ONO PHARMACEUTICAL CO.,LTD.

August 24, 2022

A Short-Acting Selective β_1 Blocker, Onoact® for Intravenous Infusion 50mg/150mg Approved for Additional Indication of Tachyarrhythmia in Pediatric Patients with Low Cardiac Function 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 in Japan for additional indication of tachyarrhythmia (supraventricular tachycardia, atrial fibrillation and atrial flutter) in pediatric patients with low cardiac function for a partial change in the approved items of the manufacturing and marketing approval.

This approval is based on the results of a multi-center, open-label, uncontrolled late Phase II/III study (Heartful study: ONO-1101-31) conducted in Japan in pediatric patients with tachyarrhythmia accompanied by low cardiac function. In this study, the percent of patients with a reduction in heart rate ≥20% from the initial rate of tachycardia or termination of tachycardia at 2 hours after starting Onoact, the primary endpoint, was 48.0% (12/25 patients). The safety profile of Onoact in this study was consistent with that observed in studies of approved indications, and no new safety concerns were observed.

In case of low cardiac function with unstable hemodynamics, such as after open-heart surgery for congenital heart diseases in pediatric patients, if tachyarrhythmia persists, it may be potentially serious or fatal. Therefore, the treatment for tachyarrhythmia is immediately required. Since non-drug treatment such as catheter ablation may be sometimes difficult in pediatric patients due to their physique and age, drug treatment is an important and main treatment method. However, there are few antiarrhythmic drugs approved for pediatric indications and treatment options are limited in Japan.

Onoact is a short-acting selective β_1 blocker that reduces heart rate by selectively blocking β_1 receptor which is present predominantly in the heart. Therefore, Onoact is expected to become a new treatment option for tachyarrhythmia in pediatric patients with low cardiac function.

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

Product name	Onoact® for Intravenous Infusion 50mg/150mg
Generic name	Landiolol hydrochloride
Indication	<Adults> ○ Emergency treatment of the following intraoperative tachyarrhythmia: Atrial fibrillation, atrial flutter and sinus tachycardia ○ Emergency treatment of the following postoperative tachyarrhythmia occurring under the monitoring of circulatory dynamics: Atrial fibrillation, atrial flutter and sinus tachycardia ○ Following tachyarrhythmia in patients with low cardiac function: Atrial fibrillation and atrial flutter ○ Following the refractory and urgent fatal arrhythmia: Ventricular fibrillation and hemodynamically unstable ventricular tachycardia ○ Following tachyarrhythmia associated with sepsis: Atrial fibrillation, atrial flutter and sinus tachycardia <Pediatrics> ○ Following tachyarrhythmia with low cardiac function: Supraventricular tachycardia, atrial fibrillation and atrial flutter
Dosage and administration	**<Emergency treatment of intraoperative tachyarrhythmia>** 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. **<Emergency treatment of postoperative tachyarrhythmia occurring under the monitoring of circulatory dynamics>** 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. **<Tachyarrhythmia in adult and pediatric patients with low cardiac function>** 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. **<Refractory and urgent fatal arrhythmia>** 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. **<Tachyarrhythmia associated with sepsis>** 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	August 24, 2022

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

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