ONO PHARMACEUTICAL CO.,LTD.

July 6, 2016

**European Commission approves ONGENTYS® (opicapone)**
**a novel treatment for Parkinson´s disease patients with motor fluctuations**

Porto, 5 July 2016 – BIAL announced that the medicinal product ONGENTYS® (opicapone) for the treatment of adult Parkinson´s disease patients with motor fluctuations was approved by the European Commission. BIAL will make ONGENTYS® available for Parkinson's disease patients across Europe in 2016 and 2017.

Opicapone is a novel once-daily, catechol-*O*-methyltransferase (COMT) inhibitor and is indicated as adjunctive therapy to preparations of levodopa/DOPA decarboxylase inhibitors (DDCIs) in adult patients with Parkinson's disease with motor fluctuations. This EC approval is based on a large and comprehensive clinical development programme more than 900 patients exposed to opicapone in 30 countries worldwide and 28 human pharmacology studies completed.

In April 2013, ONO PHARMACEUTICAL CO., LTD. (Osaka, Japan, President and Representative Director: Gyo Sagara) entered into a license agreement with BIAL to exclusively develop and commercialize opicapone (ONO-2370) in Japan. Phase II clinical study with ONO-2370 is ongoing for the treatment of Parkinson's disease in Japan. Opicapone shows a long-lasting effect on COMT inhibition from once daily dosing in clinical studies so far, and is expected to improve patient outcomes and offer dosing convenience compared to the existing COMT inhibitor.

Attached from the following page is the press release made by BIAL for your information.

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

**Media enquiries**

**BIAL**
Susana Vasconcelos
T. +351 229866100
E. susana.vasconcelos@bial.com

**iS Health**
Elise Rattigan
T. +44 1252 733353
E. elise@is-health.co.uk

# European Commission approves ONGENTYS® (opicapone) – a novel treatment for Parkinson´s disease patients with motor fluctuations

**Porto, 5 July 2016** – BIAL announced today that the medicinal product ONGENTYS® (opicapone) for the treatment of adult Parkinson´s disease patients with motor fluctuations was approved by the European Commission. BIAL will make ONGENTYS® available for Parkinson's disease patients across Europe in 2016 and 2017.

ONGENTYS® is indicated as adjunctive 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.

"We are very pleased to achieve this major regulatory milestone for ONGENTYS®, which offers patients living with Parkinson´s disease an effective, once-daily, adjunctive treatment option. We have been developing ONGENTYS® for many years and this approval is a landmark in BIAL's ongoing commitment to the quality of life of patients and their caregivers. This approval strengthens our track record of bringing new medicines to market," said António Portela, CEO of BIAL.

Professor Joaquim Ferreira, Professor of Neurology and Clinical Pharmacology at the University of Lisbon, said, "Motor complications in Parkinson's disease remain an unmet medical need for a significant number of patients. Opicapone is a new treatment option and fulfils the need for a more potent COMT inhibitor, offering an important alternative to the currently available armamentarium for the treatment of motor fluctuations."

Professor Heinz Reichmann, Professor and Chair Department of Neurology and Dean of Medical Faculty at the University of Dresden, added, "Opicapone is a new option to treat patients with motor complications with the convenience of once-daily dosing. It may become the treatment of choice when levodopa-treated patients need additional help to improve motor symptoms such as wearing off in Parkinson´s disease."

A large and comprehensive clinical development programme supports the European Commission approval, including 28 human pharmacology studies completed and more than 900 patients exposed to opicapone in 30 countries worldwide. The two pivotal phase III studies, BIPARK-I[1] and BIPARK II[2] demonstrated that ONGENTYS® once-daily achieved an absolute reduction in OFF-time of 2 hours without increasing ON-time with troublesome dyskinesia, statistically significant reductions in absolute OFF-time compared to placebo (P=0.0015) and statistically significant increases in ON-time without troublesome dyskinesia compared to placebo (P=0.002).

ONGENTYS® (opicapone) once-daily was also associated with significant improvements in both patient and clinician global assessments of change. BIPARK-I was an active-controlled trial and included an entacapone arm: opicapone once-daily was successfully demonstrated to be at least as effective as entacapone dosed multiple times per day (non-inferiority test). The data from the phase III trials demonstrated that opicapone improves motor fluctuations in levodopa-treated patients regardless of concomitant dopamine agonist or monoamine oxidase type B inhibitors use. It has also been demonstrated to be well-tolerated in the whole trial population and in the subset of patients over 70 years, and is not associated with relevant electrocardiographic or hepatic adverse events.

Both phase III trials included a 1-year open-label extension and opicapone demonstrated an OFF-time reduction from the double-blind phase baseline that was sustained over the open-label phase and was noted to have slightly improved compared to the end of the double-blind phase. In BIPARK-I, during the 1-year open-label follow-up period, patients switching from entacapone to ONGENTYS® once-daily achieved significant reductions in OFF-time (additional 39.3 min reduction) and significant increases in ON-time (additional 46 min increase).

Parkinson's disease is a neurodegenerative, chronic and progressive disease. The clinical manifestations usually start after the age of 50 years (average age for diagnosis is approximately 60 years) and the prevalence is estimated at 300 per 100,000 inhabitants, increasing to 1/100 over the age of 55–60 years. The European Parkinson's disease Association (EPDA) estimates that 1.2 million people have Parkinson's disease in the European Union.

BIAL will bring ONGENTYS® (opicapone), a new treatment option, to patients with Parkinson's disease and motor fluctuations as early as possible and thus make a contribution to addressing the needs and improving quality of life of patients.

###

**About ONGENTYS® (opicapone)**

Opicapone is a third-generation catechol-*O*-methyltransferase (COMT) inhibitor. It was rationally designed to provide a peripherally selective high COMT inhibitory potency and to avoid cell toxicity[3].

Opicapone increases the bioavailability of levodopa by up to 55% vs placebo and this translates into a dose-dependent reduction in OFF time[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].

**About the BIPARK-I study**

BIPARK-I[1] was a phase III, randomized, double-blind, active- and placebo-controlled, parallel group efficacy and safety study with an open-label 1-year extension phase in levodopa-treated patients with idiopathic Parkinson's disease and motor fluctuations.

The efficacy and safety of three different doses (5, 25 and 50 mg) of opicapone administered once-daily, compared with entacapone (200 mg) or placebo administered with each dose of levodopa, were assessed. Opicapone 50mg once-daily successfully achieved superiority compared to placebo and non-inferiority against entacapone.

The study enrolled 600 patients from 106 study sites in Europe. Patients were 34–83 years-old and had a diagnosis of idiopathic Parkinson's disease for at least 3 years; had a modified Hoehn & Yahr Scale stage of ≤3 in the ON state; had to receive optimum levodopa therapy (3–8 daily doses), stable for at least 4 weeks; had signs of end-of-dose deterioration (wearing-OFF) for at least 4 weeks with a mean daily OFF-time of 1.5 hours while awake, not including morning pre-first dose OFF-time; and had the ability to keep accurate 24-hour diaries. Patients were randomly assigned in a 1:1:1:1:1 ratio to opicapone 5 mg, 25 mg or 50 mg, entacapone and placebo.

The primary endpoint was the mean change from baseline in absolute OFF-time, as measured by 24-hour diaries. Secondary endpoints included proportion of responders, Investigators' and Subjects' Global Assessment of Change, UPDRS, quality of life, non-motor symptoms and sleep scales, tolerability and safety assessments. Ninety percent (542/600) of patients completed the study.

**About the BIPARK-II study**

BIPARK-II[2] was a phase III, randomized, double-blind placebo-controlled study with an open-label 1-year extension phase in levodopa-treated patients with idiopathic Parkinson's disease and end-of-dose motor fluctuations.

The efficacy and safety of two different doses (25 and 50 mg) of opicapone, administered once-daily, compared with placebo, administered with each dose of levodopa, were assessed. Mean reduction in absolute OFF-time in both the 25 and 50 mg OPC groups was considerably greater than in the placebo arm.

286 patients completed the study from 69 multinational study sites. Patients' inclusion criteria and trial assessments (primary and secondary outcomes) were similar to BIPARK-I.

**About Parkinson's disease**

Parkinson's disease (PD) is a neurodegenerative, chronic and progressive disease, characterized by massive depletion of striatal dopamine because of degeneration of dopaminergic neurons in the brain (substantia nigra).

Epidemiological evidence points to a complex interaction between genetic vulnerability and environmental factors. The clinical manifestations usually start after the age of 50 years (average age for diagnosis is approximately 60 years) and the prevalence is estimated at 300 per 100,000 inhabitants, increasing to 1/100 over the age of 55–60 years. The European Parkinson's disease Association (EPDA) estimates that 1.2 million people have PD in the European Union.

PD diagnosis is based on clinical observation. A diagnosis of PD can be made in patients who present with at least two of the three cardinal signs: resting tremor, rigidity and bradykinesia. Tremor is particularly important, as it is present in 85% of patients with true PD; a diagnosis of PD is particularly difficult when tremor is absent. Other frequent PD symptoms are postural instability, masked face and decreased eye blinking, stooped posture, and decreased arm swing.

Several therapeutic strategies are available to improve the signs and symptoms of the disease, mainly dopaminergic drugs providing, avoiding the degradation of or mimicking dopamine physiological effects. Levodopa remains the gold-standard treatment for PD, although its long-term use causes what is known as motor complications, like end-of-dose motor complications or wearing-off. This will lead to progressively shorter intervals during which symptoms remain adequately controlled. In other words, the effects of medication will start to "wear off' in between medication doses. "OFF-time" refers to periods of the day when the medication is not working well, causing worsening of Parkinsonian symptoms. In contrary, the term "ON-time" refers to periods of adequate control of PD symptoms. "Wearing-off" episodes may occur predictably and gradually, or they may emerge suddenly and unexpectedly. The episodes may be improved with appropriate changes in the medication regimen, i.e. adding an extra dose of levodopa or using a COMT inhibitor.

**About BIAL**

Founded in 1924, BIAL is an international pharmaceutical company with the mission to discover, develop and provide therapeutic solutions within the area of health. In recent decades, BIAL has focused on quality, innovation and internationalization.

Being the partner of choice for many companies, BIAL is strongly committed to therapeutic innovation, investing more than 20% of its turnover in Research and Development (R&D) every year.

BIAL has established an ambitious R&D programme centred on the central nervous system, cardiovascular system and allergy immunotherapy. BIAL's innovative programmes focus on continuing the clinical development of its anti-epileptic ZEBINIX® (eslicarbazepine acetate) on the market in Europe and the USA. The company's second compound for the treatment of Parkinson's disease, ONGENTYS® (opicapone) has just received approval by the European Commission.

The company expects to continue to introduce new medicines and vaccines to the market in the years to come, strengthening its position worldwide and accomplishing the company's purpose of "Caring for your Health".

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

**References:**

1. Ferreira JJ et al. Lancet Neurol 2016; 15(2): 154–165
2. Lees A et al. J Neurol Sci 2013; 333,Suppl 1:e116.
3. Kiss LE et al. J Med Chem 2010;53(8):3396–3411.
4. Ferreira JJ et al. Eur J Neurol 2015;22:815–825
5. Rocha JF et al. Br J Clin Pharmacol 2013;76(5):763–775.