GEDEON RICHTER

AbbVie Submits Supplemental New Drug Application to U.S. FDA for cariprazine (VRAYLAR®) for the Adjunctive Treatment of Major Depressive Disorder

- *Submission is based on clinical trial results that include findings showing clinically and statistically significant improvement in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score in patients with major depressive disorder (MDD) treated with cariprazine (VRAYLAR®) and an antidepressant*
- *If approved, this milestone will be the fourth indication for cariprazine (VRAYLAR®) joining approvals for the treatment of adults with schizophrenia, the acute treatment of manic or mixed episodes associated with bipolar I disorder and the treatment of depressive episodes associated with bipolar I disorder*

Budapest, Hungary – 22 February 2022 – Richter's partner, AbbVie today announced that it has submitted a supplemental New Drug Application (sNDA) for cariprazine (VRAYLAR®) to the U.S. Food and Drug Administration (FDA) for the adjunctive treatment of major depressive disorder (MDD) in patients who are receiving ongoing antidepressant therapy. The submission is supported by results from previously announced clinical trials.

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 compared with placebo. 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 compared with placebo. In both of these studies, safety data were consistent with the established safety profile of cariprazine across indications, with no new safety events identified. Also supporting the submission is study RGH-MD-76 that examined the long-term safety and tolerability of cariprazine over 26 weeks.

'It is with great pleasure to know that the label extension of cariprazine in the USA has been submitted,' - said Gábor Orbán, Chief Executive Officer of Richter. 'We are confident that our partner AbbVie will co-operate with the FDA to bring a potential new adjunctive therapy to people suffering from MDD while undergoing antidepressant treatment and seeking additional symptom relief.'

Cariprazine is marketed as VRAYLAR® in the United States and is FDA-approved to treat adults with depressive, acute manic and mixed episodes associated with bipolar I disorder, as well as schizophrenia. Cariprazine is being 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.

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About Major Depressive Disorder (MDD)
MDD is one of the most common mental disorders in the United States. In 2020, an estimated 21 million adults had at least one major depressive episode. For some individuals, MDD can result in severe impairment which may interfere with or limit one's daily activities.[1] The World Health Organization lists depression as the third-leading cause of disability worldwide and as a major contributor to the overall global burden of disease. Symptoms can include depressed mood, loss of pleasure or interest in activities, changes in appetite or weight, changes in sleep, psychomotor retardation, loss of energy, feelings of worthlessness, indecisiveness, and recurrent thoughts of death.[2] In the United States, the estimated economic burden of MDD has been estimated to be around $326 billion.[3]

About Study 3111-301-001
Study 3111-301-001 is a randomized, double-blind, placebo-controlled, multicenter trial with 759 participants conducted in 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. Preliminary study findings were announced on October 29th, 2021 and will be presented at a future medical meeting.

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 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*.[4]

About Study RGH-MD-76
Study RGH-MD-76 is a long-term, multi-center, open label, flexible-dose safety and tolerability study with 347 participants, conducted in the United States. The study had one treatment group that received caripriazine 1.5-4.5 mg/d + ADT for 26 weeks. Patients entering from the 8-week lead-in study continued ADT at their lead-in study dose; new patients continued their protocol-allowed ADT. On day 1, cariprazine was initiated at 0.5 mg/day; the dosage was increased by 0.5 mg/day until the target dose of 3.0 mg/day was received on days 6 and 7. Dosages could be decreased to 1.5 mg/day for tolerability reasons at any time beginning at week 1 or increased to 4.5 mg/day for inadequate response between weeks 2 and 10. Data from Study RGH-MD-76 were published in *International Clinical Psychopharmacology*.[5]

More information can be found on www.clinicaltrials.gov (NCT03738215, NCT01469377, NCT01838876).

About VRAYLAR® (cariprazine)
VRAYLAR is an oral, once-daily atypical antipsychotic approved for the acute treatment of adults with manic or mixed episodes associated with bipolar I disorder (3 to 6 mg/day) and for the treatment of depressive episodes associated with bipolar I disorder (bipolar depression) in adults (1.5 or 3 mg/day). VRAYLAR is also approved for the treatment of schizophrenia in adults (1.5 to 6 mg/day). Use of VRAYLAR in adjunctive treatment of major depressive disorder is not approved and its safety and efficacy have not been evaluated by regulatory authorities.

While the mechanism of action of VRAYLAR is unknown, the efficacy of VRAYLAR could 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.[6] The clinical significance of these *in vitro* data is unknown.

VRAYLAR is being 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).

About Richter
Gedeon Richter Plc. (www.richter.hu), headquartered in Budapest/Hungary, is a major pharmaceutical company in Central Eastern Europe, with an expanding direct presence in Western Europe, in China and in Latin America. Having reached a market capitalization of EUR 3.8 billion (USD 4.7billion) by the end of 2020, Richter's consolidated sales were approximately EUR 1.6 billion (USD 1.8 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.

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VRAYLAR® (cariprazine) Uses and Important Safety Information

VRAYLAR is a prescription medicine used in adults:

- to treat schizophrenia
- for short-term (acute) treatment of manic or mixed episodes that happen with bipolar I disorder
- to treat depressive episodes that happen with bipolar I disorder (bipolar depression)

What is the most important information I should know about VRAYLAR?

Elderly people with dementia-related psychosis (having lost touch with reality due to confusion and memory loss) taking medicines like VRAYLAR are at an increased risk of death. VRAYLAR is not approved for treating patients with dementia-related psychosis.

Antidepressants may increase suicidal thoughts or actions in some children and young adults within the first few months of treatment and when the dose is changed. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Patients on antidepressants and their families or caregivers should watch for new or worsening depression symptoms, especially sudden changes in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant is started or when the dose is changed. Report any change in these symptoms immediately to the doctor.

VRAYLAR may cause serious side effects, including:

- **Stroke (cerebrovascular problems) in elderly people with dementia-related psychosis that can lead to death**
- **Neuroleptic malignant syndrome (NMS):** Call your healthcare provider or go to the nearest hospital emergency room right away if you have high fever, stiff muscles, confusion, increased sweating, or changes in breathing, heart rate, and blood pressure. These can be symptoms of a rare but potentially fatal side effect called NMS. VRAYLAR should be stopped if you have NMS
- **Uncontrolled body movements (tardive dyskinesia or TD):** VRAYLAR may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop taking VRAYLAR. Tardive dyskinesia may also start after you stop taking VRAYLAR
- **Late-occurring side effects:** VRAYLAR stays in your body for a long time. Some side effects may not happen right away and can start a few weeks after starting VRAYLAR, or if your dose increases. Your healthcare provider should monitor you for side effects for several weeks after starting or increasing dose of VRAYLAR
- **Problems with your metabolism, such as:**
  - **High blood sugar and diabetes:** Increases in blood sugar can happen in some people who take VRAYLAR. Extremely high blood sugar can lead to coma or death. Your healthcare provider should check your blood sugar before or soon after starting VRAYLAR and regularly during treatment. Tell your healthcare provider if you have symptoms such as feeling very thirsty, very hungry, or sick to your stomach, urinating more than usual, feeling weak, tired, confused, or your breath smells fruity
  - **Increased fat levels (cholesterol and triglycerides) in your blood:** Your healthcare provider should check fat levels in your blood before or soon after starting VRAYLAR and during treatment

    - **Weight gain:** Weight gain has been reported with VRAYLAR. You and your healthcare provider should check your weight before and regularly during treatment
- **Low white blood cell count:** Low white blood cell counts have been reported with antipsychotic drugs, including VRAYLAR. This may increase your risk of infection. Very low white blood cell counts, which can be fatal, have been reported with other antipsychotics. Your healthcare provider may do blood tests during the first few months of treatment with VRAYLAR
- **Decreased blood pressure (orthostatic hypotension):** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position
- **Falls:** VRAYLAR may make you sleepy or dizzy, may cause a decrease in blood pressure when changing position (orthostatic hypotension), and can slow thinking and motor skills, which may lead to falls that can cause fractures or other injuries
- **Seizures (convulsions)**
- **Impaired judgment, thinking, and motor skills:** Do NOT drive, operate machinery, or do other dangerous activities until you know how VRAYLAR affects you. VRAYLAR may make you drowsy
- **Increased body temperature:** Do not become too hot or dehydrated during VRAYLAR treatment. Do not exercise too much. In hot weather, stay inside in a cool place if possible. Stay out of the sun. Do not wear too much clothing or heavy clothing. Drink plenty of water
- **Difficulty swallowing** that can cause food or liquid to get into your lungs

Who should not take VRAYLAR?
Do not take VRAYLAR if you are allergic to any of its ingredients. Get emergency medical help if you are having an allergic reaction (eg, rash, itching, hives, swelling of the tongue, lip, face or throat).

What should I tell my healthcare provider before taking VRAYLAR?

Tell your healthcare provider about any medical conditions and if you:

- have or have had heart problems or a stroke
- have or have had low or high blood pressure
- have or have had diabetes or high blood sugar in you or your family
- have or have had high levels of total cholesterol, LDL-cholesterol, or triglycerides; or low levels of HDL-cholesterol
- have or have had seizures (convulsions)
- have or have had kidney or liver problems
- have or have had low white blood cell count
- are pregnant or plan to become pregnant. VRAYLAR may harm your unborn baby. Talk to your healthcare provider about the risk to your unborn baby if you take VRAYLAR during pregnancy. If you become pregnant or think you are pregnant during treatment, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or http://www.womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
- are breastfeeding or plan to breastfeed. It is not known if VRAYLAR passes into breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with VRAYLAR

Tell your healthcare provider about all medicines that you take, including prescriptions, over-the-counter medicines, vitamins, and supplements. VRAYLAR may affect the way other medicines work, and other medicines may affect how VRAYLAR works. Do not start or stop any medicines while taking VRAYLAR without talking to your healthcare provider.

What are the most common side effects of VRAYLAR?

- The most common side effects were difficulty moving or slow movements, tremors, uncontrolled body movements, restlessness and feeling like you need to move around, sleepiness, nausea, vomiting, and indigestion.

These are not all possible side effects of VRAYLAR.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

If you are having difficulty paying for your medicine, AbbVie may be able to help. Visit AbbVie.com/myAbbVieAssist to learn more.

Please see the full Prescribing Information, including Boxed Warnings, and Medication Guide.

Globally, prescribing information varies; refer to the individual country product label for complete information.

References:

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