ONO PHARMACEUTICAL CO.,LTD.

March 25, 2020

ONO Receives a Manufacturing and Marketing Approval for Velexbru® Tablet 80mg, a BTK inhibitor, for Treatment of Recurrent or Refractory Primary Central Nervous System Lymphoma in Japan

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director: Gyo Sagara; "ONO") announced today that ONO received a manufacturing and marketing approval of Velexbru® (generic name: tirabrutinib hydrochloride) Tablet 80mg ("Velexbru"), a Bruton's tyrosine kinase ("BTK") inhibitor, for the treatment of recurrent or refractory primary central nervous system lymphoma in Japan.

This approval is based on the results from a multi-center, open-label, uncontrolled Phase I/II study (ONO-4059-02), evaluating an efficacy and safety of Velexbru in 44 patients with recurrent or refractory primary central nervous system lymphoma (PCNSL), receiving Velexbru orally once daily. In this study, the overall response rate (ORR) assessed by an independent review committee (IRC), a primary endpoint, was 52.9% (9/17 patients) in 17 patients who received 480 mg of Velexbru in the fasting which is the approved dosage and administration this time. Grade 3-4 neutropenia, leucopenia and hypertriglyceridemia each occurred in 11.8% (2/17) of patients.

This approval represents that Velexbru is the first BTK inhibitor approved for the treatment of recurrent or refractory PCNSL in the world where no standard of care has been established.

On November 27, 2019, ONO also submitted an application of Velexbru in Japan for the treatment of Waldenstrom macroglobulinemia (WM) and lymphoplasmacytic lymphoma (LPL).

About Primary Central Nervous System Lymphoma (PCNSL)

PCNSL is a malignant lymphoma in which the lesion is localized in the cerebrospinal cord (including the eyes) at the first onset. It is estimated that there are approximately 980 new cases with PCNSL per year in Japan[*1, 2]. The signs and symptoms presented by patients with PCNSL vary depending on the site of the lesion, and include localized neuropathy, neuropsychiatric symptoms, symptoms associated with increased intracranial pressure, seizure, eye symptoms, headache, difficulty in movement, cranial neuropathy and radiculopathy.

Currently, untreated PCNSL patients receive high-dose methotrexate-based treatment followed by whole-brain radiation therapy, by which a certain patient population shows long-term remissions, but many patients will relapse. There are also refractory patients who do not respond to the drug treatment. Standard treatment has not been established for patients with recurrent or refractory PCNSL, and treatment options are limited for them. Therefore, a new treatment drug is expected for patients with recurrent or refractory PCNSL[*3].

[*1]: Neurol Med Chir (Tokyo). 2017;57(Supplement 1):9-102.

[*2]: Jpn J Neurosurg VOL.24 NO.10 2015.10

[*3]: Practical Guidelines for Neuro-Oncology 2019

About ONO-4059-02 Study

This study is a multi-center, open-label, single-arm Phase I/II study, evaluating the efficacy and safety of tirabrutinib hydrochloride monotherapy in patients with recurrent or refractory PCNSL. In this study, 44 patients were recruited and received tirabrutinib hydrochloride 320 mg (20 patients), 480 mg (7 patients) and 480 mg fasted (17 patients), once daily in either groups. Patients were treated until disease progression or unacceptable toxicity was observed.

About Velexbru

Velexbru (tirabrutinib hydrochloride), discovered and developed by ONO, is a highly selective, oral BTK inhibitor and has been developed for the treatment of patients with B-cell tumors and autoimmune diseases in Japan. B-cell receptor (BCR) signaling plays a core role in the survival, activation, proliferation, maturation and differentiation of B-cell lymphocyte. The BCR signaling pathway is known to be permanently activated, particularly in B-cell non-Hodgkin lymphoma (B-NHL) and chronic lymphocytic leukemia (CLL). Velexbru is expected to have a therapeutic effect because it inhibits BTK, a mediator located downstream of BCR.

In December 2014, ONO out-licensed tirabrutinib hydrochloride to Gilead Sciences, Inc. (Gilead) to allow the right to develop and commercialize the product in all countries of the world, except Japan, South Korea, Taiwan, China and ASEAN countries where ONO retains the development and commercialization rights of the product.

Overview of Velexbru® Tablet 80mg

Product Name	Velexbru® Tablet 80mg
Generic name (JAN)	tirabrutinib hydrochloride
Indication	Relapsed or refractory primary central nervous system lymphoma
Dosage and administration	Usually, for adults, administer at 480 mg of tirabrutinib orally once a day in the fasting. The dose should be decreased based on patients' condition.
Manufacturer/distributor	Ono Pharmaceutical Co., Ltd.
Approval date	March 25, 2020

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