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

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Postpartum depression (PPD) approval based on results from two Phase 3 clinical trials; in the SKYLARK Study treatment with ZURZUVAE rapidly improved symptoms of PPD at Day 15 and as early as Day 3 with sustained effect to Day 45

Mental health conditions are the leading cause of maternal mortality[1] with PPD among the most common complications during and after pregnancy[2]

CAMBRIDGE, Mass., Aug. 04, 2023 (GLOBE NEWSWIRE) -- Biogen Inc. (Nasdaq: BIIB) and Sage Therapeutics, Inc. (Nasdaq: SAGE) announced the U.S. Food and Drug Administration (FDA) approved ZURZUVAE™ (zuranolone) 50 mg for adults with postpartum depression (PPD). ZURZUVAE is the first and only oral, once-daily, 14-day treatment that can provide rapid improvements in depressive symptoms for women with PPD. ZURZUVAE is expected to launch and be commercially available in the fourth quarter of 2023 shortly following scheduling as a controlled substance by the U.S. Drug Enforcement Administration, which is anticipated to occur within 90 days.

Additionally, the FDA issued a Complete Response Letter (CRL) for the New Drug Application (NDA) for zuranolone in the treatment of adults with major depressive disorder (MDD). The CRL stated that the application did not provide substantial evidence of effectiveness to support the approval of zuranolone for the treatment of MDD and that an additional study or studies will be needed. Biogen and Sage are reviewing the feedback and evaluating next steps.

“The approval of ZURZUVAE to treat postpartum depression is a major milestone for the hundreds of thousands of women who experience this underdiagnosed and undertreated condition,” said Christopher A. Viehbacher, President and Chief Executive Officer at Biogen. “We appreciate the support of patients, patient advocates and researchers who helped to reach this milestone. We believe that ZURZUVAE will be an important option to treat PPD and we will thoroughly review the feedback from the FDA on the use of zuranolone in MDD to determine next steps.”

“Maternal mental health has been sidelined for far too long, but today’s approval of ZURZUVAE helps to change that. Women have been waiting for an oral medicine that can specifically and rapidly improve the symptoms of PPD and we are proud to be able to deliver that,” said Barry Greene, Chief Executive Officer at Sage Therapeutics. “In regard to the CRL for MDD, we are highly disappointed for patients, particularly amid the current mental health crisis and millions of people with MDD struggling to find symptom relief. We remain committed to our mission to deliver life-changing brain health medicines.”

The approval of ZURZUVAE to treat women with PPD is based on the NEST clinical development program, which included two studies in adult women with PPD (ROBIN and SKYLARK Studies). Both studies met their primary endpoint, 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 as compared to placebo. In the SKYLARK Study evaluating ZURZUVAE 50 mg, all key secondary endpoints were met, with significant reduction in depressive symptoms seen as early as Day 3 and sustained through Day 45. ZURZUVAE was generally well-tolerated with a consistent safety profile across both studies. The most common side effects ≥ 5% and greater than placebo in patients treated with ZURZUVAE 50 mg were somnolence, dizziness, diarrhea, fatigue and urinary tract infection. The labeling includes a boxed warning that instructs healthcare providers to advise people that ZURZUVAE causes driving impairment due to central nervous system (CNS) depressant effects. People who take ZURZUVAE should not drive a motor vehicle or engage in other potentially hazardous activities that require complete mental alertness until at least 12 hours after ZURZUVAE administration for the duration of the 14-day treatment course. Patients may not be able to assess their own degree of impairment.

“Today marks a groundbreaking day for the treatment of PPD, as with ZURZUVAE we now have an oral treatment option that can provide rapid improvements in depressive symptoms in as early as three days for women with PPD,” said Dr. Kristina Deligiannidis, a principal investigator in the ZURZUVAE clinical development program and Professor, The Feinstein Institutes for Medical Research in Manhasset, New York. “As a perinatal psychiatrist, I see the devastating impact PPD has on mothers particularly on the important mother-infant bond and long-term child development. Once available, I believe ZURZUVAE will be a meaningful option for patients in need.”

According to the Centers for Disease Control and Prevention, mental health conditions are the leading cause of maternal mortality[1] with PPD among the most common complications during and after pregnancy.[2] In the U.S., it is estimated approximately 1 in 8 women experience symptoms of PPD.[3] Approximately half of all PPD cases may go undiagnosed without appropriate screening.[4,5] Research shows only 15.8% of women with PPD symptoms receive treatment.[6] PPD symptoms may persist beyond the postpartum period and can lead to prolonged maternal morbidity.[7-9] Symptoms of PPD can include depressed mood, loss of interest in activities, changes in sleep patterns and appetite, decreased energy, feelings of guilt or worthlessness, trouble concentrating and in some cases thoughts of suicide.[9]

“Today’s approval is welcome news for the estimated 500,000 women in the United States who report experiencing symptoms of this devastating and often misunderstood illness each year,” said Wendy N. Davis, Ph.D., PMH-C, Executive Director at Postpartum Support International. “Women with PPD desperately need prompt care and additional treatment options that can provide quick relief so they can be healthy and present during this momentous time in their lives.”

Indication and Important Safety Information for ZURZUVAE

What is ZURZUVAE?
ZURZUVAE is a prescription medicine used to treat adults with postpartum depression (PPD).
It is not known if ZURZUVAE is safe and effective in children.

IMPORTANT SAFETY INFORMATION
What is the most important information I should know about ZURZUVAE?
ZURZUVAE may cause serious side effects, including:

- **Decreased ability to drive or do other dangerous activities.** ZURZUVAE may decrease your awareness and alertness, which can affect your ability to drive safely or safely do other dangerous activities.
    - **Do not** drive, operate machinery, or do other dangerous activities **until at least 12 hours after taking each dose** during your 14-day treatment course of ZURZUVAE.
    - You may not be able to tell on your own if you can drive safely or tell how much ZURZUVAE is affecting you.
- **Decreased awareness and alertness [central nervous system (CNS) depressant effects].** ZURZUVAE may cause sleepiness, drowsiness, slow thinking, dizziness, confusion, and trouble walking.
    - Because of these symptoms, you may be at a higher risk for falls during treatment with ZURZUVAE.
    - Taking alcohol, other medicines that cause CNS depressant effects, or opioids while taking ZURZUVAE can make these symptoms worse and may also cause trouble breathing.
    - Tell your healthcare provider if you develop any of these symptoms, or if they get worse during treatment with ZURZUVAE. Your healthcare provider may decrease your dose or stop ZURZUVAE treatment if you develop these symptoms.

ZURZUVAE is a federally controlled substance (C-XX) because it contains zuranolone that can be abused or lead to dependence. Keep ZURZUVAE in a safe place to protect it from theft. Do not sell or give away ZURZUVAE because it may harm others and is against the law.

Before taking ZURZUVAE, tell your healthcare provider about all of your medical conditions, including if you:

- drink alcohol
- have abused or been dependent on prescription medicines, street drugs, or alcohol
- have liver or kidney problems
- are pregnant or plan to become pregnant. ZURZUVAE may harm your unborn baby.
- are breastfeeding or plan to breastfeed. ZURZUVAE passes into breast milk, and it is not known if it can harm your baby. Talk to your healthcare provider about the risks and benefits of breastfeeding and about the best way to feed your baby during treatment with ZURZUVAE.

Females who are able to become pregnant:

- Tell your healthcare provider right away if you become pregnant during treatment with ZURZUVAE.
- You should use effective birth control (contraception) during treatment with ZURZUVAE and for 1 week after the final dose.
- There is a pregnancy registry for females who are exposed to ZURZUVAE during pregnancy. The purpose of the registry is to collect information about the health of females exposed to ZURZUVAE and their baby. If you become pregnant during treatment with ZURZUVAE, talk to your healthcare provider about registering with the National Pregnancy Registry for Antidepressants at 1-844-405-6185 or visit online at https://womensmentalhealth.org/research/pregnancyregistry/antidepressants/.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZURZUVAE and some medicines may interact with each other and cause serious side effects. ZURZUVAE may affect the way other medicines work and other medicines may affect the way ZURZUVAE works.

Especially tell your healthcare provider if you take antidepressants, opioids, or CNS depressants such as benzodiazepines.

What should I avoid while taking ZURZUVAE?

- **Do not** drive a car, operate machinery, or do other dangerous activities **until at least 12 hours after taking each dose of ZURZUVAE** because ZURZUVAE may make you feel sleepy, confused, or dizzy.
- **Do not** drink alcohol or take other medicines that make you sleepy or dizzy while taking ZURZUVAE without talking to your healthcare provider.

See **"What is the most important information I should know about ZURZUVAE?"**

ZURZUVAE may cause serious side effects, including:

- See **"What is the most important information I should know about ZURZUVAE?"**
- **Increased risk of suicidal thoughts or actions.** ZURZUVAE and other antidepressant medicines may increase the risk of suicidal thoughts and actions in people 24 years of age and younger**. ZURZUVAE is not for use in children.**

How can I watch for and try to prevent suicidal thoughts and actions?

- Pay close attention to any changes, especially sudden changes in mood, behavior, thoughts, or feelings, or if you develop suicidal thoughts or actions. This is very important when an antidepressant medicine is started or when the dose is changed.
- Tell your healthcare provider right away if you have any new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with your healthcare provider as scheduled. Call your healthcare provider between visits as needed, especially if you have concerns about symptoms.

Tell your healthcare provider right away if you have any of the following symptoms, especially if they are new, worse, or worry you:

- Attempts to commit suicide, thoughts about suicide or dying, new or worse depression, feeling very agitated or restless, trouble sleeping (insomnia), new or worse anxiety, panic attacks, new or worse irritability, acting aggressive, being angry or violent, an extreme increase in activity and talking (mania), acting on dangerous impulse, other unusual changes in behavior or mood

The most common side effects of ZURZUVAE include:

- Sleepiness or drowsiness, dizziness, common cold, diarrhea, feeling tired, weak, or having no energy, and urinary tract infection

These are not all of the possible side effects of ZURZUVAE. Call your doctor for medical advice about side effects. You can report side effects to FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the Full Prescribing Information, including Boxed WARNING, and Medication Guide for ZURZUVAE.

About ZURZUVAE™ (zuranolone)
ZURZUVAE is a once-daily, oral, 14-day medicine for the treatment of adults with postpartum depression (PPD). ZURZUVAE is a neuroactive steroid (NAS) GABA-A receptor positive allosteric modulator (PAM). The GABA system is the major inhibitory signaling pathway of the brain and central nervous system and contributes to regulating brain function.

About Biogen
Founded in 1978, Biogen is a leading global biotechnology company that has pioneered multiple breakthrough innovations including a broad portfolio of medicines to treat multiple sclerosis, the first approved treatment for spinal muscular atrophy, and two co-developed treatments to address a defining pathology of Alzheimer's disease. Biogen is advancing a pipeline of potential novel therapies across neurology, neuropsychiatry, specialized immunology and rare diseases and remains acutely focused on its purpose of serving humanity through science while advancing a healthier, more sustainable and equitable world.

We routinely post information that may be important to investors on our website at www.biogen.com. Follow us on social media - Twitter, LinkedIn, Facebook, YouTube.

About Sage Therapeutics
Sage Therapeutics is a biopharmaceutical company fearlessly leading the way to create a world with better brain health. Our mission is to pioneer solutions to deliver life-changing brain health medicines, so every person can thrive. For more information, please visit www.sagerx.com.

Biogen Safe Harbor
This news release contains forward-looking statements, relating to the potential, benefits, safety and efficacy of ZURZUVAE; our next steps in the regulatory process with respect to zuranolone for the treatment of MDD; the potential benefit, safety and efficacy of ZURZUVAE in the treatment of adults with MDD, if approved; the potential of Biogen's commercial business and pipeline programs, including ZURZUVAE; the anticipated benefits and potential of Biogen's collaboration arrangement with Sage; and risks and uncertainties associated with drug development and commercialization. These forward-looking statements may be accompanied by words such as "aim," "anticipate," "believe," "could," "estimate," "expect," "forecast," "intend," "may," "plan," "potential," "possible," "will," "would" and other words and terms of similar meaning. Drug development and commercialization involve a high degree of risk and only a small number of research and development programs result in commercialization of a product. Results in early-stage clinical trials may not be indicative of full results or results from later stage or larger scale clinical trials and do not ensure regulatory approval. You should not place undue reliance on these statements, or the scientific data presented.

These statements involve risks and uncertainties that could cause actual results to differ materially from those reflected in such statements, including without limitation, uncertainty of success in the development and potential commercialization of ZURZUVAE for PPD, and if approved, for MDD; uncertainty with respect to the regulatory pathway for zuranolone for the treatment of MDD; uncertainty as to whether additional studies will be required with respect of zuranolone for the treatment of MDD; unexpected concerns may arise from additional data, analysis or results of clinical studies of zuranolone; regulatory authorities may require additional information or further studies, or may fail or refuse to approve or may delay approval of Biogen's drug candidates, including zuranolone for the treatment of MDD; the occurrence of adverse safety events; the risks of other unexpected hurdles, costs or delays; failure to protect and enforce data, intellectual property and other proprietary rights and uncertainties relating to intellectual property claims and challenges; product liability claims; third party collaboration risks; and the direct and indirect impacts of COVID-19 on our business, results of operations and financial condition. The foregoing sets forth many, but not all, of the factors that could cause actual results to differ from Biogen's expectations in any forward-looking statement. Investors should consider this cautionary statement as well as the risk factors identified in Biogen's most recent annual or quarterly report and in other reports Biogen has filed with the U.S. Securities and Exchange Commission. These statements speak only as of the date of this news release. Biogen does not undertake any obligation to publicly update any forward-looking statements.

Sage Therapeutics Safe Harbor
Various statements in this release concern Sage's future expectations, plans and prospects, including without limitation our statements regarding: our expectations as to the timing of completion of DEA scheduling and commencement of planned launch, availability and commercialization of ZURZUVAE in the treatment of women with PPD; our plans for commercial launch of ZURZUVAE in this indication; our belief in our readiness for commercial launch of ZURZUVAE; our plans to evaluate next steps after receipt of the CRL for zuranolone in MDD; the potential benefit of ZURZUVAE in the treatment of adults with PPD; the number of women with PPD and the potential market for ZURZUVAE for the treatment of women with PPD; and the mission and goals for our business. These statements constitute forward-looking statements as that term is defined in the Private Securities Litigation Reform Act of 1995. These forward-looking statements are neither promises nor guarantees of future performance, and are subject to a variety of risks and uncertainties, many of which are beyond our control, which could cause actual results to differ materially from those contemplated in these forward-looking statements, including the risks that: our launch and commercialization efforts in the U.S. with respect to ZURZUVAE for the treatment of women with PPD may not be successful, and we may be unable to generate revenues at the levels or on the timing we expect or at levels or on the timing necessary to support our goals; the number of women with PPD, the unmet need for additional treatment options, and the potential market for ZURZUVAE in this indication may be significantly smaller than we expect; ZURZUVAE may not achieve the clinical benefit, clinical use or market acceptance we expect in the treatment of women with PPD or we may encounter reimbursement-related or other market-related issues that impact the success of our commercialization efforts; we may never achieve regulatory approval of zuranolone in MDD; the FDA has taken the position that an additional clinical trial or clinical trials of zuranolone are required to support approval in MDD and may not change that position; such trial or trials could be time-consuming, significantly increase our expenses, and may not be feasible; even if we conduct such clinical trials, they may not be successful; the FDA may decide that the design, conduct or results of such clinical trials, even if positive, are not sufficient for approval in MDD or may find other deficiencies in our development program, data, processes, or manufacturing sites; even if we receive regulatory approval of zuranolone for the treatment of MDD, the FDA may approve zuranolone for only a subset of MDD patients or with limitations or restrictions; we may encounter

adverse events for ZURZUVAE at any stage that negatively impact commercialization in women with PPD, the potential for regulatory approval in MDD, or if approved, potential commercialization in MDD; if we run additional clinical trials to obtain approval of zuranolone in MDD, we may encounter delays in initiation, conduct, completion of enrollment or completion of any such clinical trials, including as a result of slower than expected site initiation, slower than expected enrollment, the need or decision to expand the trials or other changes, that may impact our ability to meet our expected timelines and increase our costs; decisions or actions of the FDA may affect the initiation, timing, design, size, progress and cost of such clinical trials and our ability to proceed with further development or may impair the potential for successful development; the need to align with our collaborators may hamper or delay our development and commercialization efforts or increase our costs; our business may be adversely affected and our costs may increase if any of our key collaborators fails to perform its obligations or terminates our collaboration; and the internal and external costs required for our ongoing and planned activities, and the resulting impact on expense and use of cash, may be higher than expected which may cause us to use cash more quickly than we expect or to change or curtail some of our plans or both; as well as those risks more fully discussed in the section entitled "Risk Factors" in our most recent quarterly report, as well as discussions of potential risks, uncertainties, and other important factors in our subsequent filings with the Securities and Exchange Commission. In addition, any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. We explicitly disclaim any obligation to update any forward-looking statements.

References:

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MEDIA CONTACTS:
Biogen
Jack Cox
+1 781 464 3260
public.affairs@biogen.com

Sage Therapeutics
Matthew Henson
+1 917 930 7147
Matthew.Henson@sagerx.com

INVESTOR CONTACTS:
Biogen
Chuck Triano
+1 781 464 2442
IR@biogen.com

Sage Therapeutics
Ashley Kaplowitz
+1 786 252 1419
Ashley.Kaplowitz@sagerx.com