GEDEON RICHTER

Established in 1901

U.S. FDA Approves VRAYLAR® (cariprazine) as an Adjunctive Treatment for Major Depressive Disorder

- *Approval marks fourth indication for VRAYLAR®, backed by proven efficacy and well-established tolerability as an adjunctive treatment for major depressive disorder (MDD) with an antidepressant therapy (ADT), showing improvement in symptoms when compared to placebo + ADT*
- *Designed for specific mood disorders, VRAYLAR® is now the first and only dopamine and serotonin partial agonist FDA-approved for the most common forms of depression – as an adjunctive treatment for MDD and for the treatment of depressive episodes associated with bipolar I disorder*
- *About one in five U.S. adults will experience MDD during their lifetime, and many of them may have partial response to the treatment with an ADT*

Budapest, Hungary - 19 December 2022 – Richter Gedeon's ('Richter') partner AbbVie ('AbbVie') today announced that the U.S. Food and Drug Administration (FDA) has approved VRAYLAR® (cariprazine) as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults. Supported by clinical data demonstrating efficacy and well-established tolerability, this additional indication provides a new option for adults who have a partial response to the treatment of an antidepressant.

'When we were in the early stages of development for cariprazine, we focused on designing a compound that covers a range of symptoms for mental health conditions and affects the dopamine D_3 receptor,' - said István Greiner Ph.D., Research and Development Director of Richter. 'While schizophrenia and bipolar manic and mixed episodes were the first indications in the U.S. market, we are thrilled to see the full potential of cariprazine unlocked with approvals in bipolar I depression, and now, as an antidepressant adjunct in major depressive disorder.'

MDD is one of the most common mental disorders in the U.S.; approximately one in five adults will experience this disorder during their lifetime.[1] In a large U.S. study of adults with MDD, approximately 50 percent still had depressive symptoms with their first antidepressant.[2] If some symptoms of depression persist while on an antidepressant, adding a different type of medication, often referred to as an adjunctive treatment, to the existing regimen may help.

'Patients with inadequate response to standard antidepressant medication are often frustrated by the experience of trying multiple medicines and still suffering from unresolved symptoms. Instead of starting over with another standard antidepressant, VRAYLAR® works with an existing treatment and can help build on the progress already made,' - said Gary Sachs, MD, clinical vice president at Signant Health, associate clinical professor of psychiatry at Massachusetts General Hospital, and lead Phase 3 clinical trial investigator. 'For adults living with major depressive disorder, because of inadequate improvement in response to standard antidepressants, VRAYLAR® is an efficacious adjunctive treatment option with a well-characterized safety profile.'

Cariprazine is marketed as VRAYLAR® in the U.S., and in addition to being approved as an adjunctive therapy to antidepressants for the treatment of MDD in adults, it is FDA-approved to treat adults with depressive, acute manic and mixed episodes associated with bipolar I disorder, as well as schizophrenia. Cariprazine is co-developed by AbbVie and Gedeon Richter Plc. More than 8,000 patients worldwide have been treated with cariprazine across more than 20 clinical trials evaluating the efficacy and safety of cariprazine for a broad range of psychiatric disorders.

'Many living with major depressive disorder find that their ongoing antidepressant therapy doesn't offer meaningful relief from the symptoms they experience every day,' - said Thomas Hudson, M.D., senior vice president, research and development, chief scientific officer, AbbVie. 'Today's approval of VRAYLAR® provides an important new treatment option to meet a critical unmet medical need. AbbVie is committed to driving progress and advancing solutions for patients living with complex neuropsychiatric conditions.'

Highlights from the clinical program supporting the approval include:

- A Phase 3 Study 3111-301-001 showed a clinically and statistically significant change from baseline to week six in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score for patients treated with cariprazine at 1.5 mg/day + ADT compared with placebo + ADT. A second registration-enabling study, RGH-MD-75, showed a clinically and statistically significant change from baseline to week eight in the MADRS total score for patients treated with cariprazine at 2-4.5 mg/day (mean dose 2.6 mg) + ADT compared with placebo + ADT.
- Cariprazine was generally well-tolerated in 6- and 8-week studies. Mean weight change was < 2lbs and ≤ 3% of patients had a weight increase of ≥ 7%.
- The starting dosage of VRAYLAR® is 1.5 mg once daily. Depending upon clinical response and tolerability, the dosage can be increased to 3 mg once daily on Day 15. In clinical trials, dosage titration at intervals of less than 14 days resulted in a higher incidence of adverse reactions. The maximum recommended dosage is 3 mg, once daily.
- Most common adverse reactions observed in the adjunctive MDD studies (≥ 5% and at least twice the rate of placebo) were:
    - Akathisia, nausea, and insomnia at the recommended doses in 6-week, fixed-dose trials,
    - Akathisia, restlessness, fatigue, constipation, nausea, increased appetite, dizziness, insomnia, and extrapyramidal symptoms in one 8-week flexible-dose trial at a titration of less than 14 days.

About Major Depressive Disorder (MDD)

MDD is one of the most common mental disorders in the U.S., characterized by symptoms such as overwhelming feelings of sadness and/or loss of interest that don't go away after two weeks.[3] MDD can cause severe functional impairment, adversely affect interpersonal relationships, and may impact the quality of life.[4] It is a leading cause of disability in the world,[5] and has a lifetime prevalence of 20% for adults in the U.S.[1] Symptoms can include depressed mood, loss of pleasure or interest in activities, feelings of worthlessness, lack of energy, poor concentration, appetite changes, sleep disturbances, suicidal thoughts, and feeling restless or moving or talking more slowly.[3] In the U.S., the estimated economic burden of MDD has been estimated to be around $326 billion in 2020.[6]

About Study 3111-301-001

Study 3111-301-001 is a randomized, double-blind, placebo-controlled, multicenter trial with 751 participants conducted in the United States, Bulgaria, Estonia, Germany, Hungary, Ukraine and the United Kingdom. Following a screening period of up to 14 days, patients with an inadequate clinical response to their antidepressant monotherapy (ADT) were randomized into three treatment groups (1:1:1). The first group received cariprazine 1.5 mg/day + ADT, the second group received cariprazine 3.0 mg/day + ADT, and the third group received placebo + ADT. For six weeks, the medication was given once daily in addition to the ongoing ADT treatment. Patients treated with cariprazine 3.0 mg/day + ADT demonstrated improvement in MADRS total score at week six over placebo + ADT but did not meet statistical significance.

About Study RGH-MD-75

Study RGH-MD-75 is a randomized, double-blind, placebo-controlled, flexible-dose, outpatient, multicenter trial with 808 participants, conducted in the United States, Estonia, Finland, Slovakia, Ukraine and Sweden. After 7-14 days of screening and washout of prohibited medications, eligible patients entered an 8-week, double-blind treatment period in which they continued antidepressant treatment and were randomized (1:1:1) to adjunctive cariprazine 1-2 mg/day, cariprazine 2-4.5 mg/day, or placebo. Data from Study RGH-MD-75 were published in the *Journal of Clinical Psychiatry*.[7] Patients treated with cariprazine 1-2 mg/day + ADT demonstrated improvement in MADRS total score at week eight over placebo + ADT but did not meet statistical significance.

About VRAYLAR® (cariprazine)

VRAYLAR® is an oral, once-daily atypical antipsychotic approved as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD) in adults (1.5 or 3 mg/day), for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (1.5 or 3 mg/day), and for the acute treatment of adults with manic or mixed episodes associated with bipolar I disorder (3 to 6 mg/day). VRAYLAR® is also approved for the treatment of schizophrenia in adults (1.5 to 6 mg/day).

While the mechanism of action of VRAYLAR® is unknown, the efficacy of VRAYLAR® is thought to be mediated through a combination of partial agonist activity at central dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonist activity at serotonin 5-HT_{2A} receptors. Pharmacodynamic studies with VRAYLAR® have shown that it may act as a partial agonist with high binding affinity at dopamine D_3, dopamine D_2, and serotonin 5-HT_{1A} receptors. VRAYLAR® demonstrated up to ~8-fold greater *in vitro* affinity for dopamine D_3 vs D_2 receptors. VRAYLAR® also acts as an antagonist at serotonin 5-HT_{2B} and 5-HT_{2A} receptors with high and moderate binding affinity, respectively as well as it binds to the histamine H_1 receptors. VRAYLAR® shows lower binding affinity to the serotonin 5-HT_{2C} and α_{1A}- adrenergic receptors

and has no appreciable affinity for cholinergic muscarinic receptors.[8] The clinical significance of these *in vitro* data is unknown.

VRAYLAR® is developed jointly by AbbVie and Gedeon Richter Plc, with AbbVie responsible for commercialization in the U.S., Canada, Japan, Taiwan and certain Latin American countries (including Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Mexico, Peru and Venezuela).

Visit www.vraylar.com for more information.

About Richter

Gedeon Richter Plc. (www.gedeonrichter.com), headquartered in Budapest/Hungary, is a major pharmaceutical company in Central Eastern Europe, with an expanding direct presence in Western Europe, in China, in Latin America and in Australia. Having reached a market capitalization of EUR 4.4 billion (USD 5.0 billion) by the end of 2021, Richter's consolidated sales were approximately EUR 1.8 billion (USD 2.1 billion) during the same year. The product portfolio of Richter covers many important therapeutic areas, including Women's Healthcare, Central Nervous System and Cardiovascular areas. Having the largest R&D unit in Central Eastern Europe, Richter's original research activity focuses on CNS disorders. With its widely acknowledged steroid chemistry expertise, Richter is a significant player in the Women's Healthcare field worldwide. Richter is also active in biosimilar product development.

For further information:

Investors:

Katalin Ördög: +36 1 431 5680

Media:

Zsuzsa Beke: +36 1 431 4888

References:

1. Hasin DS, Sarvet AL, Meyers JL, et al. Epidemiology of Adult DSM-5 Major Depressive Disorder and Its Specifiers in the United States. *JAMA Psychiatry.* 2018;75(4):336-346.
2. Trivedi MH, Rush AJ, Wisniewski SR, et al. *Am J Psychiatry.* 2006;163(1):28-40.
3. National Institute of Mental Health (2022). Depression. Available at: https://www.nimh.nih.gov/health/topics/depression. Accessed December 2022.
4. Bains N, Abdijadid S. Major Depressive Disorder. [Updated 2022 Jun 1]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available at: https://www.ncbi.nlm.nih.gov/books/NBK559078/. Accessed December 2022.
5. Friedrich MJ. Depression Is the Leading Cause of Disability Around the World. *JAMA.* 2017;317(15):1517.
6. Greenberg P, Fournier AA, Sistsky T, et al. *Pharmacoeconomics.* 2021;39(6):653-65.
7. Durgam S, Earley W, Guo H, et al. *J Clin Psychiatry.* 2016;77(3):371-8.
8. VRAYLAR. Package insert. Allergan USA, Inc; 2022.