitors (e.g. higher doses of clotting factor concentrate, bypassing agents, or immune-tolerance induction therapy), the cost of managing these patients may be five times greater than patients who have not developed inhibitors.[4]

In addition to the significant direct costs associated with hemophilia, patients with hemophilia and their caregivers experience significant losses in productivity due to complications of the disease that result in absences from work or school.[7] According to the Haemophilia Experiences, Results and Opportunities (HERO) initiative, 80% (N=537) of individuals surveyed reported a negative impact of hemophilia on their employment, while 40% (N=243) reported that they selected their job based on their hemophilia healthcare needs.[7] For the parents of children with hemophilia that were surveyed, 63% (N=351) reported that their child's healthcare needs had a negative impact on their employment.[7] In the managed care setting, payors have reported a number of hemophilia management issues, including lack of transparency around treatment, lack of standardization of best practices, potential waste associated with stockpiling and poor assay management, and lack of personalized therapy. This article identifies potential management solutions that can be employed by payors to address these issues.

"Some studies have estimated that the average healthcare costs for patients with hemophilia in the U.S. may be as high as $140,000 per patient per year."

Treatment of Hemophilia

World Federation of Hemophilia treatment guidelines indicate the primary goal of treatment of hemophilia is to prevent and treat bleeding episodes with the deficient clotting factor using specific factor concentrate whenever possible. For patients with severe hemophilia A or B, the Medical and Scientific Advisory Council (MASAC) to the National Hemophilia Foundation recommends prophylaxis as optimal therapy and notes that prophylactic therapy should be instituted early.[8]

Given the specific deficiencies associated with each subtype of hemophilia, clotting factor replacement with factor VIII concentrate is the treatment of choice for hemophilia A, and replacement with factor IX concentrate is the treatment of choice for hemophilia B. All of the available factor replacement products are generally effective, so the selection of a specific product is based on safety/purity, risk of developing inhibitors, the half-life of the product, and cost. Of note, the risk of inhibitor development is greater in individuals with hemophilia A than those with hemophilia B.[1] Products with a longer half-life may be preferred as they allow for less frequent administration, thus reducing the need for venous access and the risk of catheter-associated complications.[1]

MASAC also provides treatment guidelines for the management of hemophilia, which are largely consistent with the recommendations made by the World Federation of Hemophilia, and both guidelines are widely used by the majority of hemophilia treatment centers (HTCs).[8]

Available Products

There are several Food and Drug Administration (FDA)-approved factor VIII and IX products currently available that are either recombinant or derived from human plasma. Plasma-derived clotting factor concentrate is developed using commercial fractionation of screened donor plasma and various viral inactivation techniques to protect against bloodborne pathogens.[9] Recombinant clotting factor concentrate products are created using genetically engineered proteins that can be produced using animal or human cell lines.[1,9]

Recombinant factor VIII products may also have modifications to enhance their pharmacokinetic profile.[9] For example, Eloctate® contains factor VIII that has been fused with a monomeric human immunoglobulin (IgG1) Fc domain that binds to the neonatal Fc receptor present on many adult cell types.[9] This binding protects the factor from degradation, thus extending its half-life.[9] The pegylation of factor VIII products, such as Adynovate®, also extends the half-life of the clotting factor concentrate by

a factor of 1.4 to 1.5.[9] Products that are genetically modified through the fusion of the heavy and light chains of factor VIII, creating a single-chain protein (e.g. Nuwiq®), are thought to have improved stability; however, the half-life is only slightly longer compared to other recombinant products.[1,9]

Recombinant factor IX is genetically engineered using Chinese hamster ovary cell lines.[9] Given that no human or animal plasma-derived proteins are used to produce recombinant factor IX, the risk of human bloodborne viral transmission is much lower compared to plasma-derived factor IX concentrates.[9] The half-life of a standard recombinant factor IX product is approximately 16 to 17 hours; however, similar to the factor VIII products, these products may be modified to improve the pharmacokinetic profile.[9] The use of Fc fusion modifications in the development of products such as Alprolix® results in a three- to fivefold increase in the half-life compared to unmodified factor IX.[9] The factor IX gene may also be fused to the gene for albumin (i.e., Idelvion®), which results in a five- to sixfold increase in the half-life.[9] Until recently, there were no pegylated recombinant factor IX products on the market; however, on May 31, 2017, the FDA approved REBINYN® (nonacog beta pegol, Novo Nordisk), an extended half-life factor IX molecule for replacement therapy for patients with hemophilia B.[10]

Table 1 provides an overview of the products currently available, including their source and the approximate half-life. Of note, Recombinate®, AlphaNine® SD, Mononine®, and Idelvion® are only FDA-approved for use in adults and Ixinity® is FDA-approved for use in patients 12 years of age and older.[9]

Hemophilia Pipeline

There are several agents currently being developed for the treatment and prevention of bleeding episodes in patients with hemophilia. The recent FDA approval of REBINYN® (nonacog beta pegol) was based on the paradigm clinical trial program, which included 115 patients with severe or moderately severe hemophilia B.[11] Patients receiving nonacog beta pegol achieved higher levels of factor IX with less frequent dosing due to the fivefold increase in half-life compared to standard factor IX products.[11] Phase III trials demonstrated that once-weekly administration of nonacog beta pegol 40 IU/kg maintained factor IX levels above 15%, reduced the annualized bleeding rate, and demonstrated the potential to prevent bleeding into the target joints.[11] In the pivotal paradigm 2 trial (N=52), treatment with nonacog beta pegol was associated with a median annualized spontaneous bleeding rate of zero, 97% of breakthrough bleeds were resolved successfully, and 90% of target joints were no longer classified as target joints.[11] Nonacog beta pegol was also studied in pediatric patients ages 1 to 12 years in the paradigm 5 trial (N=25).[11] Treatment was found to be safe, and patients maintained mean factor levels above 15% one week after a 40 IU/kg dose.[11] The median annualized bleeding rate was 0.0 for children 1 to 6 years of age and 2.0 for children 7 to 12 years of age.[11]

The FDA convened the Blood Products Advisory Committee on April 4, 2017 to determine whether an additional study would be needed prior to or following FDA approval.[12] The safety concerns regarding nonacog beta pegol were based on preclinical data in monkeys and rats that suggested an accumulation of polyethylene glycol (PEG) in the choroid plexus following repeat dosing.[12] Although clinical studies did not uncover any safety signals clearly linked to PEG accumulation, the Advisory Committee was tasked with evaluating the risks and benefits of therapy to determine whether clinical monitoring of neurologic function should be required for mitigation of risk.[12] The Advisory Committee did not vote on whether to approve the agent; however, they did determine that if approved, standardized post-marketing monitoring would be needed to ensure safety, particularly in the pediatric and elderly populations.[12,13] The manufacturer announced that REBINYN® is expected to launch in the U.S. in the first half of 2018.[10]

Emicizumab (Roche) is an investigational monoclonal antibody that is designed to bring together clotting factors IXa and X, which are required to activate the coagulation cascade and restore hemostasis.[14] Emicizumab is being developed as a ready-to-use solution for once-weekly, subcutaneous delivery and is being studied in pivotal phase III trials of patients 12 years of age and older with hemophilia A, with or without the presence of inhibitors to factor VIII.[14] The phase III HAVEN 1 trial (N=109) achieved its primary endpoint, with patients who received prophylaxis with emicizumab having significantly fewer bleeds over time compared to patients who received no prophylaxis.[14] The study also met its secondary endpoints, including reduction in the number of bleeds over time with emicizumab prophylaxis in a sub-analysis of patients who had received prior bypassing agent prophylaxis treatment.[14] Consistent with previous studies, the

"Given that no human or animal plasma-derived proteins are used to produce recombinant factor IX, the risk of human bloodborne viral transmission is much lower compared to plasma-derived factor IX concentrates."

TABLE 1. AVAILABLE CLOTTING FACTOR CONCENTRATE PRODUCTS (FACTOR VIII AND IX ONLY)*[9,10]

Product	Source	Half-life (hours)
Factor VIII Products		
Advate®	Recombinant	9 to 12
Adynovate®	Recombinant; pegylated	13 to 16
Afstyla®	Recombinant; single-chain	10 to 14
Eloctate®	Recombinant; Fc fusion	13 to 20
Helixate® FS, Kogenate® FS	Recombinant	11 to 15
Hemofil M®	Plasma-derived; monoclonal antibody-purified	15
Kovaltry®	Recombinant	12 to 14
Monoclate-P®	Plasma-derived; monoclonal antibody-purified	18
Novoeight®	Recombinant	7 to 12
Nuwiq®	Recombinant	12 to 17
Recombinate®	Recombinant	15
Xyntha®	Recombinant	8 to 11
Factor IX Products		
AlphaNine® SD	Plasma-derived; solvent-detergent treated	18
Alprolix®	Recombinant; Fc fusion	54 to 90
BeneFIX®	Recombinant	16 to 19
Idelvion®	Recombinant; albumin fusion	104
Ixinity®	Recombinant	24
Mononine®	Plasma-derived; monoclonal antibody-purified	23
REBINYN®	Recombinant; pegylated	Fivefold prolongation vs. standard factor IX products
Rixubis®	Recombinant	23 to 26

** = List does not include bypassing agents or products containing other factor concentrates. FEIBA is a human plasma-derived activated prothrombin complex concentrate for use in patients with inherited hemophilia A or B and inhibitors to factor VIII or IX. NovoSeven® RT is a recombinant factor VIIa concentrate for use in patients with inherited hemophilia A or B and inhibitors to factor VIII or IX.*

most commonly observed adverse event was injection-site reactions.[14] Of note, in previous clinical trials, treatment with emicizumab was associated with thromboembolic events in two patients and thrombotic microangiopathy in two additional patients.[14,15] The investigators observed that all patients who experienced thromboembolic events or thrombotic microangiopathy also received activated prothrombin complex concentrate to treat breakthrough bleeding events.[14,15]

In February 2017, Roche announced that a patient enrolled in the HAVEN 1 trial had died.[15] Although the death was ruled unrelated to emicizumab, this event comes after other reports of serious adverse events, calling into question the safety of the investigational therapy.[15] In a statement issued by Roche and published on the European Haemophilia Consortium website, Roche indicated that the patient experienced a significant rectal hemorrhage followed by thrombotic microangiopathy before dying.[16] Analysts from EvaluatePharma had previously predicted that emicizumab had blockbuster potential, with $1.4 billion in annual sales expected by 2022; however, major safety concerns may hinder its uptake if and when it hits the market.[16]

Despite its potential safety concerns, emicizumab represents a unique approach to the management of hemophilia A that may provide an effective treatment option for patients who have developed inhibitors.[14] Furthermore, the more convenient subcutaneous route of administration may reduce the need for venous access and the complications that may be associated with frequent venous access. Roche does intend to evaluate less-frequent dosing in future clinical trials.[14]

Implications for Managed Care

It is estimated that over 80% of the annual cost of managing patients with hemophilia A and B is directly attributable to the use of clotting factor concentrates.[5,6,17-19] Current treatment guidelines recommend prophylaxis with clotting factor concentrate as the standard of care for patients with severe hemophilia and there is a growing body of evidence that supports the effectiveness of prophylaxis in preventing long-term impairment and improving clinical outcomes compared to on-demand treatment of bleeding episodes in patients with mild or moderate hemophilia.[1,4,8] Patients receiving prophylaxis have been shown to have fewer emergency department visits, shorter hospitalizations, and fewer bleeding episodes compared to patients receiving on-demand therapy.[4] Given the high costs of clotting factor products, payors are challenged with ensuring appropriate access to treatment while also managing drug spend. Although recent clinical trials have demonstrated the potential benefits of prophylactic therapy in patients with mild or moderate disease, such use has the potential to drastically impact payors' budgets. Since prophylactic treatment is considered the standard of care only in patients who have severe hemophilia, payors may choose to restrict coverage of clotting factor products in the prophylactic setting to patients with severe hemophilia who meet certain criteria.

To ensure appropriate management of patients with hemophilia, payors should aim to offer comprehensive hemophilia management programs that involve a multi-level approach, such as medical and pharmacy utilization management (UM), including dose optimization; fee-schedule management; specialty pharmacy services; and quality assurance programs. UM and dose optimization strategies may include UM review to ensure appropriate use and collection of clinical information, enforcement of assay and inventory management, and individualization of treatment regimens with pharmacokinetic testing. Fee-schedule management involves the analysis of hospital and home infusion claims data to determine the cost-savings potential associated with optimizing fee-schedule reimbursements. Specialty pharmacy offerings include distribution services and clinical programs that focus on disease education, assay management, and inventory management. Quality assurance programs involve data analytics to determine utilization patterns, outlier members and treating facilities, prescribing habits, and cost benchmark reporting; as well as utilizing peer-review services with key opinion leaders to review challenging cases and ensure appropriate and high-quality care is being provided.

Although the complexity of the disease and the tailored approach to treatment present significant challenges to managing cost, the payor should work closely with their pharmacy providers to ensure that patients have timely access to the necessary products to ensure optimal adherence to their regimens. Working with the pharmacy provider, the payor should strive to engage and empower the patient and their caregiver to participate in their hemophilia management.

"It is estimated that over 80% of the annual cost of managing patients with hemophilia A and B is directly attributable to the use of clotting factor concentrates."

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PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
regorafenib (Stivarga®)	Bayer	Hepatocellular carcinoma (unresectable, second-line)	Oral	Submitted; fast track; priority review	July, 2017
tocilizumab (Actemra®)	Genentech/ Roche	Giant cell arteritis	SC	Submitted; breakthrough therapy; priority review	July, 2017
pharmaceutical grade L-glutamine (PGLG)	Emmaus	Sickle cell disease	Oral	Submitted; fast track; orphan drug; priority review	7/07/17
dexamethasone SR 0.4 mg ocular insert	Ocular Therapeutix/Ora	Post-operative ocular pain	Ophthalmic	Submitted	7/19/17
romosozumab	Amgen/UCB	Postmenopausal osteoporosis	SC	Submitted	7/19/17
neratinib	Puma Biotechnology	Breast cancer (HER2-positive)	Oral	Submitted	7/21/17
dantrolene (Ryanodex®)	Eagle Pharmaceuticals	Exertional heat stroke (EHS)	IV	Submitted; fast track; orphan drug; priority review	7/23/17
aripiprazole (Abilify Maintena®)	Bristol-Myers Squibb/Otsuka	Bipolar I disorder (maintenance)	IM	Submitted	7/28/17
methylphenidate HCl	Ironshore Pharma-ceuticals & Devel-opment/Highland Therapeutics	ADHD (nighttime dosing)	Oral	Submitted	7/30/17
ceritinib (Zykadia®)	Novartis	NSCLC (first-line; ALK+)	Oral	Submitted; breakthrough therapy; orphan drug; priority review	August, 2017
inotuzumab ozogamicin	Pfizer	ALL (adults with relapsed or refractory B cell precursor ALL)	IV	Submitted; breakthrough therapy; orphan drug; priority review	August, 2017
meropenem/ vaborbactam	The Medicines Company/Rempex	Complicated UTI	IV	Submitted; priority review	Aug-Sept 2017
nivolumab	Bristol-Myers Squibb/Ono Pharmaceutical Co.	Colorectal cancer (metastatic, mismatch repair deficient [dMMR] or microsatellite instability high [MSI-H], second-line)	IV	Submitted; priority review	8/02/17
sofosbuvir/ velpatasvir/ voxilaprevir	Gilead	HCV (pangenotypic)	Oral	Submitted; breakthrough therapy	8/08/17
hepatitis B vaccine	Dynavax	Hepatitis B	IM	Submitted	8/10/17
glecaprevir/ pibrentasvir	AbbVie	HCV (pangenotypic)	Oral	Submitted; breakthrough therapy; priority review	8/18/17
amantadine ER	Adamas	Dyskinesia (levodopa-induced)	Oral	Submitted; orphan drug	8/24/17
liraglutide (Victoza®)	Novo Nordisk	CV risk reduction with T2DM	SC	Submitted	8/25/17

PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
avelumab (Bavencio®)	EMD Serono/Pfizer	Urothelial carcinoma	IV	Submitted; orphan drug; priority review	8/27/17
rabies immune globulin (human)	Kamada	Post-exposure treatment of rabies	IM	Submitted	8/29/17
deutetrabenazine	Auspex/Teva	Tardive dyskinesia	Oral	Submitted; breakthrough therapy; priority review	8/30/17
enasidenib	Agios/Celgene	AML	Oral	Submitted; fast track; orphan drug; priority review	8/30/17
adalimumab (biosimilar to AbbVie's Humira®)	Boehringer Ingelheim	RA; AS; JIA; UC; CD; PSO; PSA	SC	Submitted	September, 2017
intravenous immune globulin (human) 10% (Privigen™)	CSL Behring	Chronic inflammatory demyelinating polyneuropathy (CIDP)	IV	Submitted	September, 2017
tisagenlecleucel-T	Novartis	ALL	IV	Submitted; breakthrough therapy; priority review	September, 2017
fulvestrant (Faslodex®)	AstraZeneca	Breast cancer (first-line)	IM	Submitted	Sept-Oct 2017
pasireotide diaspartate (Signifor® LAR)	Novartis	Cushing's disease (adults)	IM, SC	Submitted	Sept-Oct 2017
gemtuzumab ozogamicin	Pfizer/PDL/UCB	AML	IV	Submitted; orphan drug	9/01/17
trastuzumab (biosimilar to Genentech's Herceptin®)	Biocon/Mylan	Breast cancer (HER2-positive)	IV	Submitted	9/03/17
abatacept (Orencia®)	Bristol-Myers Squibb	PSA	SC	Submitted	9/14/17
bevacizumab (biosimilar to Genentech's Avastin®)	Allergan/Amgen	NSCLC; cervical cancer; ovarian cancer; glioblastoma multiforme; colorectal cancer; kidney cancer	IV	Submitted	9/14/17
secnidazole	Symbiomix Therapeutics	Bacterial vaginosis	Oral	Submitted; fast track; qualified infectious disease product; priority review	9/17/17
exenatide, mini-pump	Intarcia Therapeutics	T1DM; T2DM	SC	Submitted	9/21/17
sirukumab	GlaxoSmithKline/ Janssenvartis	RA	SC	Submitted; breakthrough therapy; priority review	9/23/17
oxycodone ER (abuse deterrent)	Intellipharmaceutics	Pain (moderate to severe)	Oral	Submitted	9/25/17
abametapireotide diaspartate (Signifor® LAR)	Hatchtech/ Dr. Reddy's	Head lice	Topical	Submitted	Pending

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