ONO PHARMACEUTICAL CO.,LTD.

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ONO Submits an Application for Manufacturing and Marketing Approval of Opicapone (ONO-2370) for the Treatment of Parkinson´s Disease Patients with Motor Fluctuations in Japan

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 Opicapone (ONO-2370), a catechol-*O*-methyltransferase (COMT) inhibitor, for improvement of the end-of-dose motor fluctuations (wearing-off phenomenon) of Parkinson's disease as an adjunctive therapy to levodopa preparations.

This application is mainly based on the data of a multi-center, placebo controlled, randomized, double-blind, parallel group study and open-label, uncontrolled, long-term extension study (ONO-2370-02 study) in patients with idiopathic Parkinson's disease with wearing-off phenomenon treated with levodopa (dopamine precursor) and DOPA decarboxylase inhibitors (DDCis).

Parkinson's disease is a progressive neurodegenerative disease presenting with end-of-dose motor symptoms such as bradykinesia, tremor and muscle rigidity. The number of patients with Parkinson's disease in Japan is estimated to be approximately 163,000*. The symptoms of Parkinson's disease are caused by degenerative loss of dopamine containing neurons in the substantia nigra and the impaired dopaminergic function of the basal ganglia.

Levodopa, usually administered in combination with a DDCi, which inhibits the activity of the main pathway of levodopa metabolism (decarboxylation) and improves levodopa´s distribution in the central nervous system and short-duration response to levodopa, is the most effective symptomatic treatment for Parkinson's disease. However, levodopa/DDCi preparations are required to be taken several times per day due to levodopa's short half-life. When the patient develops wearing-off phenomenon due to Parkinson's disease progression and levodopa's short duration of action, adjunctive therapy to levodopa/DDCi is often necessary. COMT inhibitors (COMTis), one of the adjunctive therapies to levodopa/DDCi, act by inhibiting the COMT enzyme, which is responsible for alternative pathway of levodopa metabolism, and prolong levodopa's duration of action, like DDCi. Therefore, they are useful in reducing OFF-time in patients with Parkinson's disease and end-of-dose wearing-off.

Opicapone is a novel peripheral long-acting COMTi which has demonstrated efficacy in reducing OFF-time in patients with Parkinson disease and end-of-dose wearing-off. Opicapone's once daily administration is expected to contribute to reducing the burden on patients taking medication as well as improving patient medication adherence.

In April 2013, ONO entered into a license agreement with BIAL to exclusively develop and commercialize Opicapone (under license from BIAL) for the treatment of end-of-dose motor fluctuations (wearing-off phenomenon) of Parkinson's disease in Japan.

In Europe, Opicapone was approved by the European Commission in June 2016 as adjunct therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCis) in adult patients with Parkinson's disease and end-of-dose motor fluctuations who cannot be stabilized on those combinations. BIAL has been marketing Opicapone under the product name of ONGENTYS®.

*: Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare. Patient Survey 2014 (Disease and Injury).

About Opicapone

Opicapone is a third-generation catechol-*O*-methyltransferase (COMT) inhibitor originated at BIAL. It was rationally designed to provide a peripherally selective high COMT inhibitory potency and to avoid cell toxicity[1].

Opicapone increases the bioavailability of levodopa by up to 65% vs placebo and this translates into a dose-dependent reduction in OFF-time[2,3,4]. Molecular structure resulted in an exceptionally high binding affinity (femtomolar) that translates into a slow complex dissociation rate constant and a long duration of action that allows once-daily dosing[5,6].

About BIAL

Founded in 1924, BIAL's mission is to discover, develop, and provide therapeutic solutions within the area of health. In recent decades, BIAL has strategically focused on quality, innovation, and internationalization.

BIAL is strongly committed to therapeutic innovation, investing over 20% of its annual turnover in Research and Development (R&D) centered on the neurosciences and cardiovascular system.

BIAL expects to strengthen its international presence by continuing to deliver innovative medicines to healthcare professionals, patients and their families worldwide, always inspired by its strong motivation: "Keeping life in mind".

For more information about BIAL, please visit www.bial.com.

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