ONO PHARMACEUTICAL CO.,LTD.

April 26, 2018

ONO Submits an Application for Manufacturing and Marketing Approval for Metyrosine (ONO-5371), a Tyrosine Hydroxylase Inhibitor, for Improvement of Status of Catecholamine Excess Secretion and its Accompanying Symptoms in Patients with Pheochromocytoma in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it submitted an application for manufacturing and marketing approval of metyrosine (ONO-5371), a tyrosine hydroxylase inhibitor, for the improvement of status of catecholamine excess secretion and its accompanying symptoms in patients with pheochromocytoma in Japan.

This application is based on a multi-center, open-label, non-comparative study and its accompanying continuous administration study, Phase I/II study (ONO-5371-02), in patients with the symptoms associated with catecholamine excess secretion of pheochromocytoma, conducted in Japan.

Pheochromocytoma (PC) is a neuroendocrine tumor deriving from the adrenal medulla or the extra-adrenal gland ganglion with 2,920 patients estimated in Japan*. Catecholamine excessively produced from PC causes various symptoms, such as tachycardia, headache, palpitation, sweating, constipation, including hypertension. Sympatholytic drugs, α-blocker and β-blocker, for control of blood pressure and heart rate have been usually used to improve these symptoms. As there are many cases where surgical removal of tumors is not applicable in patients with locally invasive or metastatic malignant PC, a long-term therapy, such as radiotherapy and chemotherapy is required. The chronic continuation of catecholamine excess secretion may increase a risk of causing cardiovascular-related adverse events such as heart failure or fatal arrhythmia.

Metyrosine is a product for which development companies were recruited in Japan at the "Review Committee on Unapproved or Off-label Drugs with High Medical Needs", established by the Ministry of Health, Labour and Welfare (MHLW). Further, in May 2015, the product was designated for the orphan drug by the MHLW for the indication of "Improvement of status of catecholamine excess secretion and its accompanying symptoms in patients with PC".

ONO obtained exclusive rights to develop and commercialize metyrosine in Japan for the prevention, treatment and diagnosis of PC (and conditions and symptoms related thereto), in accordance with the license agreement concluded in October 2013 with Valeant Pharmaceuticals North America LLC (Valeant), an affiliate of Valeant Pharmaceuticals International, Inc.
In the US, Valeant markets metyrosine under the tradename of "Demser®" in the indication of PC.

*: "Actual condition survey and preparation of medical guideline of pheochromocytoma" Research Report 2009, Research Project on Overcoming Intractable Diseases Project being conducted by the Ministry of Health, Labour and Welfare

Methyrosine

Metyrosine inhibits tyrosine hydroxylase related to the production of catecholamine, reduces catecholamine extremely produced from PC, and alleviates symptoms due to catecholamine excess secretion. Therefore, metyrosine is a promising drug with an efficacy in the improvement of the symptoms in patients who are not able to sufficiently control the symptoms with sympatholytic drugs.

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