ONO PHARMACEUTICAL CO.,LTD.

March 26, 2019

A Short-Acting Selective β_1 Blocker,
ONOACT® for Intravenous Infusion 50mg/150mg Approved for
Additional Indication of Ventricular Arrhythmia in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director, Gyo Sagara; "ONO") announced today that it received an approval of ONOACT® for Intravenous Infusion 50mg/150mg ("ONOACT", generic name: landiolol hydrochloride), a short-acting selective β_1 blocker for additional indication of refractory and urgent fatal arrhythmia (ventricular fibrillation and hemodynamically unstable ventricular tachycardia) as a partial change in the approved items of the manufacturing and marketing approval in Japan.

This approval is based on the result from a multi-center, open-label, non-comparative study, late Phase Ⅱ/Ⅲ study (ONO-1101-30), conducted in Japan, in patients with recurrent ventricular arrhythmia.

Ventricular arrhythmia that occurs in the ventricle responsible for pumping blood to the whole body is classified as ventricular tachycardia (VT) and ventricular fibrillation (VF). Since ventricular arrhythmia is fatal one that causes sudden cardiac death, it is necessary to stop the arrhythmia by electrical defibrillation as soon as it occurs and to prevent the recurrence of ventricular arrhythmias. It is known that the tension of sympathetic nerve in the ventricle is related to the occurrence of ventricular arrhythmia as one of pathogenic mechanisms. The use of beta blockers is recommended in guidelines for ventricular arrhythmias and sudden cardiac death in Japan and abroad.

ONOACT is a short-acting selective β_1 blocker discovered and developed internally by ONO, which relaxes the tension of sympathetic nervous by selectively blocking β_1 receptors existing mostly in the heart. It is expected that expect that ONOACT can contribute to the therapy of fatal arrhythmia requiring emergency treatment. The product was designated as an orphan drug by the Ministry of Health, Labour and Welfare (MHLW) in August 2016 for the indication of "refractory and urgent fatal arrhythmia (VF and hemodynamically unstable VT).

ONOACT was approved for emergency treatment of intra-operative tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) in July 2002. Then, it was also approved for emergency treatment of post-operative tachyarrhythmia (atrial fibrillation, atrial flutter and sinus tachycardia) occurring under the monitoring of circulatory dynamics in October 2006 and for the treatment of tachyarrhythmia (atrial fibrillation and atrial flutter) in deteriorated cardiac function in November 2013.

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
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.
Manufacturer/ distributor	Ono Pharmaceutical Co., Ltd
Approval Condition	Risk Management Plan should be designed appropriately implemented.

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

Contact
ONO PHARMACEUTICAL CO., LTD.
Corporate Communications
public_relations@ono.co.jp