ONO PHARMACEUTICAL CO.,LTD.

September 7, 2016

ONO Launches KYPROLIS® for Intravenous Injection 10 mg and 40 mg
Proteasome Inhibitor

ONO PHARMACEUTICAL CO., LTD. (Osaka, Japan; President, Representative Director and CEO: Gyo Sagara; hereinafter, "ONO") announced that it launched a proteasome inhibitor, KYPROLIS® for Intravenous Injection 10 mg and 40 mg (Generic name: carfilzomib, hereinafter, "Kyprolis") in Japan for the treatment of patients with relapsed or refractory multiple myeloma on August 31, 2016.

Multiple myeloma results from an abnormality of plasma cells, usually in the bone marrow and there are about 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 has been expected.

Kyprolis is in a class of drugs called proteasome inhibitors. ONO licensed Kyprolis for development and commercialization in Japan from U.S.-based Onyx Pharmaceuticals, Inc. (now an Amgen subsidiary) in September 2010. 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.

Outside Japan, the U.S. 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. Kyprolis is currently used in combination with either lenalidomide and dexamethasone or dexamethasone alone for the treatment of adult patients with multiple myeloma who have received at least one prior therapy

ONO considers it to be important to compile further clinical data in order to ensure that Kyprolis will be used properly and effectively. In compliance with the conditional approval, ONO is committed to taking actions necessary for 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.

*: 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

Product name	KYPROLIS® for Intravenous Injection 10 mg KYPROLIS® for Intravenous Injection 40 mg
Generic name	Carfilzomib
Indication	Relapsed or refractory multiple myeloma
Dosage and administration	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) 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.
Characteristics	1. KYPROLIS is an irreversible and selective proteasome inhibitor. 2. KYPROLIS suppresses proteasome chymotrypsin-like activity, consequently accumulates polyubiquitinated proteins and induces apoptosis of cancer cell. 3. In the Phase III study conducted outside Japan (PX-171-009) where 792 patients with relapsed or refractory multiple myeloma who have received 1 to 3 prior therapies were enrolled, the combination therapy of KYPROLIS with lenalidomide and dexamethasone (KRd regimen) showed significant prolongation in the progression-free survival, compared to the combination therapy of lenalidomide and dexamethasone (Rd regimen) (Hazard ratio: 0.690 [95% confidence interval: 0.570 to 0.834] due to stratified Cox' proportional hazard model, $p < 0.0001$ [stratified log-rank test]). 4. In the Japanese Phase I study (ONO-7057-05) where 26 patients with relapsed or refractory multiple myeloma who had received at least 1 prior therapy were enrolled, the overall response rate (ORR) of combination therapy of KYPROLIS with lenalidomide and dexamethasone was 88.5% (90% confidence interval: 72.8 to 96.8) *Ratio of sCR, CR, VGPR and PR according to assessment by the IMWG-URC (International Myeloma Working Group-Uniform Response Criteria) 5.• In the Japanese Phase I study (ONO-7057-05) in patients with relapsed or refractory multiple myeloma, adverse drug reactions (including laboratory test abnormalities) were reported in 26 (100%) of 26 patients given KYPROLIS. The main adverse drug reactions (incidence of 10% or higher) were thrombocytopenia in 12 patients (46.2%), lymphopenia in 11 patients (42.3%), hyperglycaemia in 10 patients (38.5%), ALT (GPT) increased in 7 patients (26.9%), rash in 7 patients (26.9%), constipation in 6 patients (23.1%), muscle spasms in 6 patients (23.1%), hypophosphataemia in 5 patients (19.2%), leukocytosis in 5 patients (19.2%), AST (GOT) increased in 4 patients (15.4%), neutropenia in 4 patients (15.4%), neutrophilia in 4 patients (15.4%), pyrexia in 4 patients (15.4%), neuropathy peripheral in 4 patients (15.4%), blood bilirubin increased in 4 patients (15.4%), leukopenia in 4 patients (15.4%), hyperkalaemia in 3 patients (11.5%), hypokalaemia in 3 patients (11.5%), nausea in 3 patients (11.5%), hypertension in 3 patients (11.5%), diarrhoea in 3 patients (11.5%), pneumonia in 3 patients (11.5%), upper respiratory tract inflammation in 3 patients (11.5%), dysgeusia in 3 patients (11.5%), erythema in 3 patients (11.5%), blood cholesterol increased in 3 patients (11.5%), haemoglobin decreased in 3 patients (11.5%), and hyponatremia in 3 patients (11.5%) (at the time of approval).

Characteristics	• In the Phase III study (PX-171-009) conducted outside Japan in patients with relapsed or refractory multiple myeloma, adverse drug reactions (including laboratory test abnormalities) were reported in 332 (84.7%) of 392 patients given KYPROLIS. The main adverse drug reactions (incidence of 10% or higher) were neutropenia in 142 patients (36.2%), anaemia in 104 patients (26.5%), thrombocytopenia in 99 patients (25.3%), fatigue in 88 patients (22.4%), diarrhoea in 74 patients (18.9%), muscle spasms in 72 patients (18.4%), insomnia in 56 patient (14.3%), respiratory tract infection in 50 patients (12.8%), hypokalaemia in 43 patients (11.0%), hyperglycaemia in 41 patients (10.5%), and asthenia in 41 patients (10.5%) (at the time of approval). The frequencies of adverse drug reactions have been described according to the results of the Phase III study (PX-171-009) conducted outside Japan. *: The frequencies of adverse drug reactions reported in studies other than the study PX-171-009 are shown as incidence unknown. The following adverse drug reactions have been reported as clinically significant adverse drug reactions: 1) cardiac disorders, 2) interstitial lung disease, 3) pulmonary hypertension, 4) hepatic failure and hepatic function disorder, 5) renal failure acute, 6) tumor lysis syndrome, 7) bone marrow depression, 8) infusion reactions, 9) thrombotic microangiopathy, 10) posterior reversible encephalopathy syndrome and encephalopathy, 11) hypertension and hypertensive crisis, 12) venous thromboembolism, 13) hemorrhages, 14) infections and 15) gastrointestinal perforation.
Packaging	KYPROLIS® for Intravenous Injection 10 mg: 1 vial KYPROLIS® for Intravenous Injection 40 mg: 1 vial
Manufacturing and marketing approval date	July 4, 2016
Drug price listing date	August 31, 2016
Drug price	KYPROLIS® for Intravenous Injection 10 mg vial: ¥23,982 KYPROLIS® for Intravenous Injection 40 mg vial: ¥86,255
Launch date	August 31, 2016
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Conditions for approval	1. Risk Management Plan should be established and implemented appropriately. 2. Because of the very limited number of patients treated with the product in Japanese clinical trials, a post-marketing use-results survey covering all cases should be performed until data on a certain minimum number of patients have been accumulated. Through these activities, the characteristics of patients to be treated with the product should be identified and the safety and efficacy data be collected as soon as possible, thereby taking actions necessary to ensure the proper use of the product.

Product photograph

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