Prix Galien Product Awards:

Product: ZURZUVAE

Category: Best Pharmaceutical Product

I: General Information

Company Name: Biogen, Sage Therapeutics

Product/Solution Name: Zurzuvae® (zuranolone) capsules Schedule IV

Compound/Tech Name: Zuranolone

Date of Approval: ZUR was approved by FDA on 8/4/2023 pending DEA scheduling which occurred on 10/31/2023.

Indications: For adults with postpartum depression

II: Background

Background information and need for solution/product:

For pregnant women, the perinatal period is often a time filled with joy — but it's also one of enormous change. In addition to the expected physical changes, the range of hormonal, emotional, and psychological shifts that can occur during pregnancy and after childbirth may bring intense, unfamiliar feelings. In some cases, these symptoms can interfere with a new mother's ability to care for and bond with her newborn. At the same time, access to mental health care is increasingly difficult across the country, so when women do seek help, it can be hard to receive it.

Postpartum depression (PPD) is one of the most common medical complications of childbirth, with approximately 500,000 women experiencing symptoms of PPD annually in the U.S. PPD symptoms can be debilitating and include depressed mood, loss of interest in activities, changes in sleep patterns and appetite, decreased energy, feelings of guilt or worthlessness, and trouble concentrating. In some cases, PPD can also bring thoughts of suicide, which is a leading cause of maternal mortality. It's believed that up to half of all PPD cases may go undiagnosed and research has showed that only 15.8% of women with PPD symptoms receive treatment.

PPD can impact women of all races, ethnicity, socio-economic status, and community, though there are disproportionate impacts on Black and Brown women. Adequate postpartum care, such as screening for depression, has also been significantly less likely to be received by racial and historically marginalized groups, those on Medicaid, and women living in rural areas.

Prior to Zurzuvae, there were no oral treatments specifically indicated for PPD. Women were often treated off-label with selective serotonin reuptake inhibitors (SSRIs), which were developed for use in treating major depressive disorder and not clinically tested in the treatment of PPD. SSRIs – which are often taken indefinitely – typically take six to eight weeks to take effect, which means women can continue to struggle with symptoms during a critical period while trying to take care of a newborn.

In addition to its impact on mothers, PPD has also been associated with potential impacts on childhood development. In addition to bonding difficulties between mother and child, a few studies have suggested that PPD may have impacts on infant and childhood development, but no conclusionary evidence exists.

III: Development

History of the development of the solution/product:

The idea for zuranolone stemmed from work on the role of GABA-A modulators in depression. The causes of PPD are multifactorial and may result from brain network dysregulation, including dysfunctional signaling and altered regulation of stress response pathways, in addition to contributing factors such as fluctuations in hormone levels. The novel mechanism of action of zuranolone is hypothesized to restore network balance in brain areas dysregulated in depression through a positive allosteric modulator (PAM) of synaptic and extra synaptic GABA-A receptors.

In 2020, the Phase 3, randomized, double-blind, placebo-controlled SKYLARK study was initiated to assess the efficacy and safety of zuranolone 50 mg compared to placebo in adult women with severe PPD. The 200 patients enrolled in the study were randomized to receive zuranolone 50 mg or a placebo once nightly for 14 days. People in the study were then followed for an additional four weeks. The SKYLARK study was part of the NEST clinical development program which included two placebo-controlled studies in adult women with PPD (ROBIN and SKYLARK studies). Both studies met their primary endpoint which was a significant mean reduction from baseline in the 17-item Hamilton Rating Scale for Depression (HAMD-17) total score, a common measure of depression severity, at Day 15 compared to placebo. The SKYLARK study also met all key secondary endpoints. In November 2020, shortly after this study commenced, Biogen and Sage Therapeutics announced a global collaboration to develop and commercialize Zurzuvae for postpartum depression.

In June 2022, Biogen and Sage announced that the SKYLARK study met its primary and all key secondary endpoints, with study participants demonstrating rapid and significant improvements in depression symptoms as early as Day 3 that were sustained at Day 45. The U.S. Food and Drug Administration (FDA) approved Zurzuvae as the first oral treatment for adults with postpartum depression on August 4th, 2023 pending scheduling by DEA which occurred on October 31, 2023.

IV: Innovation

Why this drug or device is innovative, the broad implications for future research, and/or how it will improve the human condition:

Zurzuvae has transformed the landscape of PPD management – by providing the only FDA approved oral treatment option for postpartum women and sparking significant conversation nationwide on maternal mental healthcare. Following the landmark approval of ZURZUVAE, a national discussion sparked in the U.S. about PPD, bringing greater awareness to maternal mental health and stigmas mothers can face.

In and of itself, it's significant that Zurzuvae is the first and only FDA-approved oral treatment specifically indicated for women with postpartum depression. But beyond this – Zurzuvae has the potential to make a real difference in women's lives. Zurzuvae is taken for only 14 days with results shown as early as Day

3. So it's both short-course and rapid acting during a time in a women's life where every moment matters. With this rapid treatment, patients now have another option in the care that they receive after having a baby.

Dysregulation of the brain, and its associated symptoms can be particularly trying and challenging for new mothers. Zurzuvae is a next-generation positive allosteric modulator of the gamma-aminobutyric acid (GABA-A) receptor. The GABA-A system is the major inhibitory signaling pathway of the brain and central nervous system (CNS) and contributes significantly to regulating CNS function. This mechanism of action is a novel approach.

Since its launch in December 2024, women diagnosed with PPD and treated with Zurzuvae have reported positive results, including improvements in their depressive symptoms, caring for themselves and being more able to discuss how they're feeling. In some cases, women are experiencing results within the first three days of treatment.

Since its approval, we've seen over 1,500 articles published that have shed light on the negative impact of PPD, and the promising treatment, Zurzuvae. A few particularly inspiring examples include:

1. How Giving Birth Impacts Mental Health | Healthnews
    a. "Pratt eventually reached out to her doctor and was prescribed regular antidepressants, though she didn't experience much relief. So when she saw an ad for a clinical trial for Zurzuvae — the very first oral medication specifically meant to treat PDD, approved by the FDA in August — she was interested.
    b. Pratt quickly discovered she was eligible for the trial and that she would only have to take a 14-day course of medicine to experience the benefits. She says the drug pulled her out of her depression and allowed her to feel like herself again within days.
2. First pill for postpartum depression is finally reaching patients (nbcnews.com)
    a. "She tells me she feels like she just woke up," Richards said, adding: "I truly feel like I'm meeting her for the first time. Her husband was in tears, super grateful. Just a major, grand slam success story — which, by the way, we don't tend to see in psychiatry."
3. CBS News: A Promising Treatment for Postpartum Depression
4. CBS News: Recognizing the Signs of Postpartum Depression
    a. Dr. Deligiannidis ran one of the trials, and says the pill, taken for 14 days, provides rapid relief. That quick reaction, she said, gave her goosebumps: "It was a little unreal. We just aren't trained in this way, to think our therapies can work this quickly."

V References:

Please provide appropriate references (PubMed, IndMED, MEDIND, Indian Journal of Medical Research, DOAJ:

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5. Georgiopoulos AM et al. J Fam Pract. 2001;50(2):117-122.
6. Evins GG et al. Am J Obstet Gynecol. 2000;182(5):1080-1082.
7. Cox EQ, et al. J Clin Psychiatry. 2016;77(9):1189-1200.
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11. Cannon C, Nasrallah HA. *Ann Clin Psychiatry*. 2019;31 (2):138-143.
12. Interrante JD, et al. JAMA Health Forum. 2022;3(10):e223292.
13. FDA Approves ZURZUVAE™ (zuranolone), the First and Only Oral Treatment Approved for Women with Postpartum Depression, and Issues a Complete Response Letter for Major Depressive Disorder | Biogen
14. SSRIs (Selective Serotonin Reuptake Inhibitors): Uses (clevelandclinic.org)
15. Interrante JD, et al. Association of Health Insurance, Geography, and Race and Ethnicity With Disparities in Receipt of Recommended Postpartum Care in the US. *JAMA Health Forum.* 2022;3(10):e223292.
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