ONO PHARMACEUTICAL CO.,LTD.

September 20, 2019

ONO Receives a Manufacturing and Marketing Approval for Coralan® Tablet for the Treatment of Chronic Heart Failure in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan, President and Representative Director: Gyo Sagara; "ONO") announced today that it received a manufacturing and marketing approval of Coralan® (generic name: ivabradine hydrochloride) 2.5mg, 5mg and 7.5mg ("Coralan"), a HCN (hyperpolarization-activated cyclic nucleotide-gated) channel blocker, for the treatment of patients with chronic heart failure with sinus rhythm and baseline resting heart rate ≥75 beats per minute (limited to patients receiving standard treatment of chronic heart failure, including β-blocker) in Japan.

This approval 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) *1, conducted in Japan in 254 patients with chronic heart failure (CHF): 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) *2, conducted overseas in 6,505 patients with CHF (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, fatigue 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. CHF is the condition where the situation of HF chronically continues, and the number of patients with CHF in Japan is estimated to reach 1.2 million in 2020*3. The drugs used for the treatment of CHF include angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, β-blockers, anti-aldosterone drugs, diuretics, etc. for the purpose of controlling symptoms of patients, preventing hospitalization, and avoiding death in patients with CHF.

In patients with CHF, 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 has been shown that higher heart rates have a negative impact on the prognosis in patients with CHF. Coralan provides a new treatment options for patients with high heart rate even if they take existing drugs for the treatment of CHF.

*1： Tsutsui H, Momomura S, Yamashina A, et al. Efficacy and safety of ivabradine in Japanese patients with chronic heart failure－J-SHIFT Study. Circ J 2019. doi: 10.1253/circj.CJ-19-0227.

*2： 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

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

Overview of Coralan® Tablet 2.5 mg, 5mg and 7.5mg

Product Name	Coralan® Tablet 2.5 mg, 5mg and 7.5mg
Generic name (JAN)	Ivabradine hydrochloride
Indication	Chronic heart failure with sinus rhythm and baseline resting heart rate ≥75 beats per minute (limited to patients receiving standard treatment of chronic heart failure, including β-blocker)
Dosage and administration	Usually, for adults, start the administration at 2.5 mg of ivabradine orally after meal twice a day. Thereafter, adjust dose in more than 2-weeks interval as needed in a stepwise manner, to achieve and maintain a target resting heart rate while assessing the tolerability. One-dose should be settled either 2.5, 5 or 7.5 mg. In either dose, administer ivabradine orally after meal twice a day. The dose should be decreased based on patients' condition.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	September 20, 2019

About Ivabradine (Coralan® Tablet)

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 CHF. In the US, Amgen, a collaboration partner of Servier, received an NDA approval for Ivabradine to reduce the risk of hospitalization for worsening heart failure in patients with 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 124 countries or regions, among which it has been approved in 116 countries for both indications of CHF and chronic stable angina pectoris.

About the ONO and Servier Collaboration

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 CHF.
(Servier is an independent international pharmaceutical company, governed by a non-profit foundation, with headquarters in France (Suresnes). More information: www.servier.com.)

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