



June 17, 2022

| | |
|------------------------|------------------------------------------------------------------------------------|
| Company Name | Otsuka Holdings Co., Ltd. |
| Name of Representative | Tatsuo Higuchi President and Representative Director, CEO |
| Code Number | 4578, Prime market of the Tokyo Stock Exchange |
| Contact | Yuji Kogure Director, Investor Relations Department (Phone: +81-3-6361-7411) |

European Medicines Agency Commences Review of Aripiprazole 2-Month Long-Acting Injectable for the Maintenance Treatment of Schizophrenia in Adult Patients Stabilised with Aripiprazole

LONDON, UK, 16 June 2022 – Otsuka Pharmaceutical Europe Ltd. (“Otsuka”) and H. Lundbeck A/S (“Lundbeck”) today announce that the European Medicines Agency (EMA) has accepted the Marketing Authorisation Application (MAA) for aripiprazole as a 2-month ready-to-use (RTU) long-acting injectable (LAI) for the maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.

Aripiprazole 2-month RTU LAI is a new formulation provided in a single chamber prefilled syringe that does not require reconstitution¹. It is intended for dosing every two months via intramuscular injection into the gluteal muscle, in the same patient population as indicated for Abilify Maintena[®] (aripiprazole once-monthly LAI)¹. If approved, aripiprazole 2-month RTU LAI would be the first 2-month LAI antipsychotic licensed in the EU indicated for the maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole.

Medication adherence in patients with schizophrenia is generally poor² and several studies have demonstrated that a predictor for further relapse is nonadherence to antipsychotic medications³. A long-acting injectable formulation ensures continuous exposure to medication and through a simplified treatment regimen, many of the challenges with poor treatment adherence may be mitigated, resulting in a potential positive impact on patient outcomes⁴. In patients with schizophrenia, long-acting injectable formulations have been shown to increase adherence and reduce relapse rates versus oral antipsychotics^{4,5,6}.

The MAA is supported by findings from a pharmacokinetic bridging study that examined the safety, tolerability and pharmacokinetics of aripiprazole 2-month RTU LAI 960 mg in 266 adults with schizophrenia or bipolar I disorder over the course of 32 weeks as compared to those from monthly administrations of aripiprazole 400 mg once-monthly over the same time course¹. Results from the pivotal trial NCT04030143 (clinicaltrials.gov), demonstrated that aripiprazole RTU LAI 960 mg met the primary endpoint of establishing similar concentrations of aripiprazole over a 2-month dosing interval to those achieved with aripiprazole 400 mg once-monthly¹. Multiple-dose administrations of aripiprazole 2-month RTU LAI 960 mg were generally well-tolerated in subjects with schizophrenia or bipolar I disorder and did not show any new safety concerns compared to aripiprazole 400 mg once-monthly¹.

About Aripiprazole

Aripiprazole is dopamine D₂ partial agonist with weak 5-HT_{1a} partial agonism and 5-HT_{2A} receptor antagonism⁷. It is available as a daily oral tablet, orally disintegrating tablet, and oral solution (Abilify[®]), or a once monthly LAI formulation (Abilify Maintena[®])⁸. Abilify is also available as a short-acting Intramuscular (IM) Injection⁷.

Aripiprazole was discovered by Otsuka and is being co-developed under a collaboration and license agreement between Otsuka Pharmaceutical Europe Ltd. and H. Lundbeck A/S.

About Schizophrenia

Schizophrenia is a chronic, disabling and progressive mental illness, characterised by delusions, hallucinations, and disordered cognition which may occur at varying intervals between periods of relative symptomatic stability⁹. Schizophrenia affects approximately 24 million people or 1 in 300 people (0.32%) worldwide¹⁰. Onset is most often during late adolescence and the twenties, and onset tends to happen earlier among men than women¹⁰. Schizophrenia is frequently associated with significant distress and impairment in personal, family, social, educational, occupational, and other important areas of life¹⁰. It is one of the top 15 leading causes of disability worldwide¹¹.

About Otsuka

Otsuka Pharmaceutical is a global healthcare company with the corporate philosophy: “Otsuka-people creating new products for better health worldwide.” Otsuka researches, develops, manufactures and markets innovative products, focusing on pharmaceutical products to meet unmet medical needs and nutraceutical products for the maintenance of everyday health. In pharmaceuticals, Otsuka is a leader in the challenging area of mental health and also has research programs in several under-addressed diseases including tuberculosis, a significant global public health issue.

Otsuka Europe employs over 500 people and focuses on psychiatric and neurologic disorders, infectious disease, nephrology, oncology, and digital medicines. Otsuka Pharmaceutical Europe Ltd. is a part of Otsuka Pharmaceutical Company, Ltd., a subsidiary of Otsuka Holdings Co., Ltd. headquartered in Tokyo, Japan.

The Otsuka group of companies employed 47,000 people worldwide with consolidated sales of approximately €11.6 billion and a spend of €1.8 billion on research and development in 2021.

About H. Lundbeck A/S

H. Lundbeck A/S is a global pharmaceutical company specialized in brain diseases. For more than 70 years, we have been at the forefront of neuroscience research. We are tirelessly dedicated to restoring brain health, so every person can be their best.

Too many people worldwide live with brain diseases – complex conditions often invisible to others that nonetheless take a tremendous toll on individuals, families and societies. We are committed to fighting stigma and discrimination against people living with brain diseases and advocating for broader social acceptance of people with brain health conditions. Every day, we strive for improved treatment and a better life for people living with brain disease.

We have approximately 5,300 employees in more than 50 countries, and our products are available in more than 100 countries. Our research programs tackle some of the most complex challenges in neuroscience, and our pipeline is focused on bringing forward transformative treatments for brain diseases for which there are few, if any therapeutic options. We have research facilities in Denmark and the United States, and our production facilities are located in Denmark, France, and Italy. Lundbeck generated revenue of DKK 16.3 billion in 2021 (EUR 2.2 billion; USD 2.6 billion).

References

1. Data on file. Otsuka UK/Pharma Europe Ltd. Aripiprazole 2M RTU LAI 960mg 031-201-00181 Ph1b Study- Primary endpoint results. OPE-AM-2200049.8-Jun-2022.
2. Brissos S, et al. *Ther Adv Psychopharmacol* 2014; 4(5): 198–219

3. Emsley R et al. BMC Psychiatry 2013;13:50
4. Zhornitsky S & Stip E. Schizophr Res Treatment 2012; 2012:407171
5. Agid O, et al. Expert Opin Pharmacother 2010; 11 (14): 2301–2317
6. Leucht C, et al. Schizophr Res 2011;127(1–3): 83-92
7. NICE. Aripiprazole. Available at: <https://bnf.nice.org.uk/drug/aripiprazole.html> [Accessed: June 2022]
8. NICE. Aripiprazole. Medicinal forms. Available at: <https://bnf.nice.org.uk/drugs/aripiprazole/medicinal-forms/#solution-for-injection> [Accessed: June 2022]
9. Kahn RS, et al. Nat Rev Dis Primers 2015; 1 (15067)
10. World Health Organisation. Factsheet, Schizophrenia. Available at: <https://www.who.int/news-room/factsheets/detail/schizophrenia> [Accessed: June 2022]
11. Global Burden of Disease Study 2016. Lancet 2017;390 (10100): 1211–1259