ONO PHARMACEUTICAL CO.,LTD.

June 29, 2020

A Short-Acting Selective β_1 Blocker, Onoact® for Intravenous Infusion 50mg/150mg Approved for Additional Indication of Tachyarrhythmia Associated with Sepsis in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that ONO received an approval of Onoact® (generic name: landiolol hydrochloride) for Intravenous Infusion 50mg/150mg ("Onoact"), a short-acting selective β_1 blocker for additional indication of tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) associated with sepsis for a partial change in the approved items of the manufacturing and marketing approval in Japan.

This approval is based on the result of a multi-center, randomized, open-label, parallel-group, late Phase Ⅱ / Ⅲ study (J-Land 3S study: ONO-1101-32) conducted in Japan, in patients with tachyarrhythmia associated with sepsis. In this study, Onoact demonstrated significantly larger proportion of patients of 54.7% (41 of 75 patients), compared to the currently available therapeutic drugs of 33.3% (25 of 75) in the primary endpoint of the proportion of patients whose heart rate at 24 hour after randomization could be adjusted to 60 ~ 94 beats/min. The safety profile of Onoact observed in this study was consistent with that observed in studies of approved indications. The results of this study are published in The LANCET Respiratory Medicine. Please visit the following website: https://www.sciencedirect.com/science/article/abs/pii/S2213260020300370?via%3Dihub

Sepsis is defined as a condition that causes severe organ dysfunction due to infection. It is known that sympathetic hyperactivity promotes the organ dysfunction. Tachyarrhythmia may develop in sepsis patients as a result of sympathetic hyperactivity and increases in inflammatory cytokines.

Onoact, discovered and developed internally by ONO, is a short-acting selective β_1 blocker which relaxes the tension of sympathetic nervous by selectively blocking β_1 receptor existing mostly in the heart. It is expected that Onoact can contribute to patients for the therapy of tachyarrhythmia associated with sepsis.

ONO launched Onoact for emergency treatment of intra-operative tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) in September 2002. Then, it was approved for additional indication of emergency treatment of post-operative tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) occurring under the monitoring of circulatory dynamics in October 2006, for treatment of tachyarrhythmia (atrial fibrillation and atrial flutter) in deteriorated cardiac function in November 2013 and for treatment of refractory and urgent fatal arrhythmia (ventricular fibrillation and hemodynamically unstable ventricular tachycardia) in March 2019.

Overview of Onoact® for Intravenous Infusion 50mg/150mg

Product Name	Onoact® for Intravenous Infusion 50mg/150mg
Generic name	Landiolol hydrochloride
Indication	1. Emergency treatment of the following intraoperative tachyarrhythmia: Atrial fibrillation, atrial flutter and sinus tachycardia 2. Emergency treatment of the following postoperative tachyarrhythmia occurring under the monitoring of circulatory dynamics: Atrial fibrillation, atrial flutter and sinus tachycardia 3. Following tachyarrhythmia in patients with deteriorated cardiac function: Atrial fibrillation and atrial flutter 4. Following the refractory and urgent fatal arrhythmia: Ventricular fibrillation and hemodynamically unstable ventricular tachycardia 5. Following tachyarrhythmia associated with sepsis: Atrial fibrillation and flutter, and sinus tachycardia
Dosage and administration	**1. Emergency treatment of the following intraoperative tachyarrhythmia:** **Atrial fibrillation, atrial flutter and sinus tachycardia** After continuous intravenous administration at 0.125 mg/kg/min as landiolol hydrochloride for 1 min, continue its intravenous administration at 0.04 mg/kg/min. During administration, heart rate and blood pressure should be measured and the dose adjusted within the range of 0.01 to 0.04 mg/kg/min. **2. Emergency treatment of the following postoperative tachyarrhythmia occurring under the monitoring of circulatory dynamics:** **Atrial fibrillation, atrial flutter and sinus tachycardia** After continuous intravenous administration at 0.06 mg/kg/min as landiolol hydrochloride for 1 min, continue its intravenous administration at 0.02 mg/kg/min. If the heart rate is not reduced to the desired level within about 5 to 10 min, then administer at 0.125 mg/kg/min for 1 min by the same route and subsequently at 0.04 mg/kg/min. During administration, heart rate and blood pressure should be measured and the dose adjusted within the range of 0.01 to 0.04 mg/kg/min. **3. Following tachyarrhythmia in patients with deteriorated cardiac function:** **Atrial fibrillation and atrial flutter** Start continuous intravenous administration at 1 μg/kg/min as landiolol hydrochloride. During administration, heart rate and blood pressure should be measured and the dose adjusted within the range of 1 to 10 μg/kg/min. 4. **Following refractory and urgent fatal arrhythmia:** **Ventricular fibrillation, hemodynamically unstable ventricular tachycardia** Start continuous intravenous administration at 1 μg/kg/min as landiolol hydrochloride. During administration, heart rate and blood pressure should be measured and the dose adjusted within the range of 1 to 10 μg/kg/min. If ventricular fibrillation or hemodynamically unstable ventricular tachycardia recurs and administration is necessary, the dose can be increased up to 40 μg/kg/min, while measuring heart rate and blood pressure. **5. Following tachyarrhythmia associated with sepsis:** **Atrial fibrillation, atrial flutter and sinus tachycardia** Start continuous intravenous administration at 1 μg/kg/min as landiolol hydrochloride. During administration, heart rate and blood pressure should be measured, and the maintenance dose should be adjusted as appropriate. The maximum dose should not exceed 20 μg/kg/min.

Manufacturer/ distributor	Ono Pharmaceutical Co., Ltd
Date of Approval	June 29, 2020

Note: Underlined parts show the revised ones according to this approval.

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