ONO PHARMACEUTICAL CO.,LTD.

November 22, 2019

ONO Receives Supplemental Approval of KYPROLIS® for Intravenous Injection, a Proteasome Inhibitor, in Japan for Additional Dosage and Administration for a Kd Once-weekly Regimen 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 KYPROLIS® (Generic name: carfilzomib) for Intravenous Injection 10 mg and 40 mg ("Kyprolis"), a proteasome inhibitor, in Japan for additional dosage and administration in patients with relapsed or refractory multiple myeloma, for a partial change in approved items of the manufacturing and marketing approval.

This additional approval is based on the result from a global multiple-center, randomized, open-label Phase 3 study (ONO-7057-06/A.R.R.O.W. study), evaluating the efficacy and safety of Kyprolis in combination with dexamethasone, comparing Kyprolis 20/70 mg/m^2 once-weekly dosing regimen (Kd70) versus Kyprolis 20/27 mg/m^2 twice-weekly regimen (Kd27) in patients with relapsed or refractory multiple myeloma. In the result of interim analysis of progression-free survival (PFS), a primary endpoint, the median PFS was 11.2 months in the Kd70 arm versus 7.6 months in the Kd27 arm, demonstrating a statistically significant improvement (Hazard ratio: 0.69; 95% confidence interval: 0.54 - 0.88). The most frequently reported adverse events (≥20%) reported in either treatment regimen were anemia, diarrhea, fatigue, hypertension, insomnia and pyrexia.

The supplemental approval allows Kyprolis to expand its dosage and administration in combination with dexamethasone at a dosage of 20 mg/m^2 only on Day 1 in Cycle 1, then escalating to 70 mg/m^2 once-weekly thereafter. Kyprolis has been required so far to be administered twice-weekly under the previously approved dosage and administration, but the additional approval allows Kyprolis to be administered once-weekly leading to superior convenience.

Multiple myeloma is a blood cancer caused by an abnormality of plasma cells in the bone marrow. It is reported that there are nearly 25,000 patients* in Japan. Several treatments 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 complications have been reported following long-term treatment, making continued treatment a challenge. The development of new therapeutic options for multiple myeloma is expected.

*: Vital Statistics and Patients Survey, 2017 (Statistics and Information Department, Minister's Secretariat, Ministry of Health, Labour and Welfare).

About Kyprolis

Kyprolis is a highly selective proteasome inhibitor. 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 September 2010, ONO entered into a license agreement with US-based Onyx Pharmaceuticals, Inc., now an Amgen subsidiary, to exclusively develop and commercialize it for all oncology indications in Japan.

In Japan, ONO received a manufacturing and marketing approval of Kyprolis for the treatment of relapsed or refractory multiple myeloma in July 2016, in combination with lenalidomide and dexamethasone and launched it in August 2016. Kyprolis was approved for additional dosage and administration in combination with dexamethasone at a dosage of 20 mg/m^2 only on Day 1 and 2 in Cycle 1, then escalating to 56 mg/m^2 twice-weekly thereafter.

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

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:** 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) only 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. **2. In combination with dexamethasone:** (Twice-weekly administration) 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. Kyprolis is administered intravenously over 30 minutes at 20 mg/m^2 (body surface area) only on Days 1 and 2 in Cycle 1 and then at 56 mg/m^2 (body surface area) afterwards. The dose should be reduced as needed according to each patient's condition. (Once-weekly administration) Kyprolis is usually administered intravenously in adults once a day on Days 1, 8 and 15 followed by a 13-day rest period. Each 28-day period is considered one treatment cycle, and the treatment is continued. Kyprolis is administered intravenously over 30 minutes at 20 mg/m^2 (body surface area) only on Day 1 in Cycle 1 and then at 70 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	Risk Management Plan should be designed and appropriately implemented.

* 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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