Epilepsy: Advances in Treatment and Management

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HIV Update: Therapeutic Advances and Managed Care Implications

Measuring Total Cost of Care: Challenges and Potential Solutions

Magellan Rx Report

MEDICAL AND PHARMACY BENEFIT MANAGEMENT

Fall 2019

Artificial Intelligence: Advances in Healthcare Innovation

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A NOTE FROM OUR CMO

Dear Managed Care Colleagues,

Welcome to our fall 2019 issue of the Magellan Rx™ Report! 2019 has been a busy and exciting year. The U.S. Food and Drug Administration (FDA) has approved 10 novel drugs since our summer issue, with many more in the year's pipeline. As always, Magellan Rx Management has prioritized keeping our clients informed with our MRx Pipeline, offering valuable insights and intelligence on anticipated drugs.

This issue of the Report dives into the exciting ways artificial intelligence (AI) — a feature rapidly changing the healthcare landscape — can impact care management. Our feature (page 32) highlights different applications of AI that can improve the face of patient engagement, ultimately changing the way people access providers and support.

A second feature (page 10) gives readers an update on epilepsy treatment, focusing on new and emerging therapies for rare epileptic disorders and pipeline treatments, evidence-based updates to treatment guidelines, and how the changing treatment of epilepsy will impact managed care.

Showcasing a topic featured recently on an MRx *Clinical Connections* webinar, this issue also explores the utilization of precision medicine in oncology (page 19). We use lung cancer as a model to delve into how advances in precision medicine may present opportunity in the diagnosis and treatment of this often-fatal condition.

Other timely topics include an update on HIV treatment and management (page 38), a discussion and overview of total cost of care (page 6), and a spotlight on the landscape of and current activity around biosimilars (page 30).

No issue of the Report would be complete without our Managed Care Newsstand highlighting current hot topics in industry news. To learn more about Magellan Rx Management and our support of payer initiatives of the future, please feel free to contact us at MagellanRxReport@magellanhealth.com. As always, we value any feedback you may have. I hope you enjoy the Report!

Sincerely,

Caroline Carney, MD
Chief Medical Officer,
Magellan Rx Management

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Catherine, living with epilepsy

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MANAGED CARE NEWSSTAND

OIG Finds Medicaid-Enrolled Children Not Receiving ADHD Follow-Up Care

In August, the Department of Health and Human Services (HHS) Office of Inspector General (OIG) released a report finding that many Medicaid-enrolled children who were treated for Attention Deficit Hyperactivity Disorder (ADHD) did not receive recommended follow-up care. According to the report, an estimated 13% of Medicaid-enrolled children are impacted by ADHD. Specifically, the Government Accountability Office found more than 500,000 Medicaid-enrolled children who were newly prescribed an ADHD medication and 3,500 children hospitalized with a primary diagnosis of ADHD did not receive follow-up care within evidence-based, appropriate time frame outlined in the Medicaid national quality measures.

CMS Releases Report on State Efforts to Rebalance LTSS

Also in August, the Centers for Medicare and Medicaid Services (CMS) released a new report reflecting states' progress toward so-called rebalancing of their Medicaid long-term services and supports (LTSS) programs from institutional care to home and community-based services (HCBS). The report, "Selected Characteristics of 10 States with the Greatest Change in Long-Term Services and Supports System Balancing, 2012–2016," presents the programmatic changes and indicators of the 10 states that made the greatest progress toward increasing the share of total LTSS expenditures for HCBS, including Massachusetts and New York. Historically, 2013 was the turning point in Medicaid LTSS: the first year HCBS represented a majority of total LTSS expenditures.

> Under the final Decision Memo, CMS will pay for CAR T-cell therapies administered in healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies program.

While only half of the profiled states were above the national average in terms of the percentage of their LTSS spending on HCBS, the profiled states increased their HCBS share of expenditures by nearly twice as much as the national average between 2012 and 2016.

HHS Action Plan Outlines Potential Pathways for Drug Importation

Over the summer, HHS announced an Action Plan outlining the Trump administration's intention to pursue two potential pathways "for the safe importation of certain drugs originally intended for foreign markets." Under the first pathway, HHS and the U.S. Food and Drug Administration (FDA) would issue a proposed rule, expected later this fall, to authorize demonstration projects developed by states, wholesalers or pharmacists for importing FDA-approved eligible drugs from Canada that are manufactured consistent with FDA approval, which would be subject to HHS review. The proposed rule, which would further require importation of eligible drugs under these demonstrations, is viewed as posing no additional risk to the public's health and safety and achieving significant cost savings for consumers.

Under the second pathway, the FDA would authorize manufacturers to import into the U.S. versions of FDA-approved drugs sold in foreign countries. By using a new National Drug Code for such products, HHS suggests this approach would potentially allow manufacturers to offer a lower price than their current distribution contracts require. HHS states that it "has reason to believe that manufacturers might use this pathway as an opportunity to offer Americans lower-cost versions of their own drugs.

CMS Finalizes Rules on CAR-T Therapy Coverage in Medicare

CMS finalized a proposal in August to broaden coverage of Chimeric Antigen Receptor (CAR) T-cell therapies for cancer in Medicare. Under the final Decision Memo, CMS will pay for CAR-T-cell therapies administered in healthcare facilities enrolled in the FDA risk evaluation and mitigation strategies program. The Decision Memo also makes changes to CMS' February 2019 draft proposal, including expanding coverage to approved clinics and oncology practices. It also eliminates a provision that would have required hospitals to collect data on patient outcomes when it comes to CAR-T and does not set any payment rate guidelines for how much CMS reimburses for the treatments.

CAR-T-cell therapies are treatments that reinfuse patients with enhanced versions of their own immune cells. The FDA has

approved two CAR-T treatments: Yescarta™ (Gilead) and Kymriah™ (Novartis).

OIG Finds Medicare Part D Still Paying Millions for Part A-Payable Hospice Drugs

In late August, the HHS OIG published a new report finding Medicare Part D paid for more than $160 million in drugs during 2016 that hospices should have paid for under the Medicare Part A hospice benefit. OIG further estimates hospice organizations or hospice beneficiaries likely should have paid for much of the remaining $262 million of the $423 million total cost of hospice drugs. In light of these findings, OIG recommends CMS "develop proper controls" to ensure Part D does not pay for drugs that should be covered by the Part A hospice benefit.

Akin to the federal agency's response to a similar 2012 report, it is likely this latest OIG report will put pressure on CMS to ensure Medicare Advantage-Prescription Drug (MA-PD) plans and Prescription Drug Plans (PDPs) are applying prior-authorization criteria appropriately and MA-PD/PDP-hospice coordination of drug-coverage issues are being well managed.

USPSTF Recommends Clinicians Screen All Adults for Illicit Drug Use

The U.S. Preventive Services Task Force (USPSTF), whose Grade A and B recommendations inform requisite preventive benefits under the Affordable Care Act of 2010, issues a Grade B draft recommendation statement urging clinicians to screen all adults for illicit drug use.

If finalized as draft, the Grade B recommendation statement will replace the 2008 USPSTF recommendation, which concluded the evidence at that time was insufficient to assess the balance of benefits and harms of screening for illicit drug use in adolescents and adults, including those who were pregnant or postpartum. Magellan has long advocated clinicians screen adults for illicit drug use, especially pregnant and postpartum women.

CMS Issues Guidance on Safer Opioid Use in Medicaid

CMS' Center for Medicaid and CHIP Services released an Informational Bulletin on how states and Medicaid managed care organizations (MCOs) should be using the Medicaid drug utilization review (DUR) program to promote proper use of opioid analgesics under the Substance Use Disorder Prevention that Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act of 2018, aimed at combatting opioid misuse and abuse. The SUPPORT Act made updates to the Medicaid DUR program, including new requirements that had to be included in the Medicaid MCO contracts by October 1, 2019.

The new requirements described in the Informational Bulletin include: point-of-sale prospective safety edits (e.g., early, duplicate and quantity limits) and maximum daily morphine milligram equivalents; retrospective claims review (e.g., concurrent utilization alerts when opioids are prescribed at the same time as other drugs, like benzodiazepines or amphetamines); antipsychotic prescription monitoring for children; and fraud and abuse detection.

SAMHSA Proposes 42 CFR Part 2 Reforms to Increase Coordinated Care and Improve SUD Treatment

On August 26, the Substance Abuse and Mental Health Services Administration (SAMHSA) published proposed changes to the federal regulations governing the confidentiality of patient records created by federally assisted substance use disorder (SUD) treatment programs, known as 42 CFR Part 2. The proposed rules establish important revisions that support coordinated care among providers that treat SUD, while maintaining privacy safeguards for patients seeking treatment for SUD.

The proposed rules modify several sections of 42 CFR Part 2 to encourage care coordination among providers, including updating the definition of what constitutes a Part 2 record and its applicability. This is designed to give providers clarity about what information is protected by Part 2 and to ensure non-Part 2 providers are not discouraged from caring for SUD patients or recording SUD information due to onerous legal requirements. Importantly, however, the basic framework for confidentiality protection of SUD patient records created by federally assisted treatment programs will not be altered under the proposed rules. Further, 42 CFR Part 2 will continue to prohibit law enforcement use of SUD patient records in criminal prosecution against the patient and will also continue to restrict the disclosure of SUD treatment records without patient consent unless an existing exception otherwise applies.

SAMHSA states in the proposed rule its continued belief that it does not have statutory authority to fully align Part 2 rules with Health Insurance Portability and Accountability Act rules governing other health information but sought to align these regulatory constructs as fully as current statute allows.

Measuring Total Cost of Care:

Challenges and Potential Solutions

U.S. healthcare spend is an important financial and societal priority, and significant challenges in measuring and managing these costs persist. In 2017, Americans spent $3.5 trillion on healthcare, accounting for 17.9% of the nation's gross domestic product (GDP).

Astha Chopra
VP, Clinical Effectiveness
Magellan Rx Management

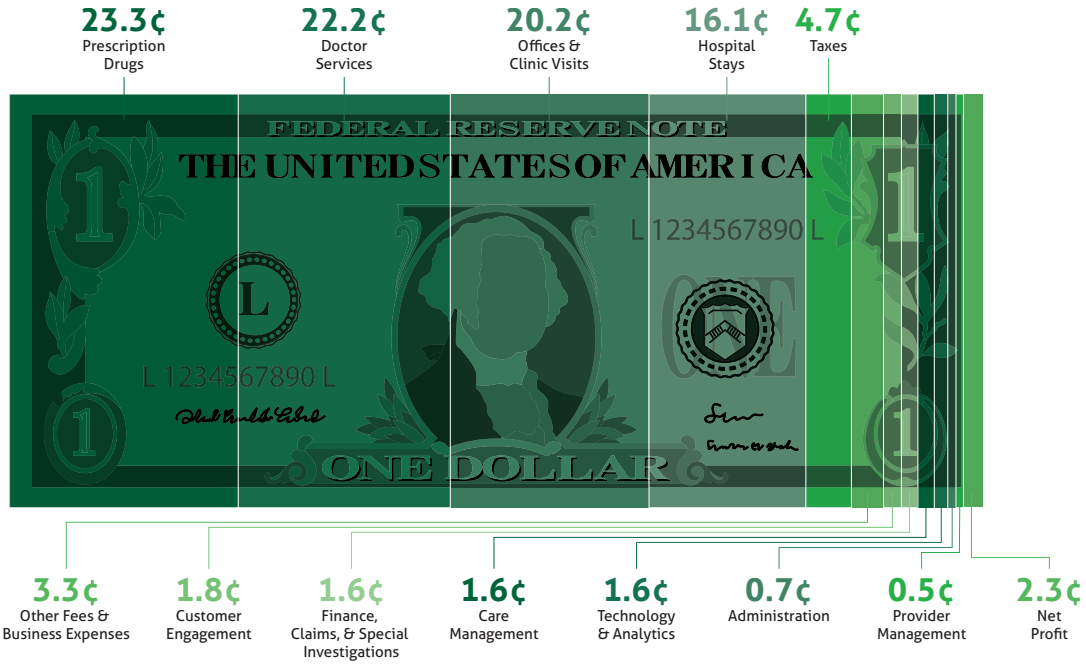
For perspective, this amount is greater than the entire GDPs of Mexico, the U.K., and Canada.[1] Overall, healthcare spending grew by only 3.9% in 2017, a downturn from the previous year's rate of 4.8% and the slowest growth rate since 2013.[1] However, even as the rate of growth slows, U.S. healthcare spending still exceeds that of other developed countries[1], and the U.S. spends more per capita on prescription drugs than most other high-income countries.[2]

The rising cost of prescription drugs is a notable and primary driver behind increasing healthcare spend. The U.S. experienced its first burst in prescription drug spending in the 1990s, as a result of new drug approvals by the U.S. Food and Drug Administration (FDA) and the expansion of prescription drug coverage by payers.[2] With the introduction of several specialty drugs and expanded coverage under the Affordable Care Act (ACA), drug spend spiked again in 2014 and 2015, by about 20%.[2]

Other healthcare expenditure categories besides prescription drugs contribute significantly to overall healthcare costs. Milliman analyzed spending within a typical U.S.-based commercial health plan by healthcare spending category and concluded that prescription drugs account for the largest proportion of spending, at 23.3%, closely followed by doctor services (defined as nondrug-related inpatient and outpatient services provided by a doctor), at 22.2%, and office and clinic visits (defined as cost of an office visit excluding doctor services), at an additional 20.2%[3] (Figure 1).

With growing patient concern about the cost of receiving care, payers have been trying to strike a balance between managing and improving costs. Against a dynamic backdrop of emerging technologies, advances in drug therapy, and changes in healthcare benefit design, payers face the challenge of effectively assessing and managing the total of all costs associated with providing care.

Figure 1. Cost-of-Care Allocation[3]



Source: Milliman. "Where Does Your Health Care Dollar Go?" America's Health Insurance Plans, May 22, 2018, https://www.ahip.org/health-care-dollar/.

Challenges in Measuring Total Cost of Care

Attributing Costs

Attribution is a method that assigns responsibility for a patient's care to a particular provider or physician.[4] The first step in developing a management strategy for total cost of care is attributing specific cost categories to the stakeholders most equipped to impact that cost. For example, a nonemergent patient seeking care at the emergency department (ED) typically ends up with a costly bill to pay, but the event also proves costly to the insurer. This common occurrence leads to several questions surrounding cost management.

Payers may evaluate which stakeholder is accountable for these incurred costs by exploring opportunities for earlier intervention that may have prevented the unnecessary ED visit. Follow-up inquiries may include the following:

- Could the patient have seen a primary care physician before they felt the urgency to visit the ED?
- Might the ED have redirected the member to an urgent care center?
- What other support might have been cost-effective?

A study of Medicare members found that patients with one to two chronic conditions and highly fragmented care were 13% more likely to visit the ED and 14% more likely to have a hospital admission.[5] An engaged case manager may be a valuable resource for patients with one or more chronic conditions; for example, in this instance, a case manager may have provided the patient alternative options for obtaining necessary care, potentially preventing a costly ED visit. Additionally, for patients with behavioral conditions as a component of or in addition to a physical ailment, timely access to behavioral health support is critical for preventing waste and unnecessary costs.

Retroactively evaluating and categorizing costs attributable to various stakeholders can present a complex challenge to payers. However, this type of assessment helps to identify potential strategies for helping to more effectively utilize resources and manage costs in the future.

Timely Data Sharing

An efficient, functional healthcare system relies on the collection of a variety of data, ranging from clinical data to social determinants of health. Data sharing can be valuable in a variety of healthcare functions, including but not limited to genetic studies, cancer and chronic disease registries, substance abuse, population health management, larger-scale analytics, epidemiology and disease tracking, and interoperability for routine patient care in the emergency department.[6]

While data collection has seen significant progress, improved connectivity will be essential to seamlessly sharing that data. The U.S. Department of Health and Human Services holds access to

a wealth of valuable health data and has reported that it lacks a consistent, transparent, and standardized framework for sharing restricted and nonpublic data among its agencies in a timely and efficient manner.[7] Critically, addressing this lack of connectivity must include proper security and privacy protocols governing any capture, sharing, or analysis of patient data.

Expanding the exchange of health information and connecting various facilities and provider groups has created additional considerations. For example, a significant challenge to interoperability is lack of standardization in the type of data and manner in which it is collected, which causes most payers and providers to end up operating at a deficit, as they lack timely access to all the clinical and nonclinical data pertaining to a patient that could impact the future course of that patient's care.

Evolving Mix of Membership

An additional challenge: Previously uninsured individuals are entering the healthcare system via exchange plans and as a result of the expansion of Medicaid. Enrollment in Medicaid grew from 48 million members in 2008 to 75 million members in 2018, with a corresponding increase in expenditure from $352 billion to $630 billion.[8] The lack of historical clinical data on these members creates a challenge in forecasting the potential costs associated with their care. With regard to exchange plans, payers have observed unexpected risk associated with new members who have no coverage history. A number of health plans have experienced negative financial implications due to adverse selection, including some with ACA provisions such as risk corridors intended to prevent this from occurring. The scarcity of data on new entrants into the health insurance market is an obstacle payers must overcome before developing any effective plans to manage cost.

> Retroactively evaluating and categorizing costs attributable to various stakeholders can present a complex challenge to payers.

Types of Cost Incurred

A critical factor of cost-of-care management is differentiation between avoidable and unavoidable costs. Patients with high-cost, high-risk disease conditions often follow a strict treatment plan under the care of an appropriate specialist. Therefore, while the top 1% to 2% of utilizers might account for more than 50% of total spending, a large portion of these costs may be unavoidable, if they are the result of the cost of care associated with best-practice adherence.[9]

Nonadherence is considered one of the biggest drivers of avoidable prescription drug costs. Information Medical Statistics Health found the U.S. spends $200 billion in healthcare costs each year due to improper adherence to medication plans.[9] Patients who fill medications yet do not adhere to their treatment regimen or complete a full course of therapy are seen as driving up costs, since nonadherence potentially leads to unnecessary inpatient admissions and ED visits. In total, 8% of annual healthcare spending goes to these nonadherence-associated issues.[9] Therapy utilizers must be stratified appropriately in an effort to estimate costs, with current and forecasted avoidable and manageable costs taken into account in order to develop effective tactics to manage the overall cost.

Possible Solutions

While there are obstacles in the way of measuring total cost of care, payers have made progress in identifying potential solutions.

Centralizing care coordination for members by developing a care team creates an environment where the various stakeholders are communicating with each other to collectively manage the cost and quality of care. The Centers for Medicare and Medicaid Services (CMS) have embraced the need to provide services beyond medical care for chronically ill members in their 2020 Final Call Letter, calling for "supplemental benefits … such as providing meals beyond a limited basis, transportation for nonmedical needs, and home-environment services if these benefits have a reasonable expectation of improving or maintaining the health or overall function of the patient as it relates to their chronic condition or illness."[10]

Continued focus on building channels for timely data sharing is critical to improving cost-of-care management. In a January 2019 report to Congress, the Office of the National Coordinator for Health Information Technology (ONC) described the current gaps in interoperability and recommended that "healthcare

> Information Medical Statistics Health found the U.S. spends $200 billion in healthcare costs each year due to improper adherence to medication plans.

organizations focus on improving health IT interoperability and technical capabilities so that patients can securely access, amass, and transfer health information via their mobile devices and providers can easily send, receive, and analyze patient data."[11]

Payers are also leveraging risk-scoring methodologies for member stratification and prioritization. Better understanding patients' likelihood of driving up costs through hospitalizations or ED visits will help support more efficient planning and strategizing.

No cost-of-care management improvements can be attempted at the expense of the quality of care provided, and the organizational foundation for this work must be sound.[12] This overarching principle demands that any intervention or strategy is vetted with due diligence before it impacts a patient's plan of care.

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Epilepsy:

Advances in Treatment and Management

Epilepsy is a broad term referring to a chronic condition characterized by recurrent and unprovoked seizures.

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While seizures may occur in the context of a known, reversible medical condition, such as extreme hypoglycemia, high fever, or alcohol withdrawal, a diagnosis of epilepsy is made when an individual experiences at least two seizures with no known, reversible cause.[1] Although seizures in epilepsy are unprovoked, epilepsy itself may be caused by a variety of conditions that affect the brain, including traumatic brain injury, stroke, a brain tumor, or an infection of the central nervous system.[2] Epilepsy is the fourth most common neurological disorder and can affect individuals of any age. Current estimates suggest that there are approximately 3.4 million people in the U.S. living with epilepsy, including 470,000 children.[2]

There are several different forms of epilepsy and several different seizure types.[2] Individuals with epilepsy may experience multiple seizure types. Seizures are generally classified into two groups: generalized and focal. Generalized seizures, which affect both sides of the brain, include absence (or petit mal) seizures, which may be associated with rapid blinking or the appearance of staring off into space, and tonic-clonic (or grand mal) seizures, which may be associated with a loss of consciousness, muscle jerks or spasms, or falling.[2] Focal or partial seizures, which occur in one area of the brain, can be simple focal seizures, which affect a small portion of the brain and may cause less severe symptoms, such as twitching or a change in sensation (e.g., taste or smell); complex focal seizures, which may cause the individual to experience confusion, making them unable to respond to questions or simple commands for several minutes; and secondary generalized seizures, which, as the name implies, start as a focal seizure in one area of the brain but subsequently spread to both sides of the brain, resulting in a generalized seizure. Seizures typically last for a few seconds to a few minutes, depending on the type.[2]

Treatment Guidelines

Given that it is a chronic condition for which there is no cure, epilepsy management consists of three primary goals: controlling seizures, minimizing treatment side effects, and restoring quality of life.[3,4]

> Given that it is a chronic condition for which there is no cure, epilepsy management consists of three primary goals: controlling seizures, minimizing treatment side effects, and restoring quality of life.

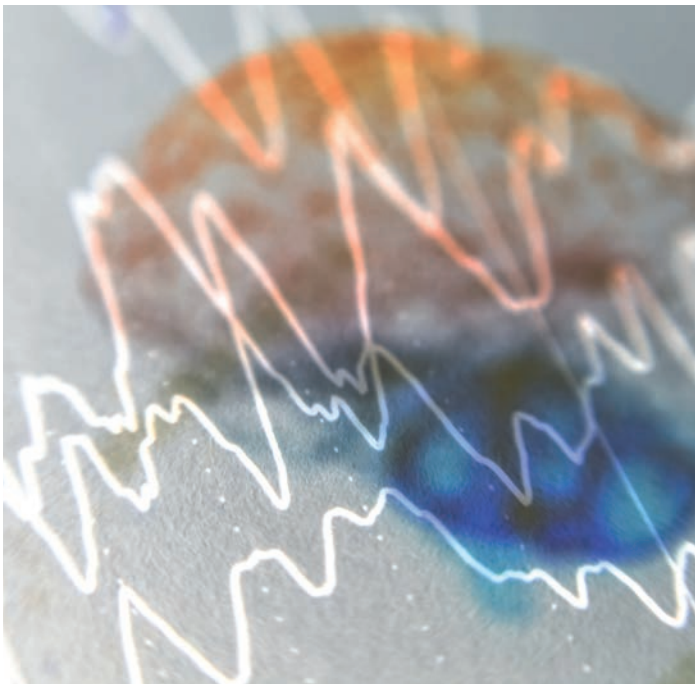
Following the first unprovoked seizure in an adult, the decision of whether to initiate antiepileptic drug therapy should be individualized, taking into consideration the risk of recurrence, the potential benefit of the antiepileptic drug, the side-effect profile of the treatment options, and the patient's preferences.[3, 4] According to the American Academy of Neurology (AAN), the risk of seizure recurrence in adults is highest in the first two years following an unprovoked first seizure, at approximately 21% to 45%.[4] The guidelines state that immediate antiepileptic drug therapy, compared with delayed treatment pending a second seizure, will likely reduce the risk of recurrence within the first two years but may not improve overall quality of life. Over a longer term (more than three years), immediate initiation of treatment is not likely to improve prognosis as measured by sustained seizure remission. Certain clinical variables, including previous brain injury, an electroencephalogram (EEG) with epileptiform abnormalities, a significant abnormality on brain imaging, or a nocturnal seizure, are associated with an increased risk of recurrence.[3, 4]

The long-term clinical benefit of initiating antiepileptic drug therapy after the first seizure can vary by patient.[3, 4] In one meta-analysis of five randomized, controlled trials, immediate initiation of therapy was associated with a 35% reduction in risk of seizure recurrence over the next one to two years; however, several studies have demonstrated similar rates of complete seizure remission at four and five years after treatment initiation regardless of whether treatment was initiated after the first seizure or deferred until a second seizure occurred.[4–9]

Once the decision to initiate antiepileptic drug therapy has been made, treatment generally begins with monotherapy, and approximately half of patients may become seizure-free with their first drug trial.[10] In selecting a specific agent, guidelines recommend that the relative efficacy and potential side effects of therapy be considered. Unfortunately, there is limited comparative efficacy and tolerability data for the currently available antiepileptic drugs, so consideration of patient-specific factors is important.[4, 11]

Table 1. American Academy of Neurology 2019 Guideline Updates for New-Onset Epilepsy[11]

Key Findings (Level of Evidence)
Recommended treatment of focal seizure in adult patients: • Lamotrigine (level B) • Levetiracetam (level C) • Zonisamide (level C)
Recommended treatment of focal seizure in adult patients ≥ 60 years old: • Lamotrigine (level B) • Gabapentin (level C)
Recommended treatment of childhood absence seizures: • Ethosuximide or valproic acid recommended before lamotrigine (level B)
The following antiepileptic drugs may be effective in treating new-onset epilepsy (no high-quality studies support this currently): • Clobazam • Gabapentin • Oxcarbazepine • Tiagabine • Eslicarbazepine • Lacosamide • Perampanel • Topiramate • Ezogabine • Levetiracetam • Pregabalin • Vigabatrin • Felbamate • Lamotrigine • Rufinamide • Zonisamide
Recommended treatment for generalized epilepsy in adults and children (1 Class III study) • Valproic Acid • Topiramate



The Standard and New Anti-Epileptic Drugs (SANAD) trial is the largest individual randomized trial to date that examines various antiepileptic drugs as monotherapy in the initial treatment of epilepsy.[12, 13] The study included 1,721 patients with focal epilepsy and 716 patients with generalized seizures. Study investigators concluded that lamotrigine should be considered the drug of choice for focal seizures while valproate should be considered the drug of choice for generalized seizures.[12, 13] The AAN's guideline for the treatment of new-onset epilepsy was updated in 2019 and the key findings from the update are outlined in Table 1.[11]

While antiepileptic drug therapy has historically been the mainstay of treatment, drug therapy is only effective for approximately two-thirds of patients.[2] For patients with focal seizures who do not adequately respond to drug therapy, surgical removal of the area of the brain causing the seizures may be considered. Surgery is most commonly used when the seizure focus is in the temporal lobe.[2] For individuals who fail to respond to drug therapy and are not candidates for surgery, treatment options are somewhat limited. One option includes vagus nerve stimulation, which involves the implantation of an electrical device below the skin on the upper chest that sends electric signals to the vagus nerve to prevent seizures from occurring. Some patients with refractory seizures may also benefit from a strict ketogenic diet, which aims for high fat and low carbohydrate intake, with limited calories.[2]

Treatment Advances

In June 2018, the U.S. Food and Drug Administration (FDA) approved cannabidiol (Epidiolex®; GW Pharmaceuticals) for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients two years of age and older, making it the first agent to be FDA-approved for use in Dravet syndrome and the first agent in its new class of antiepileptic drugs.[14] Dravet syndrome is a rare genetic condition that appears during the first year of life with frequent febrile (fever-related) seizures. Later, other types of seizures typically arise, including myoclonic seizures (involuntary muscle spasms).[14] Lennox-Gastaut syndrome begins in childhood, usually between ages three and five, and is characterized by frequent and varied seizures. More than three-quarters of affected individuals have tonic seizures, which cause the muscles to contract uncontrollably.[14] The FDA approved cannabidiol following a priority review and had previously awarded the fast-track designation for Dravet syndrome and the orphan drug designation for both Dravet syndrome and Lennox-Gastaut syndrome.[14] Cannabidiol is the first pharmaceutical-grade formulation of purified, plant-derived cannabidiol that is not associated with the "high" that is observed with marijuana.[15]

The clinical efficacy of cannabidiol was evaluated in three randomized, double-blind, placebo-controlled clinical trials that included 516 patients with Lennox-Gastaut syndrome and Dravet syndrome, more than 90% of whom were taking two or more antiepileptic drugs.[14–16] Two pivotal studies evaluated cannabidiol in patients 2 to 55 years of age with Lennox-Gastaut syndrome. In both studies, the primary endpoint was the percent change from baseline in the frequency (per 28 days) of drop seizures (including atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. In Study 1 (N=171), patients were randomized to receive either placebo or cannabidiol 20 mg/kg/day; the former group experienced a statistically significant 44% reduction in seizure frequency per 28 days during the study period, compared to a 22% reduction with placebo.[16] Similarly, patients in Study 2 (N=225) were randomized to receive either placebo or cannabidiol at a dose of 10 mg/kg/day or 20 mg/kg/day. Patients treated with cannabidiol at either dose experienced a significantly greater reduction in seizure frequency compared to patients treated with placebo (-37%, -42%, and -17% for cannabidiol 10 mg/kg/day, cannabidiol 20 mg/kg/day, and placebo, respectively; $P<0.01$ for both comparisons).[16] In both studies, the reduction in seizure frequency was observed within four weeks of treatment initiation and remained generally consistent over the 14-week treatment period.[16]

The clinical efficacy of cannabidiol in Dravet syndrome was evaluated in the third randomized, placebo-controlled trial in patients

2 to 18 years of age.[16] In Study 3 (N=120), patients were randomized to receive either placebo or cannabidiol 20 mg/kg/day, and the primary endpoint was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (including all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period. Patients treated with cannabidiol achieved a statistically significant 39% reduction in convulsive-seizure frequency, compared to a 13% reduction in patients who received placebo (P=0.01).[16]

Cannabidiol continues to be studied for use in difficult-to-treat forms of epilepsy, including tuberous sclerosis complex, for which it has been awarded the orphan drug designation by the FDA. Phase III trials for this indication are currently ongoing.[15]

More recently, the FDA approved intranasal midazolam (NAYZILAM®; UCB) in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity — including seizure clusters and acute repetitive seizures — that are distinct from a patient's usual seizure pattern, for patients 12 years of age and older.[17] Intranasal midazolam is a short-term treatment for seizure clusters, which start and stop and occur in groups one right after another, designed as a single-use device that patients can carry with them and that non-healthcare professionals can administer to a patient who is actively seizing.[17, 18]

The clinical efficacy of intranasal midazolam was evaluated in a two-part study (N=292) that included an open-label test-dose phase — a tolerability assessment in which patients received two 5 mg doses 10 minutes apart in the absence of a seizure — followed by a randomized, double-blind, placebo-controlled comparative phase (N=201), in which patients treated a single seizure-cluster episode in an outpatient setting with either a blinded dose of intranasal midazolam 5 mg or placebo.[17] If the seizure activity persisted or recurred, all patients had the option to receive an unblinded dose of intranasal midazolam between 10 minutes and six hours after the initial dose was administered. The primary endpoint of Study 1 was treatment success, which was defined as the termination of seizures within 10 minutes after the initial dose of study drug and the absence of seizure recurrence within six hours of the initial dose.[17] A significantly greater proportion of patients treated with intranasal midazolam met the primary endpoint, with 80.6% achieving seizure termination within 10 minutes of dose administration compared to 70.1% of patients in the placebo group, and 58.2% free of seizure recurrence between 10 minutes and six hours after the initial dose compared to 37.3% of patients in the placebo group.[17] The FDA approval of intranasal midazolam represents the first new medication to treat seizure clusters in more than 20 years and the first intranasal medication ever to receive FDA approval for this indication.[17]

“Even with more than 20 antiepileptic drugs currently on the market, many patients will fail to achieve adequate seizure control with these options, and many patients will experience side effects that are difficult to tolerate.

Epilepsy Pipeline

Even with more than 20 antiepileptic drugs currently on the market, many patients will fail to achieve adequate seizure control with these options, and many patients will experience side effects that are difficult to tolerate.[19] Despite continued unmet need, there has been limited development in this arena in recent years; this may be due to the number of products on the market, many of which are available generically, making it a challenging market to enter as a more-costly branded product.[19] As a result, there appears to be a shift in focus in the epilepsy pipeline; rather than attempting to develop products to treat the entire population, manufacturers are focusing on the various syndromes associated with epilepsy and well-defined subsets of the population overall, such as Lennox-Gastaut syndrome and tuberous sclerosis complex.[19]

Cenobamate

Cenobamate is an investigational antiepileptic drug currently under review by the FDA, following the acceptance of a new drug application (NDA) submission in February 2019.[20] While the exact mechanism of action is not fully understood, cenobamate is believed to work via two mechanisms, including the enhancement of inhibitory currents through positive modulation of GABA-A receptors and the reduction of excitatory currents through inhibition of the persistent sodium current.[20, 21]

The NDA submission for cenobamate for the treatment of adults

with partial-onset seizures was based on data from pivotal trials in more than 1,900 patients.[22] In one study (N=437) presented at the 2018 ANN meeting, patients were randomized to placebo or cenobamate at a dose of 100 mg/day, 200 mg/day, or 400 mg/day. Patients treated with cenobamate experienced reductions in seizure frequency of 35.5% at 100 mg/day, 55% at 200 mg/day, and 55% at 400 mg/day, compared to a reduction of 24% for patients who received placebo.[22] In terms of safety, three patients in early studies developed Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome. A slow titration schedule starting at 12.5 mg was implemented in the subsequent Phase III study to evaluate whether the approach could mitigate the occurrence of DRESS syndrome. No DRESS cases were observed in the Phase III study using the slow titration strategy.[22]

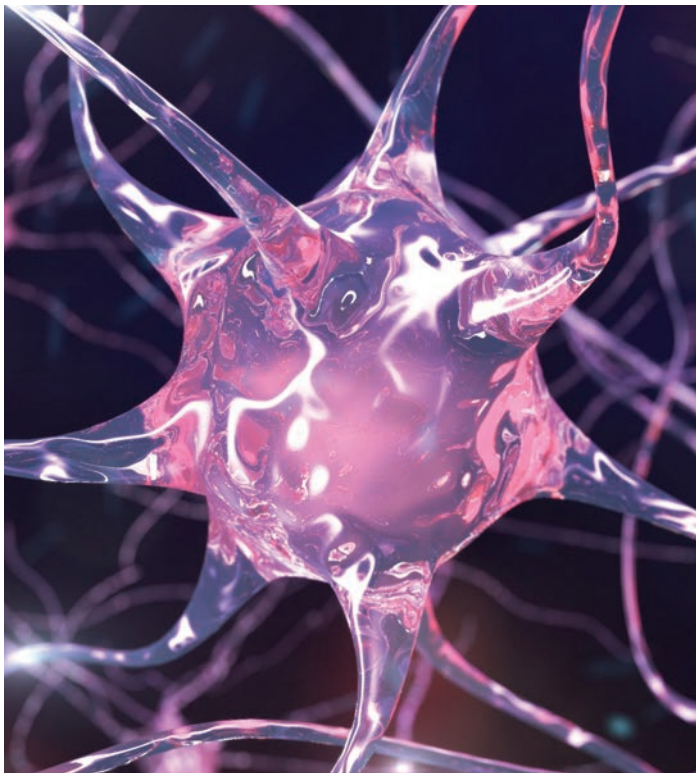
While the mechanism by which cenobamate exerts its effect is not unique from previously approved antiepileptic drugs, the drug does appear to offer significant improvements in efficacy for a common form of epilepsy.[22]

Ganaxolone

Ganaxolone is an investigational positive allosteric modulator of synaptic and extra-synaptic GABA-A receptors with demonstrated anti-seizure and anti-anxiety activity. Previously in development for focal-onset seizures in adults, the development program was terminated in 2016 after a Phase III trial failed to meet its primary endpoint.[23] Following the trial failure, the clinical development program is now focusing on status epilepticus and pediatric orphan indications, including PCDH19-related epilepsy, which is a serious and rare genetic form of the condition.[24] In March 2019, the manufacturer announced the initiation of the pivotal Phase III Violet Study, which will enroll up to 70 patients between 1 and 17 years of age with PCDH19-related epilepsy. In a previous open-label Phase II trial (N=11), treatment with ganaxolone resulted in a 25% reduction in median seizure frequency compared to baseline.[24] During the study, investigators identified preliminary evidence of a plasma neurosteroid biomarker that may correlate with seizure response in 10 of the 11 patients who received ganaxolone.[24] Further characterization of this correlation may allow for the identification of the patients who are most likely to benefit from therapy.

Diazepam Nasal Spray

In 2018, Neurelis submitted an NDA for VALTOCO™ (diazepam nasal spray) to the FDA. The drug is an on-hand rescue treatment studied in children, adolescents, and adults with epilepsy who



experience bouts of increased seizure activity while on a stable regimen of daily antiepileptic medication(s).[25] A potential alternative to Diastat® (diazepam rectal gel), it is also indicated for use in emergency situations to stop cluster seizures (episodes of increased seizure activity) in individuals who are taking other medications to treat their epilepsy.[26]

Managed Care Implications

With increasing focus on the development of antiepileptic drugs for niche populations with rare forms of epilepsy, new agents coming to the market will likely carry typical rare-disease price tags. While payers have historically managed the antiepileptic drug class with a generics-first approach, new high-cost agents are likely to lead to tighter formulary management, similar to agents with orphan-drug status.[19] Given the severity of epilepsy, it is critical that new branded and orphan antiepileptic drugs remain accessible for those who need them, but the trend toward personalized treatment of rare forms of epilepsy may present an opportunity to manage these niche and orphan drug products based on specific patient characteristics that suggest the greatest clinical benefit.

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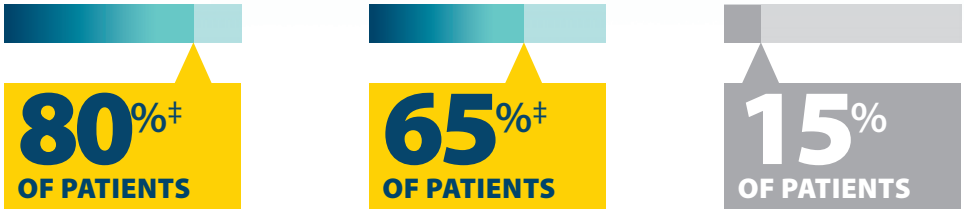
Now Approved *for an expanded indication in* ***Diabetic Retinopathy (DR)***[1]

EYLEA® (aflibercept) Injection For Intravitreal Injection

POWER AGAINST

In PANORAMA, EYLEA significantly improved DR severity scores at week 52[1]

Proportion of patients achieving a ≥2-step improvement in ETDRS-DRSS* score from baseline (primary endpoint)[1,†]



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

The recommended dose for EYLEA in DR is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months).[1]

Efficacy and safety data of EYLEA in DR are also derived from VISTA and VIVID.[1] The percentage of patients with a ≥2-step improvement on the ETDRS-DRSS from baseline at 100 weeks was 38%, 38%, and 16% in VISTA and 32%, 28%, and 7% in VIVID with EYLEA 2 mg every 8 weeks after 5 initial monthly doses, EYLEA 2 mg every 4 weeks, and control, respectively (secondary endpoint).[1]

PANORAMA study design: Multicenter, double-masked, controlled study in which patients with moderately severe to severe NPDR (ETDRS-DRSS: 47 or 53) without central-involved DME (CI-DME) (N=402; age range: 25-85 years, with a mean of 56 years) were randomized to receive 1) 3 initial monthly EYLEA 2 mg injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks; 2) 5 initial monthly EYLEA 2 mg injections, followed by 1 injection every 8 weeks; or 3) sham treatment. Protocol-specified visits occurred every 28±7 days for the first 5 visits, then every 8 weeks (56±7 days). The primary efficacy endpoint was the proportion of patients who improved by ≥2 steps on the ETDRS-DRSS from baseline to week 24 in the combined EYLEA groups vs sham and at week 52 in the EYLEA 2 mg every-16-week and EYLEA 2 mg every-8-week groups individually vs sham. A secondary endpoint was the proportion of patients developing the composite endpoint of proliferative DR (PDR) or anterior segment neovascularization.

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control), at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, efficacy endpoints included the mean change from baseline in best-corrected visual acuity (BCVA), as measured by ETDRS letters, at 52 weeks (primary endpoint) and 100 weeks (secondary endpoint).

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

EYLEA 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).

CONTRAINDICATIONS

- EYLEA 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.

*Early Treatment Diabetic Retinopathy Study–Diabetic Retinopathy Severity Scale: An established grading scale for measuring the severity of DR.
†Full analysis set.
§3 initial monthly injections, followed by 1 injection after 8 weeks and then 1 injection every 16 weeks.
‖5 initial monthly injections, followed by 1 injection every 8 weeks.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

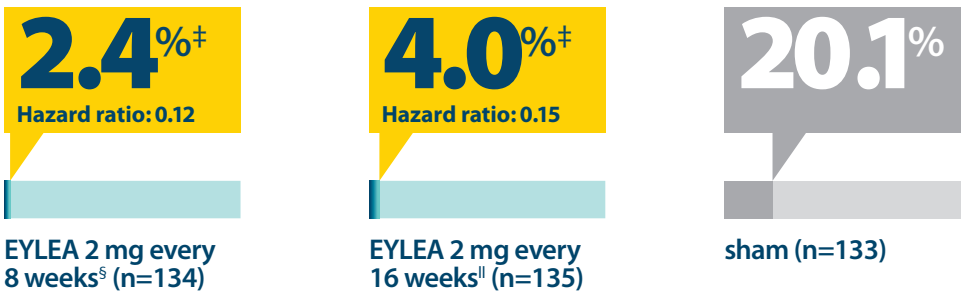
777 Old Saw Mill River Road, Tarrytown, NY 10591

DISEASE PROGRESSION[1]

EYLEA can help prevent DR vision-threatening complications that can lead to blindness[1]

Significantly fewer patients developed PDR or ASNV with EYLEA at week 52[1]

Composite endpoint of patients who developed PDR or ASNV at week 52 (event rates) (secondary endpoint)[1,†]



EYLEA 2 mg every 8 weeks[§] (n=134)

EYLEA 2 mg every 16 weeks[‖] (n=135)

sham (n=133)

‡*P*<0.01 vs sham.

All patients were treatment-naïve to focal or grid laser photocoagulation, panretinal photocoagulation, and any anti–vascular endothelial growth factor (anti-VEGF) treatment.[2] Composite endpoint of developing PDR or anterior segment neovascularization (ASNV) was diagnosed by either the reading center or investigator through week 52. Event rate was estimated using the Kaplan-Meier method.[1]

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 compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. 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 detachment, vitreous floaters, and intraocular pressure increased.

Please see Brief Summary of Prescribing Information on the following pages.

References: 1. EYLEA® (aflibercept) Injection full Prescribing Information. Regeneron Pharmaceuticals, Inc. May 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

05/2019
US-LEA-14375

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor 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).

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 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.

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 compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. 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 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 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 detachment, vitreous floaters, and intraocular pressure increased.

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, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, 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

	CRVO		BRVO	
Adverse Reactions	**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) and Diabetic Retinopathy (DR). 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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**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.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

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
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data
Animal Data
In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.
Adverse embryofetal 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 not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation
Risk Summary
There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.
The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential
Contraception
Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

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.

REGENERON

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

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019
EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306

Precision Medicine in Oncology:

A Look at Lung Cancer Treatment

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What Is Precision Medicine?

Although the terms *personalized medicine* and *precision medicine* are often used interchangeably, they are, in fact, slightly different. Personalized medicine refers to an overall holistic approach to care,[1] while precision medicine is targeted, focusing on the molecular and clinical characteristics of a patient and their disease. The Food and Drug Administration (FDA) defines precision medicine as, "an innovative approach to tailoring disease prevention and treatment that takes into account differences in people's genes, environments, and lifestyles."[2]

Before exploring the role of precision medicine in the clinical management of oncology, it should be noted that experts have long recognized that cancer is not one single disease. In fact, advances in research have demonstrated that even the same type of cancer may differ from one person to another. The reasons for these differences are often found in the histology, or cells and tissues, of the individual and in the unique characteristics of the tumor. As a result, cancer treatment is not suited to a one-size-fits-all approach. In evaluating a patient's treatment, providers must consider the genetic makeup and physical condition of the patient, the unique characteristics and complexities of the tumor, and the distinct attributes of various therapies available for treatment.

What Is the Goal of Precision Medicine in Oncology?

Improving clinical outcomes while decreasing toxicity associated with oncology therapies is a key objective of precision medicine in oncology. When successfully applied, precision medicine in oncology results in the management of the right patient with the right treatment, administered at the right time. Effective navigation of clinical, logistical, and financial complexities is imperative to achieving this lofty goal. Such navigation requires the comprehensive consideration of patient, prescriber, and payer

> Treatment options for NSCLC vary depending on the stage of cancer at diagnosis and can include radiation therapy, traditional chemotherapy, targeted therapy, immunotherapy, palliative care, or several possible combinations of these modalities.

perspectives to attain the collective goal of precision medicine: better outcomes with potentially fewer toxicities.

Significant progress in cancer treatment is being made. Over the past decade, the cancer death rate has declined annually by 1.4% for women and 1.8% for men.[3] Additionally, the number of people living five or more years after a cancer diagnosis is projected to increase 31% by 2026, according to the American Society of Clinical Oncology's 2019 Clinical Cancer Advances Report.[3] These trends generate an optimism in cancer treatment which clinicians attribute to better surgical techniques, radiation therapy modalities, symptom management, and new, emerging systemic treatment options. Appropriate access to these advances is required for individual patients to fully realize the benefits. In this respect, healthcare providers and payers are challenged to establish a means of providing access to these treatment advances for all cancer patients in a manner that is clinically, logistically, and financially responsible and attainable.

What Is Targeted Therapy?
Empiric Therapy vs. Precision Therapy[4]

Empiric therapy is best described as an educated guess, based upon historic experience of the treatments prescribed to similar patients. This historic approach to cancer treatment worked in the absence of detailed patient- and tumor-specific information. Precision therapy, on the other hand, involves drugs administered to patients who are identified in advance as likely to benefit because of an identifying signature or a prognostic biomarker associated with their specific disease. Awareness of the differences in these two approaches is crucial to improving cancer treatment.

Empiric therapy introduces challenges: It can be costly and may expose patients to toxicity from drugs that may have limited effectiveness. This may be compared to undertaking a trial of an antibiotic therapy, but cancer treatments often have a higher potential for serious toxicity compared to antibiotics. Specifically, patients treated empirically may experience unnecessary drug toxicities that will have implications for their individual health and contribute to poor allocation of healthcare resources.

Precision therapy is challenging, necessitates access to precise information, and requires the coordination of information to help providers connect the dots to select the best treatment for an individual patient. This practice is complex, and success is dependent on identifying biomarkers to guide personalized diagnosis and treatment.

Precision Medicine in Practice:
The Lung Cancer Story

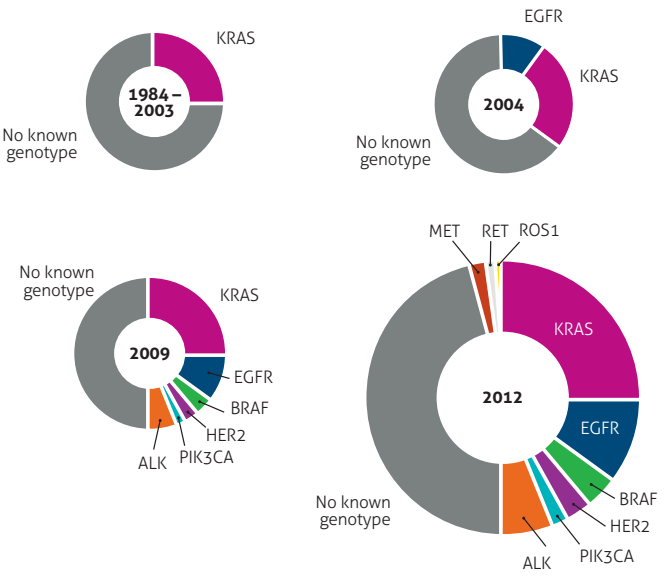
A look at the evolution of lung cancer diagnosis and treatment over the past two decades offers the opportunity to explore the tremendous advances made in precision medicine. Of the two major types of lung cancer, small-cell and non-small-cell (NSCLC), the latter accounts for 80% to 85% of all lung cancer diagnoses.[5] The most common subtypes of NSCLC are adenocarcinoma, which accounts for approximately 40% of NSCLC diagnoses; squamous cell (epidermoid) carcinoma, which accounts for approximately 25% to 30% of diagnoses; and large-cell (undifferentiated) carcinoma, which accounts for approximately 10% to 15% of diagnoses.[5] The remaining 15% of NSCLC diagnoses are attributed to adenosquamous and sarcomatoid carcinoma.

In the U.S., lung cancer is the second most common type of cancer among both men and women, not including nonmelanoma skin cancers, and is second to prostate cancer in men and breast cancer in women. Lung cancer accounts for 13% of all new cases of cancer and mainly occurs in the older population, with most patients diagnosed at 65 years or older and very few patients diagnosed younger than the age of 45.[5] Lung cancer is by far the leading cause of cancer death among both men and women. Each year, more people die of lung cancer than of colon, breast, and prostate cancers combined.[5] The American Cancer Society estimates there will be 228,150 new cases of lung cancer and 142,670 deaths from lung cancer in 2019.

Treatment Advances

Treatment options for NSCLC vary depending on the stage of cancer at diagnosis and can include radiation therapy, traditional chemotherapy, targeted therapy, immunotherapy, palliative care, or several possible combinations of these modalities.[6] Historically, most patients were treated with a double-chemotherapy combination — most commonly a platinum agent and a taxane. Success and survival outcomes for these combination therapies were similar regardless of the treatment administered, with a median survival of 7.9 months (95% confidence interval, 7.3 to 8.5 months), a 1-year survival rate of 33% (95% confidence interval, 30% to 36%), and a two-year survival rate of 11% (95% confidence interval, 8 to 12%).[7] The oral drugs, gefitinib (Iressa™) and erlotinib (Tarceva™), were the first targeted agents approved for use in NSCLC. These drugs resulted in significant improvements in progression-free survival for individuals with NSCLC and epidermal growth factor receptor (EGFR) mutations.[8] As further advances were made, dramatic effects with targeted treatment of NSCLC were also demonstrated with the use of anaplastic lymphoma kinase (ALK) inhibitors such as crizotinib for individuals with ALK mutations.[9, 10]

Figure 1. Lung Cancer Genotyping[4]

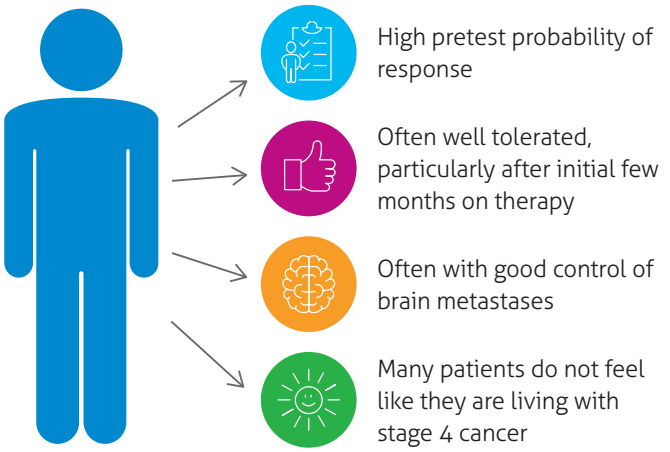


The Role of Precision Medicine in Lung Cancer

Genomic testing is used in patients diagnosed with cancer to look at traits of the specific cancer and further stratify diagnosis, guide treatment selection, and look broadly for gene alterations.

The number of biomarkers for the treatment of NSCLC is on the rise, with one genotype identified in 2003, nine genotypes noted in 2012, and 14 genotypes as of 2018.[11] The evolution to precision-targeted therapies is a different way to treat patients. This type of treatment has a higher probability of response and is often well

Figure 2. Treating patients with precision-targeted therapies is different:



tolerated by patients. Figure 1 shows that for a large percentage of patients, a specific genotype still cannot be identified, but for roughly one-third of patients, targeted treatment can help improve outcomes and potentially decrease side effects of therapy. As shown in Figure 2, patients have a high probability of response to a therapy that is well tolerated, while experiencing an improved quality of life.

Predictive and Prognostic Biomarkers[6]

There are two types of biomarkers: predictive and prognostic. Predictive biomarkers indicate the effectiveness of the therapy due to an interaction between the biomarker and therapy. Prognostic biomarkers are connected to tumor behavior and indicative of patient survival regardless of treatment. Multiple predictive markers exist for NSCLC, including ALK gene rearrangements, EGFR gene mutations, ROS1 rearrangements, neurotrophic receptor kinase (NTRK) gene fusions, and BRAF mutations (category 2A). Additional markers are emerging, including ERBB2 mutations, also known as HER2; RET gene rearrangements; and MET exon 14 skipping mutations. Lung cancer patients whose tumors express PD-L1 may respond best to immunotherapy treatments that allow activated cytotoxic T cells to attack the cancer. Due to biomarkers' ability to impact treatment selection, the 2019 National Comprehensive Cancer Network (NCCN) guidelines for NSCLC recommend broad molecular profiling for patients diagnosed with advanced or metastatic NSCLC.

Targeted and Comprehensive Assay Testing[4]

As expertise has grown in genomic testing, the approach to testing has begun to evolve. As shown in Figure 3, targeted assays have been available that focus upon a specific gene variant or mutation, such as EGFR or ALK. With growing knowledge and advances in technology, comprehensive assays are becoming increasingly available.

Figure 3. Genomic Testing

Targeted Assays
Example:
EGFR/ALK
Cobas® EGFR Mutation Test v2
Vysis ALK Break Apart FISH Probe Kit

Comprehensive assays
Example:
Foundation Medicine Testing
ThermoFischer Oncomine™
FoundationOne® CDx
Oncomine™ Dx Target Test

Patient Education on Precision Targeted Therapy[4]

Results from precision therapy testing may take a few weeks to be returned, which can be a difficult waiting period for a patient newly diagnosed with lung cancer. Physicians are tasked with effectively communicating to patients the importance of using these therapeutic advances as tools to optimize the chance of successful treatment. Helping patients understand the potential benefits of a medication matched to the biomarker identified for their particular cancer can help ease the anxiety of waiting the two weeks before beginning treatment. Patient education regarding precision therapy should include associated benefits such as the possibility of oral medication rather than an intravenous medication; more reliable outcomes with a higher probability of treatment success; and, possibly, better medication tolerance with fewer side effects. Anecdotally, many patients who have taken targeted therapy have reported that taking a pill once daily has helped them feel as if they are not living with lung cancer.

> Biomarkers are a tremendous tool for helping providers select the best medication for treating each patient.

Companion Diagnostics and Impact to Payers and Providers[4]

Companion diagnostics are FDA-approved assays with use outlined in the FDA-approved labeling of the corresponding therapeutic product. These agents test for select biomarkers and support the genomic testing of the tumor. In addition to product-specific companion diagnostics, other tests have been, and continue to be, developed. Assay selection and coverage offer an area for payers and physicians to collaborate in the interest of improving clinical outcomes and managing costs. For example, as shown in Figure 4, approval in the form of a national coverage determination for reimbursement by the Centers for Medicaid and Medicare Services (CMS) has been obtained for next-generation sequencing technology (NGS) in certain patients. NGS is a comprehensive assay to test for multiple markers in a single panel rather than multiple individual tests, which may offer efficiency in terms of time and cost while helping to identify therapeutic options for patients. Some examples of comprehensive assay tests include FoundationOne® CDx and Oncomine™ Dx Target Test.

Figure 4. Impact of Genomic Testing

Billing and coding have not kept pace (~400 procedural billing codes) for tens of thousands of different testing products

Lack of insight for payers who often are left questioning, "What am I paying for?"

CMS National Coverage Determination (NCD) for NGS

Patient eligibility:

- Recurrent, relapsed, refractory, metastatic, or advanced stages 3 or 4 cancer
- Not previously undergone testing using the same NGS test
- Patient wishes to pursue further treatment

NGS requirements:

- FDA approval as companion diagnostic
- A therapy with an FDA-approved or-cleared indication for use in that patient's cancer
- Results are provided to treating physician using a report template to specify treatment options for management of the patient

The complexity of navigating various testing alternatives is a challenge for all stakeholders. Payers are tasked with administering the policies for approval and reimbursement, but billing and coding related to genomic testing have not kept pace with advances. Physicians are challenged to navigate the process and advocate for access to the testing expected to yield the best information for their patients.

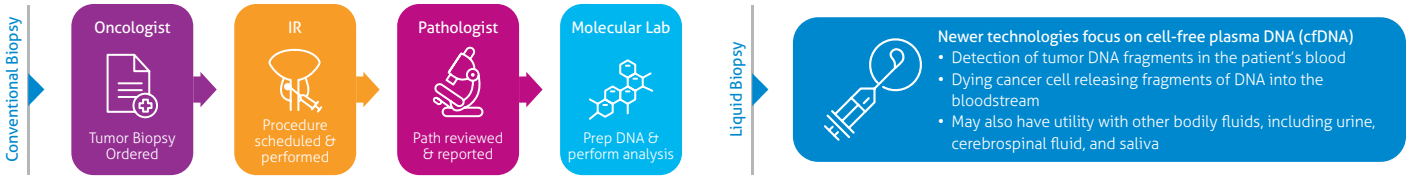
What Is Next for Testing?[4]

Liquid biopsy testing is a newer technology focusing on cell-free plasma DNA. This type of diagnostic test looks for tumor DNA fragments, released by the tumor into the patient's blood. The benefits of this testing method include the elimination of the need for a potentially invasive biopsy (Figure 5). This form of testing is limited by the type, size, and location of the tumor. An example of this limitation is a patient with advanced lung cancer with small nodules that may not reveal circulating DNA in the patients' bloodstream. Due to this limitation, liquid biopsy is approved as a screening mechanism, but a biopsy may be needed if the results are negative. The ease of ordering a blood test and faster turnaround time for receiving results have pipeline implications for liquid biopsy testing. Additional tests are expected to become available to oncologists as a diagnostic tool with the ability to shorten the time it will take to initiate therapy.

Key Insights

Biomarkers are a tremendous tool for helping providers select the best medication for treating each patient. Applying tumor-specific information to treatment selection helps patients experience favorable clinical benefits while potentially reducing side effects and improving patient satisfaction. This type of precision therapy is continuing to evolve in the management of NSCLC and across other types of cancer. The use of these biomarkers will require payers and providers to collaborate in support of the application of this expertise by ensuring crucial information is accessible and utilized to inform the selection of an appropriate treatment. In addition to these considerations, patient education regarding the timeline and

Figure 5. Conventional Biopsies vs. Liquid Biopsies



benefits of waiting for the results of biomarker testing is extremely important. Communicating the advantages of identifying a more effective drug with potentially fewer side effects is a key component of patient education and will require the coordinated support of payers and providers.

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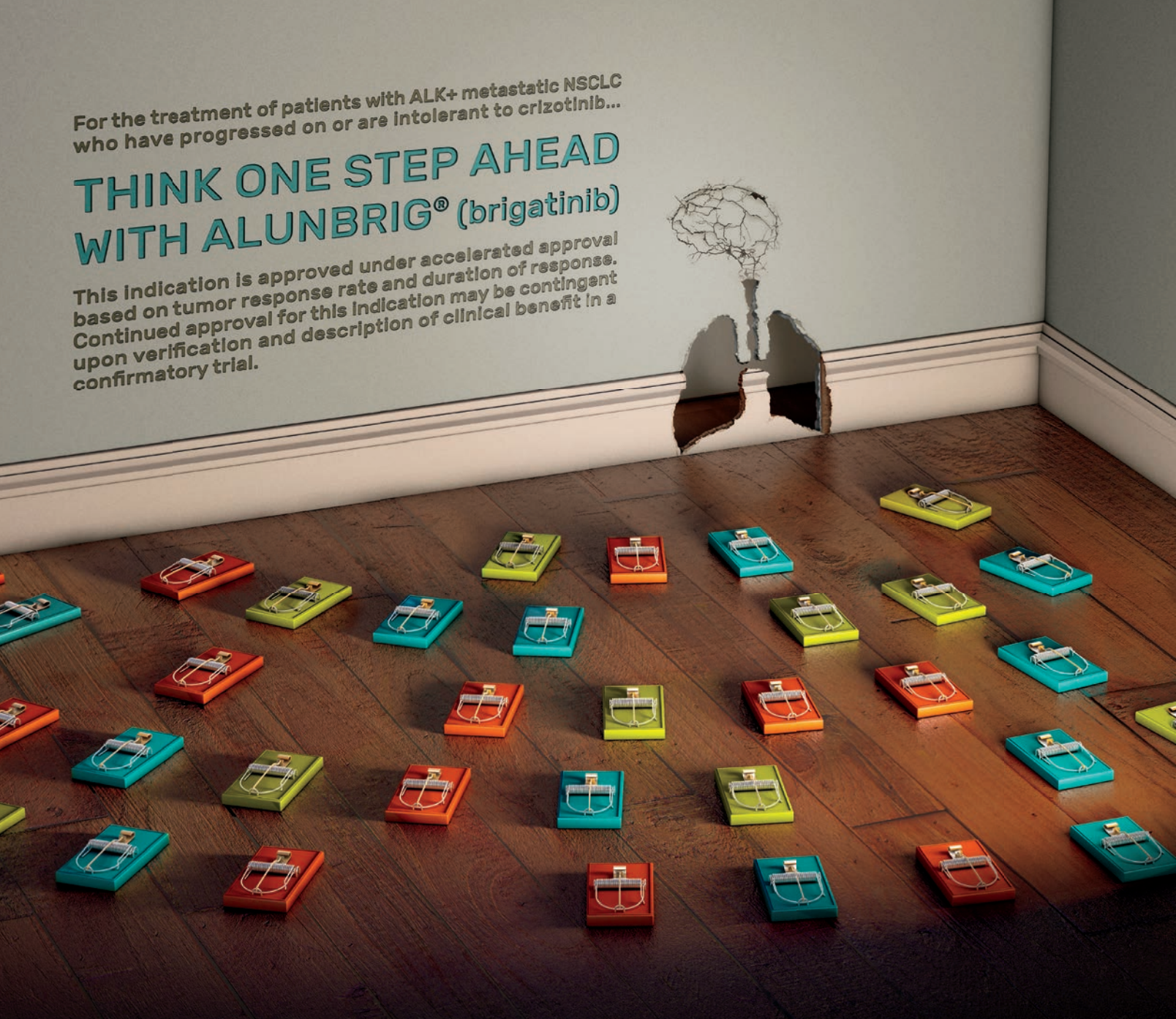

INDICATION AND IMPORTANT SAFETY INFORMATION

ALUNBRIG® (brigatinib) is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib. See accelerated approval information above.

WARNINGS AND PRECAUTIONS

Interstitial Lung Disease (ILD)/Pneumonitis: Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG. In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily). Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%. Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

ALK+, anaplastic lymphoma kinase-positive; NSCLC, non-small cell lung cancer.

ALUNBRIG®
BRIGATINIB
180mg | 90mg | 30mg
TABLETS

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

For patients with ALK+ metastatic NSCLC
who have progressed on or are intolerant to crizotinib

Think One Step Ahead With ALUNBRIG® (brigatinib)

Robust Overall Efficacy

ALTA Efficacy Results	IRC Assessment[a]		Investigator Assessment[a]	
	90 mg once daily (n=112)	90→180 mg once daily[b] (n=110)	90 mg once daily (n=112)	90→180 mg once daily[b] (n=110)
Overall Response Rate, (95% CI)	48% (39-58)	53% (43-62)	45% (35-54)	54% (44-63)
Complete Response, n (%)	4 (3.6)	5 (4.5)	1 (0.9)	4 (3.6)
Partial Response, n (%)	50 (45)	53 (48)	49 (44)	55 (50)
Duration of Response, Median in Months (95% CI)	13.8 (7.4-NE)	13.8 (9.3-NE)	13.8 (5.6-13.8)	11.1 (9.2-13.8)

[b]180 mg once daily with a 7-day lead-in at 90 mg once daily.
CI, confidence interval; NE, not estimable.

ALTA Study Design: The safety and efficacy of ALUNBRIG were evaluated in a global, two-arm, open-label, multicenter trial. The trial consisted of 222 adult patients with locally advanced or metastatic ALK+ NSCLC who had progressed on crizotinib. Patients were randomized to receive the recommended dosing regimen of 180 mg of ALUNBRIG orally once daily with a 7-day lead-in at 90 mg once daily (n=110, 18 with measurable brain metastases[c]), or 90 mg of ALUNBRIG orally once daily (n=112, 26 with measurable brain metastases[c]). The major efficacy outcome measure was confirmed objective response rate (ORR) according to Response Evaluation Criteria In Solid Tumors (RECIST v1.1) as evaluated by an Independent Review Committee (IRC). Additional efficacy outcome measures included Investigator-assessed ORR, duration of response (DOR), intracranial ORR, and intracranial DOR.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Hypertension: In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall. Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension. Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

Bradycardia: Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group. Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided. For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

Visual Disturbance: In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients treated with ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in one patient each in the 90→180 mg group. Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

Creatine Phosphokinase (CPK) Elevation: In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group. Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group. Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Pancreatic Enzyme Elevation: In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group. Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

Hyperglycemia: In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG. Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize anti-hyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

Meaningful CNS Efficacy

Intracranial Objective Response in Patients With Measurable Brain Metastases[c] in ALTA	IRC Assessment[a]	
	90 mg once daily (n=26)	90→180 mg once daily[b] (n=18)
Intracranial Overall Response Rate, (95% CI)	42% (23-63)	67% (41-87)
Complete Response, n (%)	2 (7.7)	0
Partial Response, n (%)	9 (35)	12 (67)
Duration of Intracranial Response		
Intracranial Response ≥6 Months	64% (7/11)	50% (6/12)
Intracranial Response ≥12 Months	36% (4/11)	25% (3/12)

[a]Median duration of follow-up was 8 months (range: 0.1-20.1).
[b]180 mg once daily with a 7-day lead-in at 90 mg once daily.
[c]≥10 mm in longest diameter (at baseline).

ALUNBRIG is an ALK inhibitor with a one-tablet, once-daily recommended dosage regimen that can be taken with or without food.[d]

[d]The recommended dosage regimen is 90 mg orally once daily for the first 7 days. If tolerated during the first 7 days, increase dose to 180 mg orally once daily.

Visit **ALUNBRIG.com** to learn more.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

The most common adverse reactions (≥25%) in the 90 mg group were nausea (33%), fatigue (29%), headache (28%), and dyspnea (27%) and in the 90→180 mg group were nausea (40%), diarrhea (38%), fatigue (36%), cough (34%), and headache (27%).

DRUG INTERACTIONS

CYP3A Inhibitors: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. Avoid grapefruit or grapefruit juice as it may also increase plasma concentrations of brigatinib. If coadministration of a strong or moderate CYP3A inhibitor cannot be avoided, reduce the dose of ALUNBRIG.

CYP3A Inducers: Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, increase the dose of ALUNBRIG.

CYP3A Substrates: Coadministration of ALUNBRIG with sensitive CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

USE IN SPECIFIC POPULATIONS

Pregnancy: ALUNBRIG can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.

Lactation: There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG.

Females and Males of Reproductive Potential:

Pregnancy Testing: Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

Contraception: Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility: ALUNBRIG may cause reduced fertility in males.

Pediatric Use: The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

Geriatric Use: Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

Hepatic or Renal Impairment: No dose adjustment is recommended for patients with mild or moderate hepatic impairment or mild or moderate renal impairment. Reduce the dose of ALUNBRIG for patients with severe hepatic impairment or severe renal impairment.

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

Takeda ONCOLOGY

ALUNBRIG®
BRIGATINIB
180mg | 90mg | 30mg
TABLETS

BRIEF SUMMARY OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALUNBRIG safely and effectively. See full prescribing information for ALUNBRIG.

ALUNBRIG® (brigatinib) tablets, for oral use
Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

ALUNBRIG is indicated for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib.

This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

5 WARNINGS AND PRECAUTIONS

5.1 Interstitial Lung Disease (ILD)/Pneumonitis

Severe, life-threatening, and fatal pulmonary adverse reactions consistent with interstitial lung disease (ILD)/pneumonitis have occurred with ALUNBRIG.

In Trial ALTA (ALTA), ILD/pneumonitis occurred in 3.7% of patients in the 90 mg group (90 mg once daily) and 9.1% of patients in the 90→180 mg group (180 mg once daily with 7-day lead-in at 90 mg once daily).

Adverse reactions consistent with possible ILD/pneumonitis occurred early (within 9 days of initiation of ALUNBRIG; median onset was 2 days) in 6.4% of patients, with Grade 3 to 4 reactions occurring in 2.7%.

Monitor for new or worsening respiratory symptoms (e.g., dyspnea, cough, etc.), particularly during the first week of initiating ALUNBRIG. Withhold ALUNBRIG in any patient with new or worsening respiratory symptoms, and promptly evaluate for ILD/pneumonitis or other causes of respiratory symptoms (e.g., pulmonary embolism, tumor progression, and infectious pneumonia). For Grade 1 or 2 ILD/pneumonitis, either resume ALUNBRIG with dose reduction after recovery to baseline or permanently discontinue ALUNBRIG. Permanently discontinue ALUNBRIG for Grade 3 or 4 ILD/pneumonitis or recurrence of Grade 1 or 2 ILD/pneumonitis.

5.2 Hypertension

In ALTA, hypertension was reported in 11% of patients in the 90 mg group who received ALUNBRIG and 21% of patients in the 90→180 mg group. Grade 3 hypertension occurred in 5.9% of patients overall.

Control blood pressure prior to treatment with ALUNBRIG. Monitor blood pressure after 2 weeks and at least monthly thereafter during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 hypertension despite optimal antihypertensive therapy. Upon resolution or improvement to Grade 1 severity, resume ALUNBRIG at a reduced dose. Consider permanent discontinuation of treatment with ALUNBRIG for Grade 4 hypertension or recurrence of Grade 3 hypertension.

Use caution when administering ALUNBRIG in combination with antihypertensive agents that cause bradycardia.

5.3 Bradycardia

Bradycardia can occur with ALUNBRIG. In ALTA, heart rates less than 50 beats per minute (bpm) occurred in 5.7% of patients in the 90 mg group and 7.6% of patients in the 90→180 mg group. Grade 2 bradycardia occurred in 1 (0.9%) patient in the 90 mg group.

Monitor heart rate and blood pressure during treatment with ALUNBRIG. Monitor patients more frequently if concomitant use of drug known to cause bradycardia cannot be avoided.

For symptomatic bradycardia, withhold ALUNBRIG and review concomitant medications for those known to cause bradycardia. If a concomitant medication known to cause bradycardia is identified and discontinued or dose adjusted, resume ALUNBRIG at the same dose following resolution of symptomatic bradycardia; otherwise, reduce the dose of ALUNBRIG following resolution of symptomatic bradycardia. Discontinue ALUNBRIG for life-threatening bradycardia if no contributing concomitant medication is identified.

5.4 Visual Disturbance

In ALTA, adverse reactions leading to visual disturbance including blurred vision, diplopia, and reduced visual acuity, were reported in 7.3% of patients receiving ALUNBRIG in the 90 mg group and 10% of patients in the 90→180 mg group. Grade 3 macular edema and cataract occurred in 1 patient each in the 90→180 mg group.

Advise patients to report any visual symptoms. Withhold ALUNBRIG and obtain an ophthalmologic evaluation in patients with new or worsening visual symptoms of Grade 2 or greater severity. Upon recovery of Grade 2 or Grade 3 visual disturbances to Grade 1 severity or baseline, resume ALUNBRIG at a reduced dose. Permanently discontinue treatment with ALUNBRIG for Grade 4 visual disturbances.

5.5 Creatine Phosphokinase (CPK) Elevation

In ALTA, creatine phosphokinase (CPK) elevation occurred in 27% of patients receiving ALUNBRIG in the 90 mg group and 48% of patients in the 90 mg→180 mg group. The incidence of Grade 3-4 CPK elevation was 2.8% in the 90 mg group and 12% in the 90→180 mg group.

Dose reduction for CPK elevation occurred in 1.8% of patients in the 90 mg group and 4.5% in the 90→180 mg group.

Advise patients to report any unexplained muscle pain, tenderness, or weakness. Monitor CPK levels during ALUNBRIG treatment. Withhold ALUNBRIG for Grade 3 or 4 CPK elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

5.6 Pancreatic Enzymes Elevation

In ALTA, amylase elevation occurred in 27% of patients in the 90 mg group and 39% of patients in the 90→180 mg group. Lipase elevations occurred in 21% of patients in the 90 mg group and 45% of patients in the 90→180 mg group. Grade 3 or 4 amylase elevation occurred in 3.7% of patients in the 90 mg group and 2.7% of patients in the 90→180 mg group. Grade 3 or 4 lipase elevation occurred in 4.6% of patients in the 90 mg group and 5.5% of patients in the 90→180 mg group.

Monitor lipase and amylase during treatment with ALUNBRIG. Withhold ALUNBRIG for Grade 3 or 4 pancreatic enzyme elevation. Upon resolution or recovery to Grade 1 or baseline, resume ALUNBRIG at the same dose or at a reduced dose.

5.7 Hyperglycemia

In ALTA, 43% of patients who received ALUNBRIG experienced new or worsening hyperglycemia. Grade 3 hyperglycemia, based on laboratory assessment of serum fasting glucose levels, occurred in 3.7% of patients. Two of 20 (10%) patients with diabetes or glucose intolerance at baseline required initiation of insulin while receiving ALUNBRIG.

Assess fasting serum glucose prior to initiation of ALUNBRIG and monitor periodically thereafter. Initiate or optimize antihyperglycemic medications as needed. If adequate hyperglycemic control cannot be achieved with optimal medical management, withhold ALUNBRIG until adequate hyperglycemic control is achieved and consider reducing the dose of ALUNBRIG or permanently discontinuing ALUNBRIG.

5.8 Embryo-Fetal Toxicity

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to pregnant women. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily), as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or higher.

Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months following the final dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for at least 3 months after the last dose of ALUNBRIG.

6 ADVERSE REACTIONS

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

- Interstitial Lung Disease (ILD)/Pneumonitis
- Hypertension
- Bradycardia
- Visual Disturbance
- Creatine Phosphokinase (CPK) Elevation
- Pancreatic Enzymes Elevation
- Hyperglycemia

6.1 Clinical Trials Experience

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

The safety of ALUNBRIG was evaluated in 219 patients with locally advanced or metastatic ALK-positive non-small cell lung cancer (NSCLC) who received at least 1 dose of ALUNBRIG in ALTA after experiencing disease progression on crizotinib. Patients received ALUNBRIG 90 mg once daily continuously (90 mg group) or 90 mg once daily for 7 days followed by 180 mg once daily (90→180 mg group). The median duration of treatment was 7.5 months in the 90 mg group and 7.8 months in the 90→180 mg group. A total of 150 (68%) patients were exposed to ALUNBRIG for greater than or equal to 6 months and 42 (19%) patients were exposed for greater than or equal to 1 year.

The study population characteristics were: median age 54 years (range: 18 to 82), age less than 65 years (77%), female (57%), White (67%), Asian (31%), Stage IV disease (98%), NSCLC adenocarcinoma histology (97%), never or former smoker (95%), ECOG Performance Status (PS) 0 or 1 (93%), and brain metastases at baseline (69%).

Serious adverse reactions occurred in 38% of patients in the 90 mg group and 40% of patients in the 90→180 mg group. The most common serious adverse reactions were pneumonia (5.5% overall, 3.7% in the 90 mg group, and 7.3% in the 90→180 mg group) and ILD/pneumonitis (4.6% overall, 1.8% in the 90 mg group and 7.3% in the 90→180 mg group). Fatal adverse reactions occurred in 3.7% of patients and consisted of pneumonia (2 patients), sudden death, dyspnea, respiratory failure, pulmonary embolism, bacterial meningitis and urosepsis (1 patient each).

In ALTA, 2.8% of patients in the 90 mg group and 8.2% of patients in the 90→180 mg group permanently discontinued ALUNBRIG for adverse reactions. The most frequent adverse reactions that led to discontinuation were ILD/pneumonitis (0.9% in the 90 mg group and 1.8% in the 90→180 mg group) and pneumonia (1.8% in the 90→180 mg group only).

In ALTA, 14% of patients required a dose reduction due to adverse reactions (7.3% in the 90 mg group and 20% in the 90→180 mg group). The most common adverse reaction that led to dose reduction was increased creatine phosphokinase for both regimens (1.8% in the 90 mg group and 4.5% in the 90→180 mg group).

Table 3 and Table 4 summarize the common adverse reactions and laboratory abnormalities observed in ALTA.

Table 3: Adverse Reactions in ≥10% (All Grades*) or ≥2% (Grades 3-4) of Patients by Dose Group in ALTA (N=219)

Adverse Reactions	90 mg once daily N = 109		90→180 mg once daily N = 110	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Gastrointestinal Disorders				
Nausea	33	0.9	40	0.9
Diarrhea	19	0	38	0
Vomiting	24	1.8	23	0
Constipation	19	0.9	15	0
Abdominal Pain†	17	0	10	0
General Disorders And Administration Site Conditions				
Fatigue‡	29	1.8	36	0
Pyrexia	14	0	6.4	0.9
Respiratory, Thoracic And Mediastinal Disorders				
Cough	18	0	34	0
Dyspnea§	27	2.8	21	1.8ê
ILD/Pneumonitis	3.7	1.8	9.1	2.7
Hypoxia	0.9	0	2.7	2.7
Nervous System Disorders				
Headache¶	28	0	27	0.9
Peripheral Neuropathy#	13	0.9	13	1.8
Skin And Subcutaneous Tissue Disorders				
RashÞ	15	1.8	24	3.6
Vascular Disorders				
Hypertension	11	5.5	21	6.4
Musculoskeletal And Connective Tissue Disorders				
Muscle Spasms	12	0	17	0
Back pain	10	1.8	15	1.8
Myalgiaβ	9.2	0	15	0.9
Arthralgia	14	0.9	14	0
Pain in extremity	11	0	3.6	0.9
Metabolism And Nutrition Disorders				
Decreased Appetite	22	0.9	15	0.9
Eye Disorders				
Visual Disturbanceà	7.3	0	10	0.9
Infections				
Pneumonia	4.6	2.8ê	10	5.5ê
Psychiatric Disorders				
Insomnia	11	0	7.3	0

* Per National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0
† Includes abdominal distension, abdominal pain, and epigastric discomfort
‡ Includes asthenia and fatigue
§ Includes dyspnea and exertional dyspnea
¶ Includes headache and sinus headache
# Includes peripheral sensory neuropathy and paresthesia
Þ Includes acneiform dermatitis, exfoliative rash, rash, pruritic rash, and pustular rash
β Includes musculoskeletal pain and myalgia
à Includes diplopia, photophobia, blurred vision, reduced visual acuity, visual impairment, vitreous floaters, visual field defect, macular edema, and vitreous detachment
ê Includes one Grade 5 event

Table 4: Laboratory Abnormalities in ≥20% (All Grades*) of Patients by Regimen in ALTA (N=219)				
	90 mg once daily N= 109		90→180 mg once daily N=110	
Laboratory Abnormality	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Chemistry				
Increased aspartate aminotransferase	38	0.9	65	0
Hyperglycemia†	38	3.7	49	3.6
Increased creatine phosphokinase	27	2.8	48	12
Increased lipase	21	4.6	45	5.5
Increased alanine aminotransferase	34	0	40	2.7
Increased amylase	27	3.7	39	2.7
Increased alkaline phosphatase	15	0.9	29	0.9
Decreased phosphorous	15	1.8	23	3.6
Prolonged activated partial thromboplastin time	22	1.8	20	0.9
Hematology				
Anemia	23	0.9	40	0.9
Lymphopenia	19	2.8	27	4.5

* Per CTCAE version 4.0
† Elevated blood insulin was also observed in both regimens

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ALUNBRIG

Strong or Moderate CYP3A Inhibitors

Coadministration of ALUNBRIG with a strong or moderate CYP3A inhibitor increased brigatinib plasma concentrations, which may increase the incidence of adverse reactions. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inhibitors. If coadministration of strong or moderate CYP3A inhibitors cannot be avoided, modify dose as recommended.

Strong or Moderate CYP3A Inducers

Coadministration of ALUNBRIG with a strong or moderate CYP3A inducer decreased brigatinib plasma concentrations, which may decrease the efficacy of ALUNBRIG. Avoid coadministration of ALUNBRIG with strong or moderate CYP3A inducers. If coadministration of moderate CYP3A inducers cannot be avoided, modify dose as recommended.

7.2 Effect of ALUNBRIG on Other Drugs

CYP3A Substrates

Brigatinib may decrease the concentrations of sensitive CYP3A substrates. Coadministration of ALUNBRIG with CYP3A substrates, including hormonal contraceptives, can result in decreased concentrations and loss of efficacy of sensitive CYP3A substrates.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, ALUNBRIG can cause fetal harm when administered to a pregnant woman. There are no clinical data on the use of ALUNBRIG in pregnant women. Administration of brigatinib to pregnant rats during the period of organogenesis resulted in dose-related skeletal anomalies at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily) as well as increased post-implantation loss, malformations, and decreased fetal body weight at doses of 25 mg/kg/day (approximately 1.26 times the human exposure at 180 mg once daily) or greater. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

In an embryo-fetal development study in which pregnant rats were administered daily doses of brigatinib during organogenesis, dose-related skeletal (incomplete ossification, small incisors) and visceral anomalies were observed at doses as low as 12.5 mg/kg/day (approximately 0.7 times the human exposure by AUC at 180 mg once daily). Malformations observed at 25 mg/kg/day (approximately 1.26 times the human AUC at 180 mg once daily) included anasarca (generalized subcutaneous edema), anophthalmia (absent eyes), forelimb hyperflexion, small, short and/or bent limbs, multiple fused ribs, bent scapulae, omphalocele (intestine protruding into umbilicus), and gastroschisis (intestines protruding through a defect in the abdominal wall) along with visceral findings of moderate bilateral dilatation of the lateral ventricles.

8.2 Lactation

Risk Summary

There are no data regarding the secretion of brigatinib in human milk or its effects on the breastfed infant or milk production. Because of the potential for adverse reactions in breastfed infants, advise lactating women not to breastfeed during treatment with ALUNBRIG and for 1 week following the final dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating ALUNBRIG.

Contraception

ALUNBRIG can cause fetal harm.

Females

Advise females of reproductive potential to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose. Counsel patients to use a non-hormonal method of contraception since ALUNBRIG can render some hormonal contraceptives ineffective.

Males

Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Infertility

Based on findings in male reproductive organs in animals, ALUNBRIG may cause reduced fertility in males.

8.4 Pediatric Use

The safety and effectiveness of ALUNBRIG in pediatric patients have not been established.

8.5 Geriatric Use

Clinical studies of ALUNBRIG did not include sufficient numbers of patients aged 65 years and older to determine whether they respond differently from younger patients.

8.6 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A) or moderate hepatic impairment (Child-Pugh B). Reduce the dose of ALUNBRIG for patients with severe hepatic impairment (Child-Pugh C).

8.7 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment [creatinine clearance (CLcr) 30 to 89 mL/min by Cockcroft-Gault]. Reduce the dose of ALUNBRIG for patients with severe renal impairment (CLcr 15 to 29 mL/min).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Interstitial Lung Disease (ILD)/Pneumonitis

Inform patients of the symptoms and risks of serious pulmonary adverse reactions such as ILD/pneumonitis. Advise patients to immediately report any new or worsening respiratory symptoms.

Hypertension

Advise patients of risks of hypertension and to promptly report signs or symptoms of hypertension.

Bradycardia

Advise patients to report any symptoms of bradycardia and to inform their healthcare provider about the use of heart and blood pressure medications.

Visual Disturbance

Advise patients to inform their healthcare provider of any new or worsening vision symptoms.

Creatine Phosphokinase (CPK) Elevation

Inform patients of the signs and symptoms of creatine phosphokinase (CPK) elevation and the need for monitoring during treatment. Advise patients to inform their healthcare provider of any new or worsening symptoms of unexplained muscle pain, tenderness, or weakness.

Pancreatic Enzymes Elevation

Inform patients of the signs and symptoms of pancreatitis and the need to monitor for amylase and lipase elevations during treatment.

Hyperglycemia

Inform patients of the risks of new or worsening hyperglycemia and the need to periodically monitor glucose levels. Advise patients with diabetes mellitus or glucose intolerance that antihyperglycemic medications may need to be adjusted during treatment with ALUNBRIG.

Females and Males of Reproductive Potential

Embryo-Fetal Toxicity

Advise females and males of reproductive potential that ALUNBRIG can cause fetal harm.

- Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy and to use effective non-hormonal contraception during treatment with ALUNBRIG and for at least 4 months after the final dose.
- Advise males with female partners of reproductive potential to use effective contraception during treatment with ALUNBRIG and for at least 3 months after the final dose.

Lactation

Advise females not to breastfeed during treatment with ALUNBRIG and for at least 1 week following the final dose.

Infertility

Advise males of reproductive potential of the potential for reduced fertility from ALUNBRIG.

Drug Interactions

Advise patients to inform their healthcare provider of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products. Inform patients to avoid grapefruit or grapefruit juice while taking ALUNBRIG.

Dosing and Administration

Instruct patients to start with 90 mg of ALUNBRIG once daily for the first 7 days and if tolerated, increase the dose to 180 mg once daily. Advise patients to take ALUNBRIG with or without food.

Missed Dose

Advise patients that if a dose of ALUNBRIG is missed or if the patient vomits after taking a dose of ALUNBRIG, not to take an extra dose, but to take the next dose at the regular time.

Please see full Prescribing Information for ALUNBRIG at ALUNBRIG.com.

Manufactured for:
Takeda Pharmaceutical Company Limited
40 Landsdowne Street, Cambridge, MA 02139-4234

03/19 MAT-USO-BRG-19-00029

Biosimilar Spotlight

Maryam Tabatabai, PharmD
Senior Director, Drug Information, Magellan Rx Management

In the four years since the first biosimilar approval in the U.S., biosimilars have moved past proof of concept and are slowly establishing their presence, although regulatory and legal hurdles remain. We highlighted some of the movement in the biosimilar space in "Medical Oncology Biosimilars" in our summer 2019 Report. After continued market activity, here is an overview of recent approvals, updates, and dynamics in this space.

Latest Approvals

- In June and July 2019, the U.S. Food and Drug Administration (FDA) approved four biosimilars: Kanjinti™, Zirabev™, Ruxience™, and Hadlima™, for the reference products Herceptin®, Avastin®, Rituxan®, and Humira®, respectively.
- To date, a total of 23 biosimilars have received FDA approval.
- Drug exclusivity may preclude biosimilars from receiving all the originator's indications.

At-Risk Launches

- In July 2019, Amgen launched Kanjinti™, biosimilar to Herceptin®, and Mvasi™, biosimilar to Avastin®. It appears that Kanjinti™ and Mvasi™ can be marketed at least until December 2019 and July 2020, respectively, until the courts reach appeals decisions.
- These two products mark the first therapeutic anti-cancer biosimilars launched in the U.S.
- Genentech (Herceptin®) has reached confidential settlement agreements with the other FDA-approved Herceptin® biosimilars (Ogivri™, Herzuma, Ontruzant, and Trazimera™). While the launch timeline of these four agents is unclear, Mylan may launch Ogivri™ in November 2019, and the other three agents may launch soon after.
- Despite litigation, Pfizer may launch Zirabev™, its biosimilar to Avastin®, at any time.
- Biosimilars to Humira® are not expected to launch before June 30, 2023.
- As of press time, only nine of the approved biosimilars have entered the market, in the short-acting colony-stimulating factor (CSF), long-acting CSF, immunology, and oncology classes.

Financial Dynamics

- Biosimilars in the U.S. have been estimated to cost 15% to 35% less than originator products and have come in at the lower end of that range.
- Both Mvasi™ and Kanjinti™ launched at a wholesale acquisition cost (WAC) of 15% below their respective reference products. Mvasi™ is marked at 12% below Avastin®'s average sales price (ASP), and Kanjinti™ is priced at 13% below Herceptin®'s ASP.
- Both products are available from wholesalers and specialty distributors.

Regulatory Updates

- In May 2019, the FDA issued the long-awaited final guidance on biosimilar interchangeability.
- Several states had already enacted biosimilar-substitution legislation.
- Currently, no biosimilars are considered interchangeable with their reference product(s).
- The FDA plans to transition a small subset of drugs under the Federal Food, Drug, and Cosmetics Act to be licensed as biologics.
- Starting in March 2020, drugs such as insulin and growth hormone will be deemed biologics and transition from the drug pathway to the biologics pathway.

Notable Pipeline

- Humira®: Pfizer's PF-06410293 (BsUFA October–December 2019)
- Neulasta®: Apotex's Lapelga (pending); Novartis's Ziextenzo® (10/03/2019)
- Neupogen®: Apotex (BsUFA pending), Kashiv Pharma (BsUFA pending), Tanvex BioPharma (BsUFA 08/01/2019)
- Remicade®: Amgen's ABP-710 (BsUFA 10/17/2019)

Table 1. Current Listing of FDA Approved Biosimilars

Brand Name (nonproprietary name)	Manufacturer	Approval Date	Commercially Available?
Avastin® (Genentech)			
Mvasi™ (bevacizumab-awwb)	Amgen	September 2017	✓
Zirabev™ (bevacizumab-bvzr)	Pfizer	June 2019	–
Enbrel® (Amgen)			
Erelzi™ (etanercept-szzs)	Sandoz	August 2016	–
Eticovo™ (etanercept-ykro)	Samsung Bioepis/Merck	April 2019	–
Epogen® (Amgen) / Procrit® (Janssen)			
Retacrit™ (epoetin alfa-epbx)	Pfizer/Hospira	May 2018	✓
Herceptin® (Genentech)			
Ogivri™ (trastuzumab-dkst)	Mylan	December 2017	–
Herzuma® (trastuzumab-pkrb)	Celltrion/Teva	December 2018	–
Ontruzant™ (trastuzumab-dttb)	Samsung Bioepis/Merck	January 2019	–
Trazimera (trastuzumab-qyyp)	Pfizer	March 2019	–
Kanjinti™ (trastuzumab-anns)	Amgen	June 2019	✓
Humira® (AbbVie)			
Amjevita (adalimumab-atto)	Amgen	September 2016	–
Cyltezo® (adalimumab-adbm)	Boehringer Ingelheim	August 2017	–
Hyrimoz™ (adalimumab-adaz)	Sandoz	October 2018	–
Hadlima™ (adalimumab-bwwd)	Samsung Bioepis/Merck	July 2019	–
Neupogen® (Amgen)			
Zarxio® (filgrastim-sndz)	Sandoz	March 2015	✓
Nivestym™ (filgrastim-aafi)	Pfizer	July 2018	✓
Neulasta® (Amgen)			
Fulphila® (pegfilgrastim-jmdb)	Mylan	June 2018	✓
Udenyca™ (pegfilgrastim-cbqv)	Coherus	November 2018	✓
Remicade® (Janssen)			
Inflectra® (infliximab-dyyb)	Pfizer/Celltrion	April 2016	✓
Renflexis® (infliximab-abda)	Merck	May 2017	✓
Ixifi™ (infliximab-qbtx)*	Pfizer	December 2017	–
Rituxan® (Genentech)			
Truxima® (rituximab-abbs)	Celltrion/Teva	November 2018	–
Ruxience™ (rituximab-pvvr)	Pfizer	July 2019	–

*Pfizer already has Inflectra® on the market and has not announced plans to launch Ixifi.
Reference products are bolded and noted in blue highlight.
Also available are Eli Lilly's Basaglar® insulin glargine injection, a follow-on agent to Sanofi's Lantus® insulin glargine injection, and Sanofi's Admelog® insulin lispro injection, approved as a follow-on product to Eli Lilly's Humalog®.

Artificial Intelligence:

Advances in Healthcare Innovation

The growing artificial intelligence (AI) trend has the potential to impact many facets of the healthcare industry.

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Defined as the use of computer systems to perform tasks such as visual perception, speech recognition, and decision-making that normally require human intelligence, AI's potential applications within healthcare are both broad and diverse — especially as more complex subsets of AI, such as machine learning and deep learning, continue to advance — and have potential to affect all stakeholders, including patients, manufacturers, providers, and payers. AI is already emerging as part of the drug-discovery process, in medication safety and reconciliation programs, and as a diagnostic tool.

In the managed care setting, AI presents an array of opportunities from both clinical and operational perspectives. Operationally, AI can improve processes through automation, using machine learning to mimic and perform tasks in the same manner employees would which saves hours of work and increases productivity. Clinically, AI has numerous applications, including but not limited to augmenting clinical decision-making and diagnostic capabilities, and improving care management. Focusing on care management, AI can be utilized not only to help effectively target patients who may benefit most from clinical intervention but also to provide enhanced tools to improve care.

Current Gaps in Care Management

High-Risk Patient Identification

Care management within the managed care industry often centers on engaging the "sickest" patients. Stakeholders have defined those patients in several ways, but the determination typically depends on past medical-resource utilization or prior undesirable behavior (i.e., low adherence). Unfortunately, health systems are usually limited to targeting only the highest utilizers of healthcare services, due to resource constraints.

Pharmacy managed care stakeholders often focus on improving adherence to drug therapy to prevent negative medical outcomes. The typical approach for improving adherence itself offers several challenges (Figure 1).

Figure 1. Adherence Program Challenges

- The programs can be labor-intensive (due to analytic resources and repetitive processes).
- Adherence measures are not always truly reflective of patient actions.
- Interventions are implemented retroactively.
- The programs do not always address the root cause of nonadherence.
- Incentives are misaligned and data can be manipulated.

Typically, adherence programs are completely dependent on pharmacy-claims data sets and measurements such as proportion of days covered (PDC) or medication-possession ratio (MPR), which are based on patients filling their medications over long timeframes. Running these analyses on large data sets requires analytic expertise and often must be repeated over time. After analysis, any patients that fall below a target measurement threshold are deemed nonadherent, and these patients may be targeted for interventions. One of the biggest challenges with this approach is that interventions are coming much later than they are needed, often after negative patient behavior starts occurring or negative outcomes may have already occurred.

The measurements themselves may not be telling the whole story. For example, a prescription fill at a pharmacy does not mean the patient is using the medication appropriately or at all, nor does the PDC or MPR provide insight into any root cause of nonadherence, if the patient is not taking the medication, that could help guide an intervention. Minor variations in formulas used by different stakeholders to calculate PDC and MPR can also lead to difficulty in comparing benchmarks across populations, which make it difficult to accept adherence data at face value as reported by specialty pharmacies or other vendors without a firm understanding of the calculation method.

Patient Engagement

Traditional care management often requires clinicians to use telephonic, fax, and mail-based approaches to engage patients. Telephonic and fax campaigns have shown reach rates of 45% to 65% and 25% to 35%, respectively, yet engagement rates are only 23% to 38% and 5% to 8%, respectively.[1] Experience and interactions in these formats can often be generic and typically are not adapted to specific patient preferences and needs; thus, merely reaching patients oftentimes does not inspire further engagement from the patient. Furthermore, care management teams may often be limited in scope of knowledge; for example, those with clinical expertise may lack insight into benefit structure or personal medical history, which can prevent personalized interventions from occurring.

The Impact of AI

AI creates exciting and expansive possibilities for the future of care management and patient engagement. AI can offer the tools and ability to identify high-risk patients and coordinate and customize care accordingly. AI can also enable engagement customization to the patient's own preference and needs—a convenience that may result in an improvement in the overall patient experience.

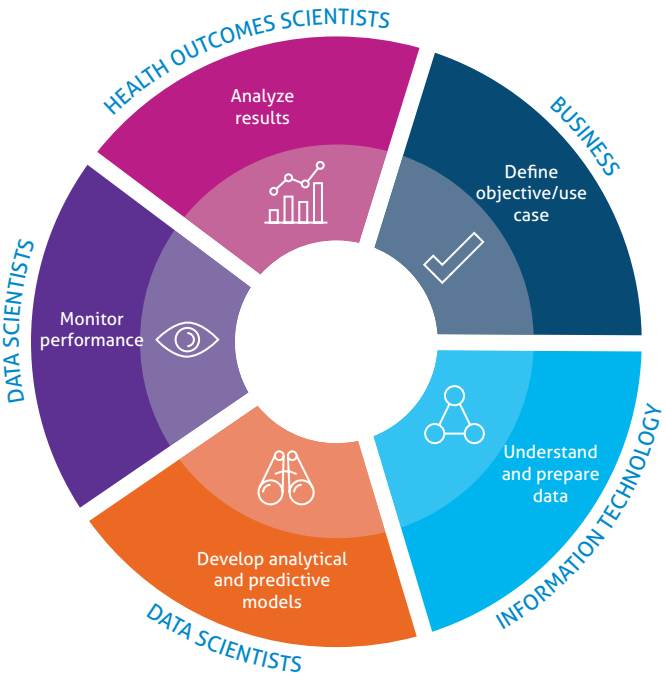
Predictive Analytics

Predictive tools leveraging machine learning allow for improved forecasting, timely care, and targeted resource utilization with a better focus on preventive treatment. Applications can include personalized formularies, more accurate budget modeling and forecasting, clinical outcome prediction, and preventive interventions. The key to predictive accuracy is the quality of the clinical data; data suficient for analysis has become available and, thus, predictive modeling in healthcare has improved.

Predictive analytics provide a variety of benefits in comparison to traditional measurements, including encouraged collaboration across the care continuum, more efficient and productive care management, identification of at-risk patients who are likely to be missed, supported operational decision-making, and improved readiness for value-based payment.[2]

In order to develop and deploy robust predictive analytics, people and process play critical roles, along with enabling technology (Figure 2). The process begins with a purpose — a reason to act — such as needing to proactively identify people at risk for nonadherence, medication misuse (e.g., opioid abuse), or conditions and therapies that will lead to increased costs. Following the identification of the problem or use case comes a multidisciplinary approach to developing robust predictive analytics that includes data preparation, model development and deployment, performance monitoring, and, finally, evaluation of effectiveness. The cycle continues to repeat through recalibrations based on new information and adjustments. The most important factor in this process is having both deep domain expertise to develop the right analytical solution for the appropriate problem and the right skills and knowledge to effectively and efficiently provide information to clinical partners and augment their intelligence.

Figure 2. Predictive Analytic Process



High-Risk Patient Identification

AI can cast a wide net to target highest-risk patients through at-risk or high-risk patient identification. Predictive algorithms developed using historical data can fuel high-accuracy models that efficiently identify at-risk or high-risk patients. Typically, these models involve five interacting dimensions, including:

- Healthcare system factors
- Patient-related factors
- Therapy-related factors
- Condition-related factors
- Economic and social factors

Predictive analytics can identify both very specific subsets of at-risk patients, such as those identified by opioid misuse or nonadherence, and at-risk groups on a much larger scale. One study developed and validated a tool for predicting patients at risk of becoming high-cost healthcare users, and results suggested that the model performed very well, predicting the top 5% of high-cost healthcare users.[3]

Stakeholders can harness data derived from predictive modeling to prioritize patients based on risk and needs, generate personalized interventions, and recommend follow-ups as needed.[4] Ultimately, the data helps providers and healthcare systems learn what the most effective interventions are and where resources should be deployed for the best overall outcomes.[4] When one predictive model was implemented in a healthcare system, results showed that of patients readmitted during the study timeframe, 45% had been identified as high-risk using predictive tools, compared to 26% using a manual process.[2] The predictive modeling allowed for earlier intervention, reduction of unnecessary cost and utilization, and prevention or better management of conditions and complications.[2]

Payers can also use predictive models to improve financial and clinical outcomes; in fact, health plans can often have more mature and accurate predictive analytics than health systems. Advanced analytics allow payers to leverage a variety of data to create a complete predictive model. Aggregating these data can help to deliver highly accurate predictions of at-risk members to help prevent unnecessary cost and improve member outcomes.

Improving the Patient Experience

Around 85% of business-customer interactions will occur without human interaction within the next five years; if that prediction is applied to the healthcare market, patients will likely soon demand the immediate answers and communication from healthcare providers that they have grown accustomed to in other markets.[5] A recent survey of 2,000 healthcare consumers showed that 55% of patients are open to virtual care visits and 58% are willing to give their providers access to health data through mobile apps. Additionally, 30% of patient respondents said they wanted their doctors to communicate with them more frequently, which may suggest an opportunity for engagement technologies such as mobile chat or other digital platforms to fill these needs.[6]

AI may lead to increased and advanced patient engagement by transitioning from traditional means of patient communication such as telephone, fax, or mail to updated methods such as chatbots, interactive voice technology, facial recognition, and digital platforms. When providers and organizations deliver care management solutions through digital technologies, the technology can create a positive-feedback loop.[7] Patients can receive more timely, personalized support and engage with their clinicians more effectively and more often. This increased engagement can lead to higher-quality data that will assist in better anticipating a patient's needs and providing customized and effective outcomes. AI can be used to assess patient-provider interaction patterns and identify opportunities to satisfy unmet needs of specific patients; using these insights, AI will drive more impactful and meaningful patient engagement.[5]

Other Digital Technologies Impacting Patient Adherence and Engagement

Real-time targeted interventions create opportunity as well, including facial and pill recognition and digital pills. In 2017, the U.S. Food and Drug Administration (FDA) gave its first approval of a digital pill: MyCite® (Abilify), for the treatment of schizophrenia and bipolar disease. The digital pill monitors a patient's usage by activating a tiny sensor inside the pill when it comes in contact with stomach acid.[8] The sensor transmits a signal to a patch along the patient's rib cage, which in turn connects to a mobile application resulting in a digital record of the consumption of the medication. Researchers are looking for digital adherence tools, including mobile technologies, digital pillboxes, and ingestible sensors, to manage and monitor tuberculosis therapy as well.[9] While research on treatment outcomes is limited, these interventions may serve a variety of functions in the management of this population, including reminding patients to take medication, facilitating digital observation of consumption, and compiling real-time patient-dosing reports that can help guide faster clinician intervention when needed.[9]

Implementing AI: Current and Future Challenges

Typically, the healthcare industry can be considered slow to adopt change compared to other industries, especially when it comes to technology. The stakes are high in healthcare; thus, any technologies or changes must be well-vetted and proven prior to implementation. Additionally, privacy concerns surrounding patient-health information and data add more hesitance to adopting change. However, considering that the current healthcare delivery system has significant unmet needs for stakeholders, specifically patients, the industry may be more inclined to introduce new technologies, adopt changes, and disrupt the system to improve outcomes. The ubiquity of networked smart devices in society coupled with the acclimation to convenience and at-home services creates the perfect environment to introduce AI interventions to this population.[10]

Figure 3. Best Practices to Incorporate AI

However, although the opportunities AI presents can be exciting, they may also be approached with some hesitation by those who are not ready to accept these changes. As with any wide-reaching transition, incorporating AI into patient care and management will present several challenges that should be strategically addressed to ensure success.

Pilot programs or initiatives can help assess the compatibility of the population, stakeholders, and technology, and evaluate outcomes before widely implementing a program or service. When implementing AI technology through a pilot program or other initiative, a specific, structured process should be followed to ensure changes are incorporated effectively and appropriately. Organization of available resources and data capabilities, along with managing the scale of the initiative (i.e., starting small), can be key to a successful start. With all the excitement that advances in technologies bring, managing expectations and setting clear, realistic objectives is crucial to implementing a program and understanding and evaluating its outcomes. Finally, programs and initiatives must be evaluated, assessed, and optimized so the AI implementation can grow slowly and steadily in a stepwise manner (Figure 3). When incorporating AI, whether through a pilot program or another initiative, hesitance from stakeholders may arise and must be addressed to ensure smooth implementation and effective outcomes.

Stakeholder Concerns

Patients: Willingness and Comfort

Patients will want to know how these technologies will improve their experience (i.e., proven success), what incentives are presented, whether their information will remain private and protected, and what barriers to access exist (i.e., lack of education, capability, or willingness to use AI tools). Despite any hesitation that may exist, healthcare consumers are growing more comfortable with the use of technology. From 2016 to 2018, healthcare consumers' comfort with the use of technology to manage health increased across all technological categories, including websites, mobile applications, wearable technology, smart scales, and remote consultation and monitoring.[11] Survey results suggested consumers were likely to use health services powered by intelligent technology to get after-hours information, help navigate healthcare services, provide lifestyle advice, seek advice about management of a diagnosed serious illness, analyze medical history, get emergency advice, and diagnose symptoms.[11] Another survey showed that 42% of patients are comfortable with doctors using AI to make healthcare decisions.[5] While undoubtedly not all patients will be prepared to engage in such technology, the growing comfort is a positive sign that these services may be effective moving forward.

Payers: Infrastructure Challenges and Fragmented Data

Payers will likely want to analyze whether (and how) the addition of AI will improve their bottom line; whether the technology is validated, accurate, explainable, and compliant; how the technology will be supported and financed; and how the technology and any associated incentives will fit within the benefit structure. However, in order to implement any effective AI solutions, the necessary data must be available to support. An estimated 75% of available healthcare data is unstructured.[12] To develop efficient and accurate predictive AI technologies, plentiful categorized data is essential. The multiple unstructured and disconnected streams of data in healthcare (i.e., medical and pharmacy claims, prior authorizations, gene profiling, and electronic health records) present a significant challenge. Obtaining and categorizing data can be costly but must be underaken in order to take advantage of the predictive value of AI technologies.

Providers: Autonomy in Practice and Confidence in Technology

Studies suggest that more than 50% of healthcare providers think face-to-face interaction is the most important patient-engagement strategy; considering that statistic, some providers may be hesitant to accept AI, as they may feel it will replace that face time with patients.[13, 14] Providers also feel that healthcare technology can and does hinder that valued face time.[14] There may also be some provider hesitance to accept support diagnostics and AI assistance if they perceive it as a threat to their autonomy around diagnostic and clinical treatment decision-making; however, providers' concerns may be addressed by a focus on AI tools that provide valuable data providers can use to support their decisions rather than dictate them.

Moving Forward

Given the rapidly evolving world of technology and the prevalence of AI, further disruption to the healthcare industry seems inevitable. AI opens a wealth of opportunities to improve both clinical and financial outcomes and change the face of care management. If approached and incorporated strategically, these changes can help improve the landscape of healthcare for patients, providers, and payers.

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HIV Update:

Therapeutic Advances and Managed Care Implications

More than 36.9 million people worldwide are living with human immunodeficiency virus (HIV), which, since the start of the epidemic in 1981, has infected more than 70 million people and led to the deaths of approximately 35 million people worldwide.[1]

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In 2017 alone, 940,000 people died of HIV-related illness.[1] The disease affects 0.8% of individuals between 15 and 49 years of age; however, there is a wide variance in incidence geographically, with much higher rates in certain African countries.[1] Those who experience the progression of HIV to acquired immunodeficiency syndrome (AIDS) have an average life expectancy of three years if the disease goes untreated.[1] HIV is transmitted through human fluids, including blood, semen or pre-ejaculate fluid, rectal fluid, vaginal fluid, and breast milk.[2] These fluids may be transmitted from an HIV-positive individual to an HIV-negative individual through contact with a mucous membrane, including the vagina, mouth, rectum, or tip of the penis, as well as through open sores or cuts or injection into the skin.[2] The most common routes of transmission are through sexual contact or sharing of used needles for injection drugs.[2] Though they pose a much lower risk of infection, additional routes of transmission include pregnancy, childbirth, and breastfeeding of a child, as well as exposure of healthcare workers to needles used in HIV patients.

HIV is a retrovirus that targets the CD4 T cells.[3] Individuals infected with HIV may experience flulike symptoms lasting for several weeks, including chills, fever, sweating, weakness, weight loss, and swelling of the lymph nodes.[3] This phase of the disease is referred to as acute HIV infection.[3] Patients in this period are extremely contagious, as they have a high viral load and are typically unaware of their HIV infection status.[3] This acute phase is followed by a period of dormancy, when the HIV reproduction rate decreases and patients are typically asymptomatic.[3] The disease may remain dormant for up to a decade while untreated, but initiation of antiretroviral treatment (ART) may allow this dormancy period to last much longer, delaying the progression to AIDS.[3, 4] ART may also decrease the viral load to undetectable levels, minimizing the risk of transmitting HIV.[3, 4] If patients are untreated or inadequately treated, the latency period eventually ends and the patient progresses to AIDS.[3] As the name suggests, AIDS is associated with an immune system that has been severely damaged by HIV and is unable to fight off infections.[3] AIDS is diagnosed when CD4 T-cell count drops below 200 cells/mm or an individual with HIV has experienced opportunistic infections — infections that develop following exposure to pathogens encountered in everyday life that would not typically cause infection

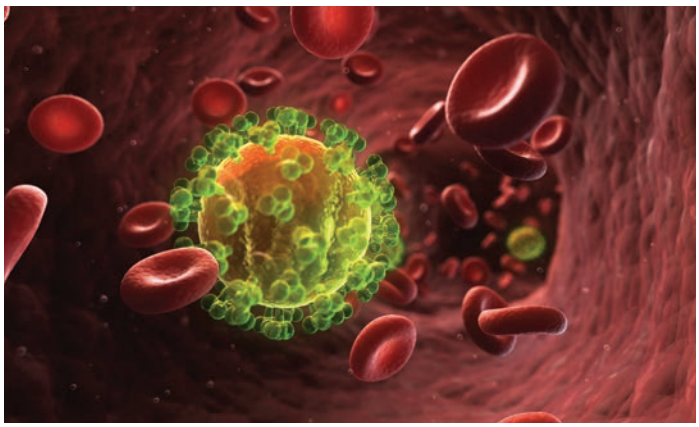
due to natural immune response.[3, 4] Opportunistic infections tend to present with more-severe symptoms in individuals with AIDS.[3]

First introduced in the 1990s, ART has since become the standard of care for patients with HIV. Immediate initiation of ART after an HIV diagnosis is critical to reduce morbidity and mortality, help prevent the progression to AIDS, and reduce the risk of transmission to other healthy individuals. Also key to reducing HIV transmission are earlier identification — which entails both screening all individuals who are at increased risk and implementing a rapid initiation protocol in those who test positive — and the promotion of medication adherence and patient monitoring.[3, 4] It is crucial to design medication regimens that work for the patient, taking into account patient-specific factors and values. These may include comorbid psychiatric conditions, substance abuse, the side-effect profile, and drug interactions with other medications the patient is taking, as well as social determinants of care such as the patient's housing situation and other social supports.[4]

Treatment Guidelines

Treatment-naïve patients in whom ART is indicated are generally initiated on a combination of two nucleoside reverse transcriptase inhibitors (NRTIs) and a third agent — either an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) — along with a pharmacokinetic booster such as cobicistat or ritonavir.[4] INSTI-based regimens are generally preferred for the majority of patients due to ease of use, clinical efficacy, and safety.[4] The preferred INSTI-based regimens are bictegravir/tenofovir alafenamide/emtricitabine, dolutegravir/abacavir/lamivudine, if HLA-B*5701 negative, and dolutegravir/tenofovir/emtricitabine.[4] There is a concern regarding dolutegravir causing neural tube defects in infants born to women taking the drug; as such, alternative treatments may be preferable in women of reproductive age who are not using effective contraception or are in the early stages of pregnancy.[4] Dolutegravir may be used after the first trimester of pregnancy after the neural tube has formed.[5] Combination therapies atazanavir/cobicistat, darunavir/cobicistat, and elvitegravir/cobicistat are also not recommended during pregnancy due to changes in pharmacokinetics that lower the level of drug exposure and may increase the risk of virologic failure.[5]

Alternative regimens are considered second-line or later, as they may have less clinical data supporting their use or clinical disadvantages such as lower efficacy or increased incidence of adverse effects.[4] These alternative regimens include some INSTI-based options, as well as boosted PI and NNRTI-based regimens.[4] In certain clinical situations, these agents may be necessary or advantageous for use, depending on adverse effects, differences in pharmacokinetics and/or pharmacodynamics, drug interactions, and resistance to different components of ART regimens.[4]



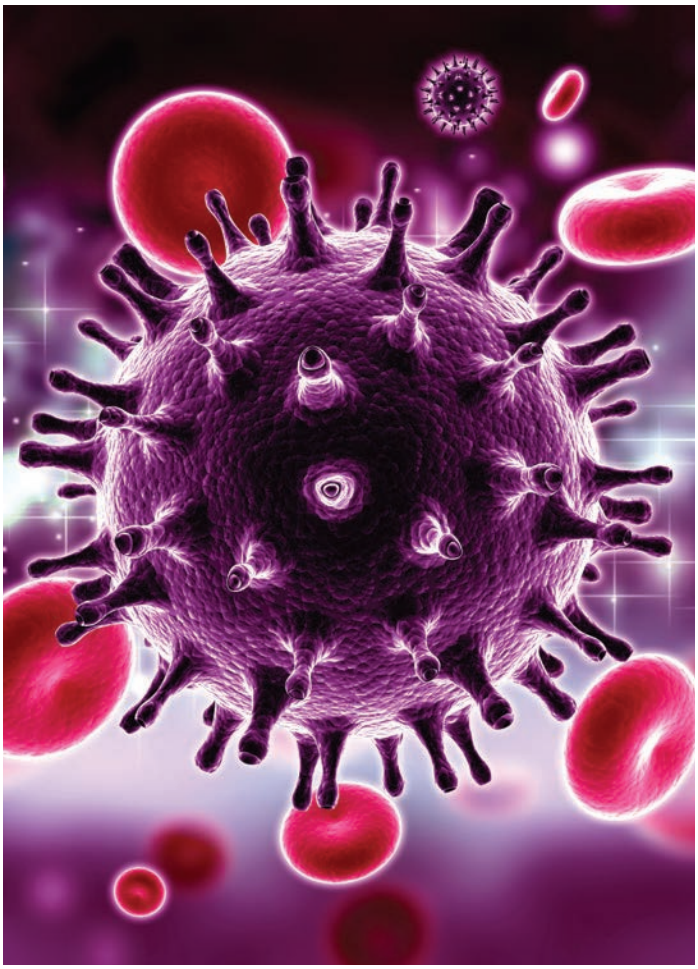
For example, some ART drugs and HCV direct-acting antivirals (DAAs) have the potential for clinically significant drug-drug interactions when used concomitantly. Before starting an HCV DAA, there are some cases in which the ART regimen may need to be modified to reduce the drug-drug-interaction potential.[5] These options are still important to consider when providing patient-centered care to promote optimal medication adherence and lower discontinuation rates.[4] It is also important to consider the pill burden associated with the selected regimen, as adherence decreases when the number of daily medications a patient must take increases.[4] For example, INSTI-based regimens containing bictegravir or dolutegravir have a lower pill burden than raltegravir-based options.[4] Combination products that have multiple ART components coformulated into one dosage form represent an important treatment option to reduce pill burden.[4] Although combination products can make dose adjustments more challenging, they may be advantageous for patients who are unable to maintain optimal medication adherence when the pill burden is higher.[4]

Recent Treatment Advances

Several new agents have been released over the past few years, including doravirine (Pifeltro™; Merck) and ibalizumab-uiyk (Trogarzo™; TaiMed Biologics Inc.).[6, 7]

Doravirine

Doravirine, a member of the NNRTI class, was recently approved by the U.S. Food and Drug Administration (FDA) both individually and in a combination tablet, coformulated with lamivudine



and tenofovir disoproxil fumarate.[7] In clinical trials, doravirine was found to be noninferior to darunavir in combination with ritonavir and was associated with fewer adverse effects and a more favorable lipid profile.[7] This agent may have some advantages: It may be taken with or without food, it does not interact with acid-reducing agents such as proton pump inhibitors, it has fewer adverse effects than efavirenz, and it has a novel resistance pathway.[6] This once-daily, single-tablet option was also found to be noninferior to tenofovir/emtricitabine/efavirenz.[7] As such, the doravirine-based combination regimen may be considered to reduce pill burden when other agents are not preferred. It appears to have some advantages over other NNRTI-based regimens as well; however, its role relative to INSTI-based regimens is unclear, as a comparison has not been tested in clinical trials.[6] Despite the lack of comparative data, it may still have a clinically important role for those who cannot tolerate INSTI-based regimens, those taking concurrent acid-reducing agents, and those resistant to other options.

Ibalizumab-uiyk

Ibalizumab-uiyk is a monoclonal antibody that targets domain two of the CD4 T-cell receptor, leading to conformational changes in the receptor and preventing the binding of HIV.[8] Although classified as an entry inhibitor, it has a unique mechanism of action based on its specific binding site.[8] The binding of ibalizumab-uiyk does not lead to an immune response at CD4, and it maintains or increases CD4 T-cell count without leading to immunosuppression, giving it a distinct clinical advantage over other entry inhibitors.[8]

Iblizumab-uiyk was initially hypothesized to have a potential role as monotherapy, but due to resistance, it appears to have much more value as a part of a patient's HIV regimen. It is administered intravenously (IV) with a loading dose, followed by an IV dose every two weeks.[8] This is an advantage over pills taken daily but does requires follow-up with the physician regularly, which may be difficult for patients to fit into their schedules.[8] Ibalizumab-uiyk has few side effects but may cause a slight rash and diarrhea.[7] Since it is not an immunosuppressant, patients are not at greater risk of opportunistic infections while using this agent.[8]

HIV Pipeline

Several new ARTs are currently in clinical development, including cabotegravir/rilpivirine, fostemsavir, albuvirtide, and leronlimab.[9]

Cabotegravir/rilpivirine

Cabotegravir/rilpivirine is a monthly maintenance injection that contains both an INSTI and an NNRTI. Early data suggests it may be able to offer comparable efficacy to a triple-agent daily regimen, which may mean a significant adherence advantage, as it only needs to be injected intramuscularly once monthly rather than taken every day.[10] A new drug application (NDA) for cabotegravir/rilpivirine has been submitted to the FDA and is currently under review.[10] In the Antiretroviral Therapy as Long-Acting Suppression (ATLAS) study, which evaluated switching patients from the standard-of-care triple-agent regimens to cabotegravir/rilpivirine, investigators observed similar rates of viral suppression with cabotegravir/rilpivirine compared to a continued standard oral regimen.[11] Treatment with cabotegravir/rilpivirine was found to be noninferior, with no significant differences in efficacy between the two groups.[11] Three patients experienced virologic failure — two of whom had been identified as having pre-existing NNRTI resistance and all of whom had HIV-1 A subtypes, which warrants further investigation to determine whether this is a potential

resistance mechanism.[11] Patients reported a statistically significant improvement in satisfaction levels while using the long-acting regimen.[11]

The ongoing First Long-Acting Injectable Regimen (FLAIR) study compares patients who switched from abacavir/dolutegravir/lamivudine to cabotegravir/rilpivirine with patients who were maintained on abacavir/dolutegravir/lamivudine.[12, 13] At 48 weeks, cabotegravir/rilpivirine had reached the noninferiority endpoint, with similar virologic suppression rates exhibited between the two groups.[12] As in the ATLAS study, all patients who experienced virologic failure had NNRTI and INSTI resistance and HIV-1 subtype A1.[12, 13] Patients also expressed statistically significant improvements in satisfaction after switching to cabotegravir/rilpivirine, with 90.8% of patients preferring this option to oral therapy.[12] If clinical development continues on the current trajectory, FDA review of an NDA may be expected in 2023.[14]

Fostemsavir

The prodrug fostemsavir (active form temsavir) is a gp120 attachment inhibitor that works to block HIV from binding to immune cells.[15] Phase III trials are currently ongoing, and no NDA is currently pending FDA review.[9] Fostemsavir has a favorable adverse-effect profile, and treatment may be advantageous in patients who have failed other options.[15] The Phase III Fostemsavir in Heavily Treatment-Experienced HIV-1-Infected Participants (BRIGHTE) study is evaluating fostemsavir in combination with existing ART compared to placebo in combination with ART.[15] The patients included in the study — all of whom had treatment-resistant HIV-1 and were unable to maintain virologic suppression on optimized background therapy — were randomized to receive either fostemsavir or placebo with optimized background therapy for eight days, followed by fostemsavir with optimized background therapy in an open-label fashion thereafter.[15, 16] At 48 weeks, 54% of patients were able to achieve virologic suppression with fostemsavir in combination with their failing background ART regimen.[15, 16] Investigators observed a statistically significant improvement in CD4 cell count, which continued to trend upwards throughout the 48-week study.[15] The study results suggest that fostemsavir may have an important role in patients who have inadequate responses to traditional treatment regimens.[15, 16] An NDA is expected to be filed with the FDA before the end of 2019.[11]

Albuvirtide

Albuvirtide, a fusion inhibitor currently undergoing Phase III trials,[9] exerts its pharmacologic effect by binding to the gp41 envelope protein of HIV and preventing it from binding the immune cells.[17, 18] The Phase III Test Albuvirtide in Experienced Patients (TALENT) study is evaluating albuvirtide/lopinavir/ritonavir compared to emtricitabine/tenofovir disoproxil fumarate/lopinavir/ritonavir in patients who are failing first-line therapy.[17] Currently available data is promising in that it shows noninferiority to the second-line treatment and a favorable safety profile.[17] At 48 weeks, 80.4% of patients receiving the albuvirtide-based regimen had HIV-1 RNA less than 50 copies/mL, compared to 6% of patients in the control group.[17] The observed treatment difference at the time of the analysis had not yet reached statistical significance, but the noninferiority criteria had been met.[19, 20] Adverse effects and medication adherence were similar between the two groups, which suggests similar tolerability for both regimens.[19, 20] Although albuvirtide had more favorable renal safety compared to tenofovir disoproxil fumarate, it was associated with a greater incidence of increased cholesterol and triglycerides.[19, 20] Albuvirtide can be administered every two weeks intravenously, which has advantages and disadvantages regarding patient adherence, as previously discussed.[19, 20] If the development of albuvirtide continues on the current trajectory, market entry may be anticipated in 2022.[14]

Leronlimab

Leronlimab, a CCR5 antagonist monoclonal antibody administered as a weekly subcutaneous injection, works by attaching to the CCR5 coreceptor and causing an inability of certain HIV strains to infect cells.[21] It is being studied specifically in R5-tropic HIV virus, as it appears to be particularly effective against this strain due to its novel mechanism.[21] Investigators are currently recruiting patients for Phase III trials.[21] In Phase II trials, investigators observed minor injection-site reactions but no other serious adverse effects.[21] Market entry for leronlimab is anticipated in 2022.[14]

Managed Care Implications

With the significant focus on development of consolidated dosage forms, including single-tablet regimens and longer-acting injectables that may reduce the number of medication administrations, the convenience of ART for patients living with HIV has never been higher. Historically, health plans have encouraged the use of cost-effective options. With the focus on optimizing patient adherence to ultimately optimize patient outcomes, health plans are now expanding coverage to convenient formulations to promote the best outcomes possible. As the field grows increasingly crowded, health plans may have the opportunity to select preferred combination products.

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PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
levonorgestrel/ethinyl estradiol (Twirla®)	Agile Therapeutics	Contraception	TD	505(b)(2)	11/15/2019
RVT-802 (postnatal thymus tissue transplant)	Enzyvant; Roivant Sciences	Congenital athymia	TBA	BLA; breakthrough therapy; orphan drug; priority review; regenerative medicine advanced therapy	November–December 2019
luspatercept	Acceleron Pharma Inc.; Celgene	Beta thalassemia	SQ	BLA; fast track; orphan drug; priority review	12/04/2019
tazarotene (IDP-123)	Bausch Health	Acne	Topical	505(b)(2)	12/20/2019
vernakalant (Brinavess™)	Correvio Pharma Corp.; Algorithm S.A.L.; AOP Orphan Pharmaceuticals AG; Aspen Pharmacare Holdings Limited; ATCO Laboratories Limited; Biospifar S.A.; Chong Kun Dang Pharmaceutical Corp.; Cipher Pharmaceuticals Inc.; Eddingpharm; Logista Pharma; UDG Healthcare plc; Vianex S.A.	Atrial fibrillation	IV	Submitted	12/24/2019
cabotegravir LAP	ViiV; Shionogi & Co. Ltd.	HIV-1 infection	PO	Priority review	12/27/2019
cabotegravir and rilpivirine, long-acting (CARLA)	ViiV; Johnson & Johnson	HIV-1 infection	IM	Priority review	12/27/2019
lemborexant	Eisai Co. Ltd.	Insomnia	PO	Submitted	12/27/2019
lumateperone	Intra-Cellular Therapies Inc.; Bristol-Myers Squibb	Schizophrenia	PO	Fast track	12/27/2019
bupivacaine ER solution (Posidur®)	Durect Corporation	Postsurgical pain	SQ	Submitted	12/27/2019
icosapent ethyl (Vascepa®)	Amarin Corporation plc; Eddingpharm; HLS Therapeutics Inc.	MCE risk reduction	PO	Priority review	12/27/2019
ubrogepant	Allergan plc; Merck & Co.	Migraine treatment	PO	Submitted	December 2019
insulin aspart (Fiasp®)	Novo Nordisk A/S	T2DM (pediatrics)	SQ	Submitted	01/01/2020
semaglutide (Ozempic®)	Novo Nordisk A/S	T2DM-related CV risk reduction	PO	Submitted	01/20/2020
semaglutide (Ozempic®)	Novo Nordisk A/S	T2DM-related CV risk reduction	SQ	Submitted	01/20/2020
tazemetostat	Epizyme Inc.; Eisai Co. Ltd.	Epithelioid sarcoma	PO	Orphan drug; priority review	01/23/2020
risperidone ER microsphere (Rykindo®)	Luye Pharma Group. Ltd.	Bipolar disorder; schizophrenia	IM	Submitted	1/28/2020

PIPELINE DRUG LIST

Name	Manufacturer	Clinical Use	Dosage Form	Approval Status	Expected FDA Approval
leuprolide mesylate depot (ready-to-use) (FP-001)	Foresee Pharmaceuticals Co. Ltd.; Accord Healthcare Ltd.; MegaPharm Ltd.; TRPharm	Prostate cancer	SQ	505(b)(2)	01/29/2020
vedolizumab (Entyvio®)	Takeda Pharmaceutical Company Ltd.	UC	SQ	sBLA	December 2019–January 2020
crizanlizumab	Novartis AG	Sickle cell disease-related vaso-occlusive crisis	IV	BLA; breakthrough therapy; orphan drug; priority review	January 2020
givosiran	Alnylam Pharmaceuticals, Inc.	Porphyria	SQ	Breakthrough therapy; orphan drug; priority review	02/04/2020
avapritinib	Blueprint Medicines; CStone Pharmaceuticals	GIST	PO	Breakthrough therapy; fast track; orphan drug; priority review; real-time oncology review	02/14/2020
pembrolizumab (Keytruda®) (6-week dose)	Merck & Co.	Every 6-week dosing regimen for select oncological conditions	IV	sBLA	02/18/2020
eptinezumab	Alder BioPharmaceuticals Inc.; Teva Pharmaceutical Industries Ltd.	Migraine prevention	IV	BLA	02/21/2020
bempedoic acid (ETC-1002)	Esperion Therapeutics Inc.; Daiichi Sankyo Co. Ltd.	Dyslipidemia/ hypercholesterolemia	PO	Submitted	02/21/2020
bempedoic acid/ezetimibe (ETC-1002/Ezetimibe FDC)	Esperion Therapeutics Inc.; Daiichi Sankyo Co. Ltd.	Dyslipidemia/ hypercholesterolemia	PO	Submitted	02/26/2020
rimegepant	Biohaven Pharmaceuticals; Bristol-Myers Squibb; Catalent Inc.; Portage Biotech Inc.; Royalty Pharma AG	Migraine	PO	Priority review	02/28/2020
trifarotene (CD5789)	Galderma S.A.	Acne	Topical	Submitted	02/28/2020
budesonide/formoterol fumarate/glycopyrronium (Breztri Aerosphere)	AstraZeneca plc	COPD	Inhaled	Submitted	January–February 2020
empagliflozin/linagliptin/ metformin ER	Boehringer Ingelheim GmbH	T2DM	PO	Submitted	January–February 2020
oslidrostat	Recordati S.p.A; Novartis AG	Cushing's syndrome	PO	Orphan drug	January–March 2020
paclitaxel injection concentrate for suspension (Taclantis™)	Sun Pharma Advanced Research Company Ltd.	Breast cancer	IV	505(b)(2)	February–March 2020

Abbreviations: BLA = biologics license application; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; ER = extended release; GIST = gastrointestinal stromal tumor; HIV = human immunodeficiency virus; IM = intramuscular; IV = intravenous; MCE = major cardiac event; PO = oral; sBLA = supplemental biologics license application; SQ = subcutaneous; T2DM = Type 2 diabetes mellitus; TBA = to be announced; TD = transdermal; UC = ulcerative colitis

Nayzilam® CIV
(midazolam) nasal spray

Brief Summary of Full Prescribing Information (See Package Insert for Full Prescribing Information)
Rx Only

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS
Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.1), Drug Interactions (7.2) in Full Prescribing Information].*

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

INDICATIONS AND USAGE

NAYZILAM is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

CONTRAINDICATIONS

NAYZILAM is contraindicated in patients with:

- Known hypersensitivity to midazolam.
- Acute narrow-angle glaucoma *[see Warnings and Precautions (5.6) in Full Prescribing Information]*.

WARNINGS AND PRECAUTIONS

Risks from Concomitant Use with Opioids

Concomitant use of benzodiazepines, including NAYZILAM, and opioids may result in profound sedation, respiratory depression, coma, and death. Because of these risks, reserve concomitant prescribing of benzodiazepines and opioids for use in patients for whom alternative treatment options are inadequate.

Observational studies have demonstrated that concomitant use of opioid analgesics and benzodiazepines increases the risk of drug-related mortality compared to use of opioids alone. If a decision is made to prescribe NAYZILAM concomitantly with opioids, prescribe the lowest effective dosages and minimum durations of concomitant use, and follow patients closely for signs and symptoms of respiratory depression and sedation. Advise both patients and caregivers about the risks of respiratory depression and sedation when NAYZILAM is used with opioids *[see Drug Interactions (7.2) in Full Prescribing Information]*.

Risks of Cardiorespiratory Adverse Reactions

Serious cardiorespiratory adverse reactions have occurred after administration of midazolam. These have included respiratory depression, airway obstruction, oxygen desaturation, apnea, respiratory arrest and/or cardiac arrest, sometimes resulting in death or permanent neurologic injury. There have also been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations, particularly in patients with hemodynamic instability. Hypotension occurs more frequently in patients premedicated with a narcotic. The danger of hypoventilation, airway obstruction, or apnea is greater in elderly patients and those with chronic disease states or decreased pulmonary reserve *[see Use in Specific Populations (8.5) in Full Prescribing Information];* patients with chronic obstructive pulmonary disease are highly sensitive to the respiratory depressant effect of midazolam.

Respiratory depression was observed with the administration of NAYZILAM during clinical trials *[see Adverse Reactions (6.1) in Full Prescribing Information]*. Cardiac or respiratory arrest caused by NAYZILAM was not reported during clinical trials.

Central Nervous System Depression from Concomitant Use with Other Central Nervous System Depressants, or Moderate or Strong CYP3A4 Inhibitors

Drug products containing midazolam, including NAYZILAM, have a central nervous system (CNS) depressant effect.

Risks from Concomitant Use with Other CNS Depressants

The potential for an increased CNS-depressant effect from concomitant use with alcohol or other CNS depressants (e.g., opioids) must be considered by the prescribing physician, and appropriate recommendations made to the patient and/or caregiver *[see Warnings and Precautions (5.1) and Drug Abuse and Dependence (9.3) in Full Prescribing Information]*.

Concomitant use of barbiturates, alcohol, or other CNS depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect *[see Drug Interactions (7.3) in Full Prescribing Information]*.

Risks from Concomitant Use with Moderate or Strong CYP3A4 Inhibitors

There is a potential for prolonged sedation from concomitant use with moderate or strong CYP3A4 enzyme inhibitors because of much higher midazolam exposures *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2) in Full Prescribing Information]*.

Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including NAYZILAM, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27,863 AED-treated patients was 0.43%, compared to 0.24% among 16,029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as one week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed. The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5-100 years) in the clinical trials analyzed. Table 1 shows absolute and relative risk by indication for all evaluated AEDs.

Table 1. Risk by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events/1000 Patients	Drug Patients with Events per 1000 Patients	Relative Risk: Incidence of Drug Events in Drug Patients/ Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4
Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials for epilepsy than in clinical trials for psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing midazolam or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, the prescriber needs to consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

Impaired Cognitive Function

Midazolam, including NAYZILAM, is associated with a high incidence of partial or complete impairment of recall for several hours following an administered dose. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. It is recommended that no patient operate hazardous machinery or a motor vehicle until the effects of the drug, such as drowsiness, have subsided, and as their medical condition permits. For pediatric patients, particular care should be taken to ensure safe ambulation.

Glaucoma

Benzodiazepines, including NAYZILAM, can increase intraocular pressure in patients with glaucoma. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. NAYZILAM may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Patients with open-angle glaucoma may need to have their ophthalmologic status evaluated following treatment with NAYZILAM. NAYZILAM is contraindicated in patients with narrow-angle glaucoma.

Other Adverse Reactions

When midazolam was used for sedation, reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, and combativeness have been reported. These reactions may be caused by inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions.

ADVERSE REACTIONS

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

- Risks from Concomitant Use with Opioids *[see Warnings and Precautions (5.1) in Full Prescribing Information]*
- Risks of Cardiorespiratory Adverse Reactions *[see Warnings and Precautions (5.2) in Full Prescribing Information]*
- CNS Depression from Concomitant Use with Other CNS Depressants or Moderate or Strong CYP3A4 Inhibitors *[see Warnings and Precautions (5.3) in Full Prescribing Information]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.4) in Full Prescribing Information]*
- Impaired Cognitive Function *[see Warnings and Precautions (5.5) in Full Prescribing Information]*
- Glaucoma *[see Warnings and Precautions (5.6) in Full Prescribing Information]*
- Other Adverse Reactions *[see Warnings and Precautions (5.7) in Full Prescribing Information]*

Clinical Trials Experience

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

NAYZILAM was studied for the outpatient treatment of a single seizure cluster in 292 adult and adolescent patients with epilepsy (Study 1) *[see Clinical Studies (14) in Full Prescribing Information]*. The study was conducted in two phases; an open-label Test Dose Phase followed by a double-blind, placebo-controlled, Comparative Phase. The mean age of patients enrolled in the Comparative Phase (N=201) was 33 years, 51% were female, and 95% were White.

Table 2 lists the adverse reactions occurring in 2% or more of the NAYZILAM-treated patients and at a rate greater than the placebo-treated patients in the Comparative Phase of Study 1.

Table 2: Adverse Reactions[a] that Occurred in ≥2% of Patients (Any NAYZILAM) and Greater than Placebo in the Comparative Phase of Study 1

Body System/ Adverse Reaction	Placebo	NAYZILAM[b]			
		NAYZILAM 5 mg	Placebo + NAYZILAM 5 mg	NAYZILAM 5 mg + 5 mg	Any NAYZILAM Treatment Group
	N = 26 %	N = 91 %	N = 41 %	N = 43 %	N = 175 %
Nervous System					
Somnolence	4	10	10	9	10
Headache	0	7	0	2	4
Dysarthria	0	2	2	2	2
Application Site					
Nasal Discomfort	8	5	7	16	9
Throat Irritation	0	2	2	7	3
Rhinorrhea	0	3	0	5	3
Product Taste Abnormal	0	4	0	0	2
Eye Disorders					
Lacrimation Increased	0	1	2	2	2

[a] Adverse reactions that occurred within 2 days after NAYZILAM administration are included
[b] Patients in Study 1 were permitted to take a second, open-label dose of NAYZILAM 5 mg between 10 minutes and 6 hours following the initial blinded dose of NAYZILAM 5 mg or placebo if they experience seizure recurrence or an incomplete resolution of the episode. The Placebo + NAYZILAM 5 mg and NAYZILAM 5 mg + 5 mg columns represent patients who received a second dose of NAYZILAM 5 mg and received a blinded initial dose of placebo or NAYZILAM 5 mg, respectively.

For patients who experienced a decrease in peripheral oxygen saturation in the Test Dose Phase of Study 1, the decreases were generally transitory. Two patients (one with a history of sleep apnea and one with intercurrent seizure) with decreases in peripheral oxygen saturation in the Test Dose Phase required therapeutic supplemental oxygen.

DRUG INTERACTIONS

Table 3: Clinically Significant Drug Interactions With NAYZILAM

CYP3A4 Inhibitors	
Clinical Impact:	Concomitant use of CYP3A4 inhibitors may result in prolonged sedation because of a decrease in plasma clearance of midazolam.
Intervention:	Avoid co-administration of NAYZILAM with moderate or strong CYP3A4 inhibitors. NAYZILAM should be used with caution when co-administered with mild CYP3A4 inhibitors.
Examples:	Moderate CYP3A4 inhibitors: erythromycin, diltiazem, verapamil Strong CYP3A4 inhibitors: ketoconazole, itraconazole, clarithromycin
Opioids	
Clinical Impact:	The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression because of actions at different receptor sites in the CNS that control respiration. Benzodiazepines interact at $GABA_A$ sites and opioids interact primarily at mu receptors. When benzodiazepines and opioids are combined, the potential for benzodiazepines to significantly worsen opioid-related respiratory depression exists.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required *[see Warnings and Precautions (5.1) in Full Prescribing Information]*.
Examples:	Morphine, hydrocodone, oxymorphone, codeine, fentanyl
Other Central Nervous System (CNS) Depressants	
Clinical Impact:	Concomitant use of barbiturates, alcohol, or other CNS depressants may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect.
Intervention:	Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required *[see Warnings and Precautions (5.3) in Full Prescribing Information]*.
Examples:	Other benzodiazepines and sedatives/hypnotics, anxiolytics, tranquilizers, muscle relaxants, general anesthetics, antipsychotics, opioids, alcohol.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as NAYZILAM, during pregnancy. Encourage women who are taking NAYZILAM during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) pregnancy registry by calling 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

There are no adequate and well-controlled studies of NAYZILAM in pregnant women.

Available data suggest that the class of benzodiazepines is not associated with marked increases in risk for congenital anomalies. Although some early epidemiological studies suggested a relationship between benzodiazepine drug use in pregnancy and congenital anomalies such as cleft lip and or palate, these studies had considerable limitations. More recently completed studies of benzodiazepine use in pregnancy have not consistently documented elevated risks for specific congenital anomalies. There is insufficient evidence to assess the effect of exposure to benzodiazepines during pregnancy on neurodevelopment.

There are clinical considerations regarding exposure to benzodiazepines during the second and third trimesters of pregnancy or immediately prior to or during childbirth. These risks include decreased fetal movement and/or fetal heart rate variability, "floppy infant syndrome," dependence, and withdrawal *(see Clinical Considerations and Human Data).*

Administration of midazolam to rats and rabbits during the period of organogenesis or to rats during late pregnancy and throughout lactation at doses greater than those used clinically did not result in any apparent adverse effects on development *(see Animal Data).* However, published data for midazolam and other benzodiazepines suggest the possibility of neuronal cell death and long-term effects on neurobehavioral and immunological function in animals following prenatal or early postnatal exposure at clinically relevant doses. NAYZILAM should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. Advise a pregnant woman and women of childbearing age of the potential risk to a fetus.

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

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Infants born to mothers who have taken benzodiazepines during the later stages of pregnancy can develop dependence, and subsequently withdrawal, during the postnatal period. Clinical manifestations of withdrawal or neonatal abstinence syndrome may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhea, and vomiting. These complications can appear shortly after delivery to 3 weeks after birth and persist from hours to several months depending on the degree of dependence and the pharmacokinetic profile of the benzodiazepine. Symptoms may be mild and transient or severe. Standard management for neonatal withdrawal syndrome has not yet been defined. Observe newborns who are exposed to NAYZILAM *in utero* during the later stages of pregnancy for symptoms of withdrawal and manage accordingly.

Labor and Delivery

Administration of benzodiazepines immediately prior to or during childbirth can result in a floppy infant syndrome, which is characterized by lethargy, hypothermia, hypotonia, respiratory depression, and difficulty feeding. Floppy infant syndrome occurs mainly within the first hours after birth and may last up to 14 days. Observe exposed newborns for these symptoms and manage accordingly.

Data

Human Data

Congenital Anomalies

Although there are no adequate and well-controlled studies of NAYZILAM in pregnant women, there is information about benzodiazepines as a class. Dolovich et al. published a meta-analysis of 23 studies that examined the effects of benzodiazepine exposure during the first trimester of pregnancy. Eleven of the 23 studies included in the meta-analysis considered the use of chlordiazepoxide and diazepam and not other benzodiazepines. The authors considered case-control and cohort studies separately. The data from the cohort studies did not suggest an increased risk for major malformations (OR 0.90; 95% CI 0.61—1.35) or for oral cleft (OR 1.19; 95% CI 0.34—4.15). The data from the case-control studies suggested an association between benzodiazepines and major malformations (OR 3.01, 95% CI 1.32—6.84) and oral cleft (OR 1.79; 95% CI 1.13—2.82). The limitations of this meta-analysis included the small number of reports included in the analysis, and that most cases for analyses of both oral cleft and major malformations came from only three studies. A follow up to that meta-analysis included 3 new cohort studies that examined risk for major malformations and one study that considered cardiac malformations. The authors found no new studies with an outcome of oral clefts. After the addition of the new studies, the odds ratio for major malformations with first trimester exposure to benzodiazepines was 1.07 (95% CI 0.91—1.25).

Neonatal Withdrawal and Floppy Infant Syndrome

Neonatal withdrawal syndrome and symptoms suggestive of floppy infant syndrome associated with administration of benzodiazepines during the later stages of pregnancy and peripartum period have been reported. Findings in published scientific literature suggest that the major neonatal side effects of benzodiazepines include sedation and dependence with withdrawal signs. Data from observational studies suggest that fetal exposure to benzodiazepines is associated with the neonatal adverse events of hypotonia, respiratory problems, hypoventilation, low Apgar score, and neonatal withdrawal syndrome.

Animal Data

When midazolam (0, 0.2, 1, or 4 mg/kg/day) was administered intravenously to pregnant rats during the period of organogenesis, no adverse effects on embryofetal development were observed. The highest dose tested, which was associated with minimal evidence of maternal toxicity, is approximately 4 times the maximum recommended human dose (MRHD) of 10 mg based on body surface area (mg/m^2).

When midazolam (0, 0.2, 0.6, and 2 mg/kg/day) was administered intravenously to rabbits during the period of organogenesis, no adverse effects on embryofetal development were reported. The high dose, which was not associated with evidence of maternal toxicity, is approximately 4 times the MRHD on a mg/m^2 basis.

When midazolam (0, 0.2, 1, or 4 mg/kg/day) was administered intravenously to female rats during late gestation and throughout lactation, no clear adverse effects were noted in the offspring. The high dose, which was not associated with evidence of maternal toxicity, is approximately 4 times the MRHD on a mg/m^2 basis.

In published animal studies, administration of benzodiazepines, including midazolam, or other drugs that enhance GABAergic neurotransmission to neonatal rats has been reported to result in widespread apoptotic neurodegeneration in the developing brain at plasma concentrations relevant for seizure control in humans. The window of vulnerability to these changes in rats (postnatal days 0-14) includes a period of brain development corresponding to that taking place during the third trimester of pregnancy in humans.

Lactation

Risk Summary

Midazolam is excreted in human milk. Studies assessing the effects of midazolam in the breastfed infant or on milk production/excretion have not been performed. Postmarketing experience suggests that breastfed infants of mothers taking benzodiazepines, such as NAYZILAM, may have effects of lethargy, somnolence, and poor sucking.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NAYZILAM and any potential adverse effects on the breastfed infant from midazolam or from the underlying maternal condition.

Pediatric Use

Safety and effectiveness of NAYZILAM have been evaluated in the age group 12 to 17 years. Use of NAYZILAM in this age group is supported by evidence from an adequate and well-controlled study of NAYZILAM in adults and adolescents with seizure clusters *[see Clinical Studies (14) in Full Prescribing Information]* and pharmacokinetic and safety data from adult and pediatric patients *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*.

Safety and effectiveness in pediatric patients below the age of 12 years have not been established.

Geriatric Use

Safety and efficacy studies of NAYZILAM did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Geriatric patients have longer elimination half-lives for midazolam and its metabolites, which may result in prolonged drug exposure. Geriatric patients may have altered drug distribution; diminished hepatic and/or renal function; and subjects over 70 years of age may be particularly sensitive *[see Clinical Pharmacology (12.3) in Full Prescribing Information]*. Administration of intramuscular (IM) midazolam to elderly patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression *[see Warnings and Precautions (5.2) in Full Prescribing Information]*. In most of these cases, the patients also received other CNS depressants capable of depressing respiration, especially narcotics *[see Warnings and Precautions (5.1, 5.3) in Full Prescribing Information].* Close monitoring of geriatric patients is recommended.

Renal Impairment

Based on a population pharmacokinetic analysis of patients administered NAYZILAM, midazolam and 1-OH midazolam pharmacokinetics are expected to be similar in subjects with mild renal impairment when compared to normal subjects. Safety and efficacy studies of NAYZILAM did not include patients with severe renal impairment and there were not enough subjects with moderate renal impairment in clinical studies for population pharmacokinetic analysis. Patients with moderate and severe renal impairment may have slower elimination of midazolam and its metabolites, which may result in prolonged drug exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

Congestive Heart Failure

Patients with congestive heart failure eliminate midazolam more slowly, which may result in prolonged drug exposure *[see Clinical Pharmacology (12.3) in Full Prescribing Information].*

DRUG ABUSE AND DEPENDENCE

Controlled Substance

NAYZILAM contains the benzodiazepine midazolam, a Schedule IV controlled substance under the Controlled Substances Act.

Abuse

Benzodiazepines, such as midazolam, may be subject to abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. Available data concerning the drug abuse and dependence potential of midazolam suggest that its abuse potential is at least equivalent to that of diazepam.

The pharmacological profile of NAYZILAM is similar to that of other benzodiazepines listed in Schedule IV of the Controlled Substance Act, particularly in its potentiation of GABAergic transmission through its action on $GABA_A$ receptors, which leads to sedation and somnolence.

Midazolam was actively self-administered in primate models used to assess the positive reinforcing effects of psychoactive drugs. Midazolam produced physical dependence of a mild to moderate intensity in cynomolgus monkeys after 5 to 10 weeks of administration.

Assessment of the abuse-related subjective effects comparing NAYZILAM to oral midazolam syrup was conducted in adult subjects with a history of benzodiazepine recreational drug use. No statistically significant or clinically-relevant differences in subjective positive effects (i.e., Drug Liking, Overall Drug Liking, Take Drug Again, and High) were observed between NAYZILAM and oral midazolam syrup. However, subjective positive effects on all these measures were significantly greater for NAYZILAM than for placebo confirming that NAYZILAM has abuse potential. Somnolence occurred at a similar rate in both midazolam groups, but euphoric mood occurred at a greater rate in NAYZILAM (4 to 16%) compared to the oral midazolam syrup (4 to 8.5%).

Dependence

Physical dependence is a state of adaptation that is manifested by a specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood levels of the drug, and/or administration of an antagonist.

Benzodiazepines can cause physical dependence. Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug. Withdrawal symptoms (i.e., convulsions, hallucinations, tremors, abdominal and muscle cramps, vomiting, and sweating), similar in characteristics to those noted with barbiturates and alcohol, have occurred following abrupt discontinuation of midazolam following chronic administration.

Chronic Use

NAYZILAM is not recommended for chronic, daily use as an anticonvulsant because of the potential for development of tolerance to midazolam. In clinical trials, patients were treated with NAYZILAM no more frequently than every 3 days.

Chronic daily use of benzodiazepines may increase the frequency and/or severity of tonic-clonic seizures, requiring an increase in the dosage of standard anticonvulsant medication. In such cases, abrupt withdrawal of chronic benzodiazepines may also be associated with a temporary increase in the frequency and/or severity of seizures.

OVERDOSAGE

Symptoms

The manifestations of midazolam overdosage reported are similar to those observed with other benzodiazepines, including sedation, somnolence, confusion, impaired coordination, diminished reflexes, coma, and untoward effects on vital signs.

Treatment

Treatment of midazolam overdosage is the same as that followed for overdosage with other benzodiazepines. Respiration, pulse rate, and blood pressure should be monitored and general supportive measures should be employed. Attention should be given to the maintenance of a patent airway and support of ventilation, including administration of oxygen. An intravenous infusion should be started. Should hypotension develop, treatment may include intravenous fluid therapy, repositioning, judicious use of vasopressors appropriate to the clinical situation, if indicated, and other appropriate countermeasures. There is no information as to whether peritoneal dialysis, forced diuresis, or hemodialysis are of any value in the treatment of midazolam overdosage.

Flumazenil, a specific benzodiazepine-receptor antagonist, is indicated for the complete or partial reversal of the sedative effects of benzodiazepines and may be used in situations when an overdose with NAYZILAM is known or suspected. There are anecdotal reports of adverse hemodynamic responses associated with midazolam following administration of flumazenil to pediatric patients. Prior to the administration of flumazenil, necessary measures should be instituted to secure the airway, assure adequate ventilation, and establish adequate intravenous access. The reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients. The prescriber should be aware of a risk of seizure in association with flumazenil treatment, particularly in long-term benzodiazepine users. The administration of flumazenil in cases of benzodiazepine overdose can lead to withdrawal and adverse reactions, including increased seizures. Its use in patients with epilepsy is typically not recommended.

PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Medication Guide and Instructions for Use) and Patient Counseling Information section in the Full Prescribing Information available at www.NAYZILAM.com or at UCBCares 1-844-599-CARE (2273).

Manufactured for:
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Nayzilam® CIV
(midazolam) nasal spray

The First Nasal Spray Indicated for the Treatment of Seizure Clusters

Brought to You by UCB, a Leader in Epilepsy

NAYZILAM® (midazolam) nasal spray CIV is a benzodiazepine indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 12 years of age and older.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS: NAYZILAM is contraindicated in patients with acute narrow-angle glaucoma.

RISKS FROM CONCOMITANT USE WITH OPIOIDS
Concomitant use of benzodiazepines, including NAYZILAM, and opioids may result in profound sedation, respiratory depression, coma, and death.

- **Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.**
- **Limit dosages and durations to the minimum required.**
- **Follow patients for signs and symptoms of respiratory depression and sedation.**

RISKS OF CARDIORESPIRATORY ADVERSE REACTIONS: Serious cardiorespiratory adverse reactions have occurred after administration of midazolam. Warn patients and caregivers about the risks of respiratory depression, cardiac and respiratory arrest. Respiratory depression was observed with the administration of NAYZILAM during clinical trials. Cardiac or respiratory arrest caused by NAYZILAM was not reported during clinical trials.

CENTRAL NERVOUS SYSTEM DEPRESSION FROM CONCOMITANT USE WITH OTHER CENTRAL NERVOUS SYSTEM DEPRESSANTS, OR MODERATE OR STRONG CYP3A4 INHIBITORS: Drug products containing midazolam, including NAYZILAM, have a central nervous system (CNS) depressant effect.

RISKS FROM CONCOMITANT USE WITH OTHER CNS DEPRESSANTS: NAYZILAM may cause an increased CNS-depressant effect when used with alcohol or other CNS depressants (e.g., opioids). Warn patients and caregivers that the use of NAYZILAM in combination with alcohol or other CNS depressant drugs may increase the risk of hypoventilation, airway obstruction, desaturation, or apnea and may contribute to profound and/or prolonged drug effect.

RISKS FROM CONCOMITANT USE WITH MODERATE OR STRONG CYP3A4 INHIBITORS: Concomitant use of NAYZILAM with moderate or strong CYP3A4 enzyme inhibitors may result in prolonged sedation because of a decrease in plasma clearance of midazolam. Caution patients against engaging in hazardous occupations requiring mental alertness, such as operating machinery, driving a motor vehicle or riding a bicycle until they have completely returned to their level of baseline functioning.

SUICIDAL BEHAVIOR AND IDEATION: Antiepileptic drugs (AEDs), including NAYZILAM, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Monitor patients treated with NAYZILAM for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Advise patients and caregivers to be alert for these behavioral changes and to immediately report them to the healthcare provider.

IMPAIRED COGNITIVE FUNCTION: Midazolam, including NAYZILAM, is associated with a high incidence of partial or complete impairment of recall for several hours following an administered dose. Counsel patients on when they can engage in activities requiring complete mental alertness, operate hazardous machinery, or drive a motor vehicle after taking NAYZILAM.

GLAUCOMA: Benzodiazepines, including NAYZILAM, can increase intraocular pressure in patients with glaucoma. NAYZILAM may be used in patients with open-angle glaucoma only if they are receiving appropriate therapy NAYZILAM is contraindicated in patients with narrow-angle glaucoma.

ADVERSE REACTIONS: In the randomized, double-blind, placebo-controlled trial, the most common adverse reactions (≥5% in any NAYZILAM treatment group) were somnolence, headache, nasal discomfort, throat irritation, and rhinorrhea.

NAYZILAM is a Schedule IV controlled substance.

Please see the NAYZILAM brief summary on pages [45-49] and refer to the full Prescribing Information at www.nayzilam.com.

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