ONO PHARMACEUTICAL CO.,LTD.

December 27, 2018

ONO Submits an Application for Manufacturing and Marketing Approval in Japan for Ivabradine Hydrochloride (ONO-1162) for the Treatment of Chronic Heart Failure

Ono Pharmaceutical Co., Ltd. (Osaka, Japan, President and Representative Director: Gyo Sagara; "ONO") announced today that it has submitted in Japan an application for manufacturing and marketing approval of ivabradine hydrochloride ("Ivabradine"), a HCN (hyperpolarization-activated cyclic nucleotide-gated) channel inhibitor, for the treatment of patients with chronic heart failure with resting heart rate ≥75 beats per minute in sinus rhythm.

This application is mainly based on the results from the following two clinical studies:

1) A multi-center, randomized, double blind, placebo controlled study (J-SHIFT study), conducted in Japan in 254 patients with chronic heart failure: NYHA (New York Heart Association) class II to IV, resting heart rate ≥75 beats per minute in sinus rhythm, and left ventricular ejection fraction (LVEF) ≤35% under optimal background therapy, and
2) A multi-center, randomized, double blind, placebo controlled study (SHIFT study) [*1], conducted overseas in 6,505 patients with chronic heart failure (resting heart rate ≥70 beats per minute in sinus rhythm) similar to the J-SHIFT study.

Heart failure is defined as a clinical syndrome in which dyspnea, malaise and edema appear as a result of failure of compensatory function of the cardiac pump due to cardiac dysfunction, resulting in a decrease in exercise tolerance. Chronic heart failure is the condition where the situation of heart failure chronically continues, and the number of patients with chronic heart failure in Japan is estimated to reach 1.2 million in 2020[*2]. The drugs used for the treatment of chronic heart failure include angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, beta blockers, anti-aldosterone drugs, diuretics, etc. for the purpose of controlling symptoms of patients, preventing hospitalization, and avoiding death in patients with chronic heart failure.

In patients with chronic heart failure, the heart rate tends to increase to compensate for the inability of the heart to exert sufficient blood volume leading to put more strain on the heart. In addition, it is thought that higher heart rates have a negative impact on the prognosis in patients with chronic heart failure. Ivabradine is expected to become one of new treatment options for patients with high heart rate even if they take existing drugs for the treatment of chronic heart failure.

In accordance with the license agreement entered in September 2011 with Servier, a French company, ONO has exclusive rights to develop and commercialize Ivabradine in Japan and has been committed to developing the product for the treatment of chronic heart failure.

*1： Swedberg K, Komajda M, Böhm M et al. Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study. Lancet 2010; 376:875-85

*2： Guidelines for Diagnosis and Treatment of Acute and Chronic Heart Failure. (JCS 2017/JHFS 2017)

About Ivabradine

Ivabradine, discovered and developed by Servier, is an innovative orally-active agent which suppresses hyperpolarization-activated cationic current (I_f), cardiac pacemaker current, by inhibiting the HCN (hyperpolarization-activated cyclic nucleotide-gated) channel expressed in the cardiac sinus node. It has the effect of decreasing only heart rate without affecting the cardiac conductivity, contractility, repolarization and blood pressure.

In February 2012, Ivabradine was approved by the European Commission (EC) for the treatment of chronic heart failure (CHF). In the US, a US-based Amgen, a collaboration partner of Servier, received an NDA approval for Ivabradine for the treatment of CHF from the US Food and Drug Administration (FDA) in April 2015.

Ivabradine was also approved for the treatment of chronic stable angina pectoris by the EC in October 2005. Ivabradine has been approved in 122 countries or regions, among which it has been approved in 115 countries for both indications of CHF and chronic stable angina pectoris.

About Servier

Servier is an international pharmaceutical company governed by a non-profit foundation, with its headquarters in France (Suresnes). With a strong international presence in 149 countries and a turnover of 4.152 billion euros in 2017, Servier employs 21,700 people worldwide. Entirely independent, the Group reinvests 25% of its turnover (excluding generic drugs) in research and development and uses all its profits for development. Corporate growth is driven by Servier's constant search for innovation in five areas of excellence: cardiovascular, immune-inflammatory and neuropsychiatric diseases, cancer and diabetes, as well as by its activities in high-quality generic drugs. Servier also offers eHealth solutions beyond drug development. More information: www.servier.com

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