ONO PHARMACEUTICAL CO.,LTD.

May 18, 2017

**ONO Receives Supplemental Manufacturing and Marketing Approval of KYPROLIS® for Intravenous Injection 10 mg and 40 mg, a Proteasome Inhibitor, in Relapsed or Refractory Multiple Myeloma**

ONO PHARMACEUTICAL CO., LTD. (Osaka, Japan; President, Representative Director and CEO: Gyo Sagara; "ONO") today announced that ONO received an approval for a partial change in approved items of the manufacturing and marketing approval (additional dosage and administration) for KYPROLIS® for Intravenous Injection 10 mg and 40 mg (Generic name: carfilzomib; "Kyprolis"), which is a proteasome inhibitor, for the treatment of patients with relapsed or refractory multiple myeloma.

Kyprolis was granted a manufacturing and marketing approval for the treatment of relapsed or refractory multiple myeloma in Japan in July 2017, in combination with lenalidomide and dexamethasone at a dosage of 20 mg/m$^2$ in Cycle 1 on Day 1 and 2, and escalate to 27 mg/m$^2$ thereafter, administered intravenously over 10 minutes. The supplemental approval allows Kyprolis to expand its dosage and administration in combination with dexamethasone at a dosage of 20 mg/m$^2$ only in Cycle 1 on Day 1 and 2, and escalate to 56 mg/m$^2$ thereafter, administered intravenously over 30 minutes.

This additional approval is based on results from the global Phase 3 study (2011-003, ONO-7057-03, or ENDEAVOR) of Kyprolis plus dexamethasone (Kd) versus bortezomib plus dexamethasone (Bd). The primary endpoint of efficacy was of progression-free survival (PFS). In the result of interim analysis of PFS, the superiority in PFS was verified with 18.7 months for Kd versus 9.4 months for Bd (Hazard ration 0.533, $p<0.0001$). Adverse events (≥20%) reported in the Kd arm were anemia, diarrhea, fatigue, dyspnea, pyrexia, insomnia, cough, hypertension, peripheral edema, thrombocytopenia, asthenia and upper respiratory tract infection.

Multiple myeloma results from an abnormality of plasma cells, usually in the bone marrow and there are nearly 18,000 patients* in Japan. Several regimens for multiple myeloma are currently available to patients; however, the disease relapses and progresses and eventually becomes no longer responding to therapies, also known as refractory disease. Additionally, adverse drug reactions and co-morbid conditions have been reported following long-term treatment, making continued treatment a challenge. The development of new therapeutic options for multiple myeloma is expected.

Kyprolis is in a class of drugs called proteasome inhibitors. ONO licensed-in Kyprolis for development and commercialization in Japan in September 2010 from US-based Onyx Pharmaceuticals, Inc., now an Amgen subsidiary. Proteasome, an intra-cellular enzyme complex, functions to mediate degradation of polyubiquitinated proteins and control proliferation and differentiation of cells, as well as functional cell-death. Kyprolis inhibits certain proteasome activity, thereby inducing functional cell-death of myeloma.

In the US, the US Food and Drug Administration (FDA) granted accelerated approval of Kyprolis as a single agent in July 2012 for the treatment of patients with multiple myeloma. Kyprolis is currently used; 1) as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have

received one or more lines of therapy, and 2) in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. In Europe, the Marketing Authorization Application for Kyprolis was approved in November 2015 in combination with lenalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy.

ONO considers the accumulation of further clinical data important in ensuring that Kyprolis will be used properly and effectively. ONO is committed to taking actions necessary for the proper use of Kyprolis by implementing a post-marketing use-results survey (all-case surveillance) and collecting clinical data on the safety and efficacy of Kyprolis according to the conditions for its approval.

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

Overview of Kyprolis® for Intravenous Injection 10 mg and 40 mg

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| Product Name | KYPROLIS® for Intravenous Injection 10 mg and 40 mg |
| Generic name (JAN) | Carfilzomib |
| Indication | Relapsed or refractory multiple myeloma |
| Dosage and administration | 1. In combination with lenalidomide and dexamethasone:<br>KYPROLIS is usually administered intravenously in adults once a day on Days 1, 2, 8, 9, 15 and 16 followed by a 12-day rest period. Each 28-day period is considered one treatment cycle, and the treatment is continued until Cycle 12. In Cycle 13 and onward, KYPROLIS is intravenously administered once a day on Days 1, 2, 15 and 16 followed by a 12-day rest period. KYPROLIS is administered intravenously over 10 minutes at a dose of 20 $mg/m^2$ (body surface area) as carfilzomib on Days 1 and 2 in Cycle 1 and then at 27 $mg/m^2$ (body surface area) afterwards. The dose should be reduced as needed according to each patient's condition.<br>2. In combination with dexamethasone:<br>KYPROLIS is usually administered intravenously in adults once a day on Days 1, 2, 8, 9, 15 and 16 followed by a 12-day rest period. Each 28-day period is considered one treatment cycle, and the treatment is continued until Cycle 12. KYPROLIS is administered intravenously over 30 minutes at a dose of 20 $mg/m^2$ (body surface area) as carfilzomib on Days 1 and 2 in Cycle 1 only and then at 56 $mg/m^2$ (body surface area) afterwards. The dose should be reduced as needed according to each patient's condition. |
| Manufacturer/ distributor | Ono Pharmaceutical Co., Ltd. |
| Conditions for approval | 1. ONO should establish Risk Management Plan to be implemented appropriately.<br>2. Because of the very limited number of patients treated with KYPROLIS in Japanese clinical trials, ONO is required to perform a post-marketing use-results survey covering all cases until data on a certain minimum number of patients have been accumulated. Through these activities, ONO should identify the characteristics of patients to be treated with KYPROLIS and collect safety and efficacy data as soon as possible, thereby taking actions necessary to ensure the proper use of KYPROLIS. |

* Underlined parts show the revised ones due to the approval for the partial change in approved items of the manufacturing and marketing approval.

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