ONO PHARMACEUTICAL CO.,LTD.

June 29, 2020

Ono Receives a Manufacturing and Marketing Approval in Japan of "Ongentys® Tablets 25mg", a Peripheral COMT Inhibitor for the Improvement of Parkinson's Disease Patients with Motor Fluctuations

Ono Pharmaceutical Co., Ltd. (Osaka, Japan, President and Representative Director: Gyo Sagara; "ONO") announced today that it has received a manufacturing and marketing approval of "Ongentys® (opicapone) Tablets 25mg" ("Ongentys"), a catechol-O-methyltransferase (COMT) inhibitor (COMTi), in Japan for the improvement of the end-of-dose motor fluctuations (wearing-off phenomenon) in Parkinson's disease in combination with levodopa–carbidopa or levodopa–benserazide hydrochloride.

This approval is mainly based on the results of a multi-center, placebo controlled, randomized, double-blind, parallel group study and an open-label, uncontrolled, long-term extension study conducted in Japan in patients with Parkinson's disease with wearing-off phenomenon which is treated with levodopa (dopamine precursor) and a DOPA decarboxylase inhibitor (DDCi) (ONO-2370-02 study). This study demonstrated superiority of opicapone compared to placebo in the primary endpoint of a change in OFF-time from baseline. In addition, the study showed that there were no newly concerned adverse drug reactions associated with opicapone and that the drug was well tolerated.

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

About ONO-2370-02 study

This study is a multi-center, placebo-controlled, randomized, double-blind, parallel-group study and an open-label, uncontrolled, long-term extension study to evaluate the efficacy and safety of ONO-2370 (opicapone) at each dose in comparison with placebo. ONO-2370 25 or 50 mg was administered once daily, for 14 to 15 weeks to Parkinson's disease patients with wearing-off phenomenon in addition to the patient's regimen of levodopa plus DDCi. The double-blind phase of the study verified the superiority of the ONO-2370 groups compared to the placebo group in the primary efficacy endpoint of change in OFF-time at 12 weeks after the end of the levodopa dose adjustment period (14-15 weeks from baseline), based on the 24-hour entries in symptom diary. This study also investigated the safety and efficacy of extended treatment with ONO-2370 50 mg for 52 weeks in an open-label phase.

About Parkinson's disease

Parkinson's disease is a progressive neurodegenerative disease presenting 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 wearing-off.

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

Overview of Ongentys® Tablets 25 mg

Product name	Ongentys® Tablets 25 mg
Nonproprietary name	Opicapone
Indications	Improvement of the end-of-dose motor fluctuations (wearing-off phenomenon) in Parkinson's disease in combination with levodopa–carbidopa or levodopa–benserazide hydrochloride
Dosage and Administration	Opicapone is used in combination with levodopa–carbidopa or levodopa–benserazide hydrochloride. For oral use, the usual adult dosage is 25 mg of opicapone once daily, at least 1 hour before or after administration of levodopa–carbidopa or levodopa–benserazide hydrochloride, and at least 1 hour before or after meal.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	June 29, 2020

About Opicapone (Ongentys® Tablets)

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. Opicapone increases the bioavailability of levodopa by up to 65% vs placebo [1] and this translates into a reduction in OFF-time in patients with Parkinson's disease and end-of-dose wearing-off [2,3]. Molecular structure resulted in a high binding affinity (femtomolar) that translates into a slow complex dissociation rate constant and a long duration of action that allows once-daily dosing [2,3].

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®.

In April 2020, the U.S Food and Drug Administration (FDA) approved opicapone as an add-on treatment to levodopa/carbidopa in patients with Parkinson's disease experiencing "off" episodes.

ONO entered into a license agreement for opicapone with BIAL in April 2013, acquiring exclusive development and commercialization rights in Japan

[1] Rocha JF, *et al*. *Br J Clin Pharmacol*. 2017;83(3):540-553
[2] Ferreira J *et al*. *Lancet Neurol* 2016;15:154–65
[3] Lees A *et al*. *JAMA Neurol*. 2017;74(2):197-206

About BIAL (Portugal)

Founded in 1924, BIAL's mission is to research, develop and provide therapeutic solutions within the area of health. In the last decades, BIAL has focused strategically on quality, innovation and internationalisation. BIAL is strongly committed to therapeutic innovation, investing more than 20% of its annual turnover into research and development within neurosciences and the cardiovascular system. The company expects to introduce new drugs on the market in the coming years, strengthening its international presence based on proprietary drugs and achieving its goal of supplying innovative products to patients worldwide. For more information about BIAL, please visit www.bial.com

Contact
Ono Pharmaceutical Co., Ltd.
Corporate Communications
public_relations@ono.co.jp