OPTUMRx®

OptumRx Drug Pipeline Insights Report

Q3 2019

Five drugs in the pharmaceutical pipeline anticipated to make the biggest impact

An Introduction

from Sumit Dutta, Chief Medical Officer at OptumRx

Our responsibility at OptumRx is to help ensure members and clients take appropriate and cost-effective medications that improve health outcomes and lower overall medical costs.

As a pharmacy care services company, our clinical foundation is what drives our drug formulary design and management. To inform that process, we have a dedicated Clinical Pipeline team that actively monitors drug developments based on a wide range of professional resources, as well as our ongoing insight into pharmaceutical companies' drug development programs.

In this Q3 2019 Drug Pipeline Insights Report, we look at several drugs expected to be reviewed and approved by the U.S. Food & Drug Administration (FDA) in the months ahead. Using our unique position in working with stakeholders across the health care system, we anticipate that these five drugs will likely have a significant impact in terms of their clinical differentiation and cost.

These pipeline products, and their associated clinical data, is shared with the OptumRx Pharmacy & Therapeutics (P&T) Committee, comprised of independent physicians and pharmacists. The P&T Committee is the driving force behind our formulary evaluations and utilization management strategies. For pipeline products like these projected to have a significant market impact upon launch, the Committee does undertake a proactive pre-FDA-determination appraisal of all scientific evidence designed to ensure timely, unbiased formulary assessment and preliminary UM protocols that can be deployed immediately at launch. The P&T Committee meets consistently throughout the year, and its quarterly live deliberations are open and transparent to OptumRx clients and prospective clients.

I hope this report adds to your understanding of this critical field.

Sumit Dutta MD

SUMIT DUTTA
CHIEF MEDICAL OFFICER AT OPTUMRX

Drug Overview

Luspatercept

Luspatercept is an investigational agent to treat anemia in adult patients with very low to intermediate-risk myelodysplastic syndromes (MDS) and beta-thalassemia. Both of these conditions often require regular blood transfusions, which are costly, and associated with their own set of side effects, including risk of infection and iron overload toxicity. The only curative treatment is stem cell transplantation. Luspatercept has the potential to address a high unmet need in these two anemias. Anemia can be caused by the body's inability to produce enough of the hormone erythropoietin. Luspatercept is an erythropoietin-stimulating agent (ESA), which helps produce more red blood cells.

In a Phase III clinical trial, 38% of patients with MDS were able to go at least eight weeks without a need for a red blood cell transfusion during the first 24 weeks of the trial with luspatercept (vs. 13% for placebo). In a second study, over 21% of beta-thalassemia patients experienced at least a 33% reduction in their blood transfusion frequency (vs. 4.5% for placebo). It is estimated that MDS is diagnosed in at least 10,000 people each year in the U.S., with more than 60,000 people living with the disease in the U.S. today. Industry analysts are projecting luspatercept will reach sales in excess of two billion dollars, based on its ability to treat MDS and beta thalassemia. The FDA has set target action dates of December 4, 2019 for the beta-thalassemia indication (priority review) and April 4, 2020 for the MDS indication.

Cabotegravir/rilpivirine combination

Cabotegravir and rilpivirine comprise a two-drug regimen for treating HIV-1 in adults. Submitted to the FDA in April 2019, if approved it would be the first long-acting, injectable treatment for adults living with HIV, potentially changing the way many patients living with HIV are managed and treated. The drug combination will require administration by a health care professional.

In 2016, it was estimated that 1.1 million individuals aged 13 and older are positive for HIV infection, with an additional 162,000 whose infections are not diagnosed. The current standard of care for HIV is a daily, oral, three-drug regimen of antiretroviral therapy (ART). But two global phase III studies have shown that once per month injections of cabotegravir/rilpivirine are as effective as a standard ART. A follow-up study (ATLAS-2M) has also shown similar effectiveness when injected every two months. Notably, there are at least ten additional long-acting HIV agents (both ART and preventive) currently in various stages of development. Dosing regimens for these agents range from weekly to annually.

ART cannot cure HIV, but consistent treatment is essential to suppress the virus and reduce the risk of HIV transmission. However, up to 25% of people stop taking their oral ART medication for some period. With dosing frequencies reduced from 365 times per year to potentially less than 12 times a year with cabotegravir/rilpivirine, we see prospect for both improved patient satisfaction and medication adherence. At this time there is no information on the potential cost for cabotegravir/rilpivirine. The FDA has set a target date of December 29, 2019 for action for the once per month regimen.

Brolucizumab

In April of 2019, the FDA accepted Novartis' filing for brolucizumab. Brolucizumab is intended to treat wet age-related macular degeneration (AMD), also known as neovascular AMD, or nAMD. Wet AMD is a leading cause of blindness, estimated to affect up to 1.75 million people in the U.S. by 2020. AMD patients may experience loss of central vision or even blindness, seriously inhibiting the ability to complete daily tasks without treatment. Currently, Eylea® (aflibercept) and Lucentis® (ranibizumab) are the primary FDA-approved treatments available in the wet AMD class. In the Phase III trials, brolucizumab was compared against Eylea and brolucizumab showed improvement in some visual measurements and more patients were able to use less frequent dosing (12 weeks versus eight weeks).

Analysts predict that brolucizumab will reach annual sales over one billion dollars globally by 2021, and that it will become the most profitable AMD drug by 2026. However, the US patents on both Lucentis and Eylea will expire in 2020, with biosimilars for both in development. These forecasts depend on the biosimilar drugs that are currently in various stages of development for the existing AMD drugs. If these should come to market, there could be additional price competition in the class. In addition to treating nAMD, brolucizumab is also in Phase III trials for diabetic macular edema (DME). It is estimated that approximately 750,000 people over age 40 in the U.S. have DME. A filing is expected for that indication in 2020. Granted priority review, FDA approval for brolucizumab could occur in or around October of 2019; Novartis expects to launch brolucizumab by the end of 2019.

Drug Overview

Oral Semaglutide

On March 21st, Novo Nordisk filed for FDA approval of oral semaglutide to treat type 2 diabetes mellitus (T2DM). The FDA had previously approved the company's once-a-week injectable form of semaglutide (Ozempic®) in December 2017. Semaglutide works by mimicking a hormone called glucagon-like peptide 1 (GLP-1). GLP-1 agonists help stimulate insulin release after meals, and they act on the appetite centers in the brain, which may help some people lose weight. If approved, oral semaglutide would be the first GLP-1 receptor agonist in a pill form.

In addition to Ozempic, other injectable GLP-1 treatments include Trulicity® (dulaglutide) and Victoza® (liraglutide), and Bydureon® (exenatide extended release). Novo Nordisk has submitted two New Drug Applications (NDAs) for oral semaglutide. The first is to control blood glucose to treat T2DM, and a second NDA is to reduce major cardiovascular (CV) events, such as heart attacks, strokes, and death, in adults with T2DM and established CV disease. The blood glucose NDA is through a priority review process that should be finished in September 2019. The CV review is expected to be ready in January 2020.

The American College of Cardiology (ACC) and the American Diabetes Association endorse GLP-1 receptor agonists for patients with T2DM and atherosclerotic CV disease. More recently, the ACC and the American Heart Association said that GLP-1 receptor agonists may also be used in primary prevention, to prevent long-term complications from heart failure. With type 2 diabetes affecting over 28 million Americans, oral semaglutide's market impact could be significant. The currently available GLP-1 agonists work well, but if an oral form becomes available, any barriers caused by the route of administration (subcutaneous injection) will be eliminated. We see great potential for increased utilization as patients who are unwilling to use an injectable, or who no longer want to continue using an injectable, may seek oral semaglutide. Additionally, GLP-1 agonists are priced significantly greater than other branded diabetes drugs and if oral semaglutide enters at a similar price point, then overall costs of treating diabetes could increase. Spending for diabetes medications consistently ranks first among all classes, outpacing even oncology. While the manufacturer has not revealed pricing plans, one analyst firm projects oral semaglutide will see sales at over two billion dollars by 2024.

Ubrogepant

Ubrogepant is a new oral migraine treatment based on the calcitonin gene-related peptide (CGRP) mechanism of action. Ubrogepant has been accepted for FDA review, and is expected to reach market in late 2019. Ubrogepant follows three injectable CGRP inhibitors introduced in 2018 (Aimovig®, Ajovy®, Emgality®). The difference is that the injectables are taken preventatively, while new oral CGRP inhibitors are intended to treat the acute migraine's symptoms – i.e., headaches currently in-progress.

Triptans are the most widely prescribed treatment for acute migraine. However, approximately one third of patients do not respond to them, while others can experience tolerability with them. As a class, triptans are associated with cardiovascular and cerebrovascular risks related to vessel vasoconstriction. However, in both clinical trials and clinical practice, serious cardiovascular adverse events appear to be extremely low. CGRP inhibitors don't constrict blood vessels, so they may serve as an alternative in CV patients.

In phase III trials, ubrogepant performed better than the placebo. In each, about 20% of patients saw pain relief and about 38% felt their other symptoms (sensitivity to light/sound, nausea) diminished within 2 hours. Ubrogepant was generally well tolerated, with limited side effects. Ubrogepant has not been compared in direct comparative clinical trials with triptan therapy.

Pricing is a concern since most triptans are available generically and cost as low as $20 to 30 per month or prescription. The injectable CGRPs have a list price at around $6,900 a year (or $575 monthly). However, these treatments may not be the best reference, since they are administered on a chronic basis for headache prevention, whereas ubrogepant will be used as needed for the acute treatment of migraine headaches.

Looking Ahead

We have noted in our previous report the increased focus on treating rare or ultra-rare diseases, also called "orphan" drugs. However, the majority of drugs on this list target common conditions like chronic migraine and type 2 diabetes. Many of these medications take a different or novel approach to treatment and are likely to benefit larger groups of patients.

It is likely that patients and providers will want to try these new treatments, particularly members with chronic, long-standing diseases who have found little success previously. We expect that introductory market prices will be similar to existing medications.

These drugs could significantly impact the current marketplace. For example, luspatercept would be the first-ever drug approved to treat beta thalassemia and will come at a high price. But it will soon be faced with increased competition from LentiGlobin, a one-time gene therapy that also treats the condition and may be approved in mid-to-late 2020.

OptumRx is continuing to monitor new drugs in the approval pipeline to determine those that will have the biggest impact on the prescription drug landscape.

About OptumRx

OptumRx is a pharmacy care services company helping clients and more than 65 million members achieve better health outcomes and lower overall costs through innovative prescription drug benefit services, including network claims processing, clinical programs, formulary management, specialty pharmacy care and infusion services. Through expertise, flexible technology and a network of over 67,000 community pharmacies and state-of-the-art home delivery pharmacies, OptumRx is putting patients at the center of the pharmacy experience and making health care more connected and less fragmented — ensuring patients get the right medication at the right time at the best cost. OptumRx is part of Optum®, a leading information and technology-enabled health services business dedicated to making the health system work better for everyone. For more information, visit optum.com/optumrx or follow @OptumRx on Twitter.

optumrxsales@optum.com | **optum.com/optumrx**

2300 Main Street, Irvine, CA 92614

OptumRx specializes in the delivery, clinical management and affordability of prescription medications and consumer health products. We are an Optum® company — a leading provider of integrated health services. **Learn more at optum.com.**