Optum Rx drug pipeline insights report

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Optum Rx®

Drugs to Watch: Summer 2023

From Sumit Dutta, Chief Medical Officer at Optum Rx

Hello, and welcome to this edition of Drugs to Watch.

Recently, this report has focused on many new orphan drugs used in the treatment of rare conditions. While the drug development pipeline contains many more orphan drugs, in this edition, we will focus on new therapies for larger patient populations.

Specifically, this report will examine:

On August 4, 2023, the U.S. Food and Drug Administration approved zuranolone as the first oral medication indicated to treat postpartum depression (PPD) in adults. It will be marketed as Zurzuvae.™ Postpartum depression affects approximately 500,000 people in the U.S.[1] Zuranolone's distinguishing feature is its rapid effect, and that it's administered as a 14-day treatment course. However, the durability of response has not been shown. Zuranolone was also reviewed for use with major depressive disorder. The FDA did not approve it for this use at this time.

Zimura® (avacincaptad pegol) for geographic atrophy, a form of age-related macular degeneration that affects more than 1 million Americans.[2] Zimura® would be the second new treatment for geographic atrophy this year, following Syfovre™ (pegcetacoplan injection), approved in February.

Lebrikizumab, which is under review for the treatment of adult and adolescent patients with moderate-to-severe atopic dermatitis. Combining children and adults, atopic dermatitis affects more than 26 million people in this country.[3]

We all know that many factors go into a provider's decision to recommend a therapy, including age, gender, safety and side effect profile, therapeutic alternatives, etc. These factors and others contribute to the adoptions of new treatments and we will explore this further in relation to the drugs in this edition.

Please refer here for additional technical background and supplemental sources.

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Zuranolone: Brand name: Zurzuvae™
FDA decision: August 4, 2023

Zuranolone, from Biogen/Sage Therapeutics, was evaluated as a 14-day, rapid-acting, once-daily, oral treatment in adults with major depressive disorder and postpartum depression.[4]

On August 4, 2023, the U.S. Food and Drug Administration approved zuranolone as the first oral medication indicated to treat postpartum depression (PPD) in adults. It will be marketed as Zurzuvae.™ The FDA did not approve it for use with major depressive disorder at this time.

Depression is one of the most common mood disorders in the U.S. More than 8% (or 21 million) U.S. adults aged 18 or older experienced a major depressive episode in 2020. An estimated 71% of people with major depressive disorder received treatment in the past year.[5]

Postpartum depression is one of the most common medical complications after pregnancy and is estimated to affect approximately 13% of women who have given birth in the U.S. or, approximately 500,000 women annually.

Zuranolone is a rapid-acting neuroactive steroid. Neuroactive steroids are a family of both natural and synthetic compounds which have been shown to impact the central nervous system.[6]

In people with depression, zuranolone is thought to work by rapidly rebalancing neuronal networks to help reset brain networks responsible for functions such as mood, arousal, behavior, and cognition.[7]

Pivotal trial data

The data submitted to the FDA for zuranolone approval included outcomes from two broad groups of studies: LANDSCAPE for major depressive disorder, and NEST for postpartum depression.

Outcomes from both sets of studies showed that treatment with zuranolone led to rapid improvement in depressive symptoms. Results for the major depressive disorder branch showed that zuranolone met the primary endpoints of change from baseline to day 15 in the score on a standard scale used in depression trials in two of the three studies. Zuranolone met the same primary endpoints in both trials in the postpartum depression branch.[8]

Zuranolone was found to be generally well-tolerated. The most commonly reported adverse events included somnolence, dizziness, headache, and sedation.

You can access an in-depth discussion of safety and trial data here (p. 3).

Competitive environment

Zuranolone will offer a fast-acting antidepressant, with benefits seen as early as day three of use. In contrast, most antidepressants now require several weeks before patients might begin to benefit. There is a strong unmet need for rapid and effective relief of postpartum

depression symptoms. This is due to the high prevalence of, and the negative effects untreated postpartum depression can have on mothers, children, and partners.[9]

Zuranolone would potentially be the second approved drug with an indication specific for postpartum depression. The other drug approved for postpartum depression is Zulresso® (brexanolone), which acts similarly to zuranolone. However, Zulresso must be administered via continuous intravenous infusion for 60 hours, versus daily oral treatment for zuranolone.

Still, zuranolone will be entering a crowded marketplace with significant generic utilization. Even for postpartum depression, selective serotonin reuptake inhibitors have been used for years and have more long-term safety data with use during breastfeeding. In the case of zuranolone, patients were not permitted to breastfeed during the 14-day treatment and for seven days after the treatment course.

Another question remains, particularly for treatment of major depressive disorder, about the durability of response. While zuranolone met its primary endpoint at day three or 15 in two of the three trials, there was diminished benefit by week six. Durability is important for major depressive disorder because patients are typically treated for a depressive episode for around four to six weeks to produce a response or remission, and then treatment is continued for several months to consolidate the response and prevent a relapse. In the case of zuranolone, there is a lack of robust long-term data.

Finally, zuranolone will likely be a controlled substance (Zulresso is also a scheduled IV controlled substance).

Avacincaptad pegol: Brand name Zimura®
Expected FDA decision: August 19, 2023

Zimura is from the manufacturer IVERIC Bio. It is under review for the treatment of geographic atrophy, an eye disease that causes vision loss in the center of the field of vision.

Geographic atrophy is an aggressive form of dry (as opposed to wet) age-related macular degeneration. Geographic atrophy is a leading cause of blindness that affects more than 1 million people in the U.S.[10]

Those most at-risk for age-related macular degeneration include those who are age 55 and older. In addition, people who have a family history of age-related macular degeneration, or who have hypertension, are overweight, or who smoke are also at-risk.[11]

Currently, there is one FDA-approved treatments for geographic atrophy, Syfovre™ (pegcetacoplan injection) approved in February 2023.[12] We recently reviewed pegcetacoplan here.

Both Zimura and Syforve are administered by injection into the eye.

Clinical profile

Zimura works by inhibiting the C5 protein, which is one of about 50 different proteins in the complement system.[13] The complement system is part of the innate immune system that cleans up damaged cells, promotes healing, and destroys invasive organisms like bacteria and viruses.[14]

The proteins in the complement system activate in a series, or cascade, similar to a domino chain reaction.[15] Researchers believe that an overactive cascade reaction involving the C5 protein is a key culprit in age-related macular degeneration and the vision loss associated with geographic atrophy.

By targeting C5, Zimura has the potential to decrease excess activity of the complement system that causes the degeneration of retinal cells.

Pivotal trial data

Zimura was evaluated in two randomized Phase 3 studies of patients with geographic atrophy secondary to age-related macular degeneration. Patients received a higher or lower dose of Zimura, or a sham injection, administered via injection once per month.

Zimura slowed geographic atrophy lesion growth by 14.3% and 27.7% in both studies at 12 months.

The most common adverse events with Zimura were conjunctival hemorrhage, increased intraocular pressure, and abnormal blood vessel growth into the retina, or wet age-related macular degeneration.

You can access an in-depth discussion of safety and trial data here (p. 10).

Competitive environment

Up until this year, there were no FDA approved treatments for geographic atrophy. There was a high unmet need since existing vascular endothelial growth factor inhibitors (e.g., Eylea®, Lucentis®) used for “wet” age-related macular degeneration are ineffective for geographic atrophy. However, in February 2023, the FDA approved Apellis Pharmaceuticals’ Syfovre™ (pegcetacoplan), a complement C3 inhibitor for geographic atrophy. If approved, Zimura would be a direct competitor to Syfovre.

Zimura and Syfovre work in similar ways, although Syfovre works earlier in the complement cascade. Right now, there are no head-to-head trials comparing the two products. For dosing, Syfovre is approved for use as a monthly or every other month injection. Data for Zimura is only available as a monthly injection.

A concern with both Zimura and Syfovre is the increase of new-onset wet age-related macular degeneration. Even with no treatment, patients with geographic atrophy can develop wet age-related macular degeneration and vice versa. But in clinical trials using these complement inhibitors, the risk of wet age-related macular degeneration increases. A higher rate of new wet age-related macular degeneration in patients treated with Zimura or Syfovre could result in more patients needing to be treated with vascular endothelial growth factor inhibitors.

For reference, the wholesale acquisition cost (WAC) for Syfovre is $2,190 per month.

Lebrikizumab: Brand name: TBD
Expected FDA decision: September 2023

Eli Lilly's lebrikizumab is under review for the treatment of adult and adolescent patients with moderate-to-severe atopic dermatitis.

Atopic dermatitis, also referred to as eczema, is a common and chronic inflammatory skin disorder. Itching is a common symptom of atopic dermatitis , affecting more than 85% of those diagnosed.[16]

Atopic dermatitis can cause rashes that can ooze, weep fluid and bleed when scratched, which leaves the skin vulnerable to infection. Skin can become dry and discolored, and repeated scratching can cause thickening and hardening.[17]

Atopic dermatitis affects more than 9.6 million children and about 16.5 million adults in the U.S. It's a chronic condition that can come and go for years in childhood or throughout life.[18]

Clinical profile

Atopic dermatitis has been linked to type 2 inflammation, which is activated by proteins called cytokines. These are signaling molecules that generate antibodies and other immune cells. Two cytokines – interleukins 4 and 13 – are linked to the debilitating itch, skin barrier deficiencies, and increased risk of skin infections associated with atopic dermatitis.[19]

Lebrikizumab is a bioengineered protein called a monoclonal antibody. It is designed to bind to IL-13 cytokines. Treatments like lebrikizumab that target IL-13 can interrupt the signaling pathway and decrease type 2 inflammation.[20]

Pivotal trial data

The efficacy of lebrikizumab was evaluated in two identical randomized Phase 3 trials. Each trial had two treatment periods: a 16-week induction period and a 36-week maintenance period. Participants included adolescent and adult patients with moderate-to-severe atopic dermatitis who were randomized to receive either lebrikizumab or placebo.[21]

There were two primary endpoints at week 16. Patients were scored on the Investigator's Global Assessment, indicating that the skin was clear or almost clear of eczema. They were also measured to see if they had achieved a 75% reduction from baseline in the Eczema Area and Severity Index.[22]

Both trials met the primary endpoints on the Investigator's Global Assessment score, 43.1% and 33.2% respectively compared to 12.7% and 10.8% of patients in the placebo group, and with the Eczema Area and Severity Index, with 58.8% and 52.1% achieving response compared to 16.2% and 18.1% for those taking the placebo.[23]

Additionally, lebrikizumab-treated individuals experienced a greater reduction in itching as well as reductions in sleep-loss compared to placebo.[24]

Adverse events included conjunctivitis, which was higher among patients who received lebrikizumab than among those who received placebo. Most adverse events were mild or moderate, and did not lead to trial discontinuation.[25]

You can access an in-depth discussion of safety and trial data here (p. 19).

Competitive environment

If approved, lebrikizumab would add another IL-13 antagonist treatment option for atopic dermatitis. Current therapy for atopic dermatitis includes topical treatments such as corticosteroids and calcineurin inhibitors, Eucrisa® (crisaborole) and Opzelura® (ruxolitinib). In patients with moderate-to-severe disease who require systemic therapy, treatment options include oral Janus kinase inhibitors such as Cibinqo® (abrocitinib) and Rinvoq® (upadacitinib). Injectable option include Adbry® (tralokinumab-ldrm), an IL-13 antagonist, and Dupixent® (dupilumab), an IL-4/IL-13 antagonist.

Compared to Janus kinase inhibitors, lebrikizumab has some of the same advantages as other injectables used for atopic dermatitis. Janus kinase inhibitors are dosed daily and have boxed warnings for serious infections, malignancy and thrombosis. In contrast, lebrikizumab is administered less frequently (once every two or four weeks) and has a more favorable safety profile.

Lebrikizumab was not compared in head-to-head trials against existing treatment options. However, the efficacy data for lebrikizumab appears to be similar to Dupixent, the current market leader in the class.

In addition, both lebrikizumab and Dupixent are indicated for patients 12 years of age and older. In contrast, Adbry is only approved for adults.

Lebrikizumab will compete not only with existing treatment options, but potential future pipeline agents. These include Galderma's nemolizumab, an injectable IL-31 antagonist, and topical agents such as Vtama® (tapinarof), Zoryve ® (roflumilast), and several topical Janus kinase inhibitors. These competitors could be on the market or receive additional approvals for atopic dermatitis as early as second quarter 2024.

For reference, the WAC for Dupixent is approximately $41,000 per year.

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[Unless otherwise indicated, all sources taken from Optum Rx Outlook® 2nd Quarter 2023.]

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