

August 17, 2020

Ohara Pharmaceutical Co., Ltd.

Glucarpidase (Genetical Recombination) “OP-07” Receives Orphan Drug Designation from MHLW

On August 17, 2020, Ohara Pharmaceutical Co., Ltd. (Head office: Koga City, Shiga Prefecture; President: Seiji Ohara) received Orphan Drug Designation from the Ministry of Health, Labour and Welfare (hereinafter “MHLW”) for Glucarpidase (genetical recombination) (hereinafter “OP-07”) as an enzyme preparation that hydrolyzes methotrexate (MTX), with “antidote for patients with delayed excretion of methotrexate in methotrexate/leucovorin salvage therapy” as an expected indication.

High-dose MTX therapy (synonymous to methotrexate/leucovorin salvage therapy) is one of the important chemotherapies for acute lymphoblastic leukemia, osteosarcoma, malignant lymphoma, etc. However, an adverse drug reaction has been reported that MTX intoxication results from the delayed excretion of MTX due to impaired renal function caused by MTX crystals deposited on kidney tubules. Existing therapies for MTX intoxication include supportive therapy aimed at excreting MTX from the body (large volume infusion, urine alkalinization and administration of diuretic), as well as leucovorin salvage therapy. However, it is known that there are rare cases where serious MTX intoxication occurs despite these preventive therapies.¹⁾ Therefore there exists an unmet medical need for fast-acting therapeutic drug with a detoxifying effect.

OP-07 is able to quickly reduce MTX levels in blood by hydrolyzing MTX, thereby detoxifying MTX intoxication. This drug was designated as an orphan drug in the U.S. and Europe in 2003, and was approved in the U.S. in January 2012. In Japan, a phase II clinical study is in progress. Upon approval of OP-07 for the indication above, it will become the first drug in Japan that directly and quickly reduces MTX levels in blood by hydrolyzing MTX in blood.

The number of patients to be included in the scope of treatment with OP-07 is estimated at around 572 to 8,500 per annum in Japan.

We are committed to continue our efforts to deliver OP-07 to patients as quickly as possible.

[References]

- 1) Chabner BA, Allegra CJ. Antifolates. In: Chabner BA and Longo DL. Cancer Chemotherapy, Immunotherapy and Biotherapy: principles and practice, Sixth Edition. Philadelphia: Wolters kluwer. 2019; 92-113.

[About OP-07]

OP-07 is a glutamate carboxypeptidase that is derived from the *Variovorax paradoxus* (*Pseudomonas* sp. RS16) strain, and is a protein with the molecular weight of approx. 83 kDa, consisting of two sub-units that have 390 amino acid residues. It hydrolyzes the C-terminal glutamic acid residue in MTX as a folic acid analog, and produces 4-deoxy-4-amino-N¹⁰-methylpteroic acid (DAMPA) and glutamic acid.

In the U.S., OP-07 was approved for the following indication in January 2012 and is marketed as Voraxaze[®] by BTG International Inc of the U.S.: "VORAXAZE is indicated to reduce toxic plasma methotrexate concentration (greater than 1 micromole per liter) in adult and pediatric patients with delayed methotrexate clearance (plasma methotrexate concentrations greater than 2 standard deviations of the mean methotrexate excretion curve specific for the dose of methotrexate administered) due to impaired renal function."

[What are orphan drugs?]

Orphan drugs refer to drugs which have been reviewed and designated by the MHLW as drugs for diseases with less than 50,000 patients in Japan and have high unmet medical needs.

[About Ohara Pharmaceutical Co., Ltd.]

Ohara Pharmaceutical Co., Ltd. is one of the unique Japanese pharmaceutical companies that focus on the development and distribution of orphan drugs mainly in the field of childhood cancer treatment as well as generic drugs taking the prevention of medical accidents into consideration. In the Midterm 3-year plan that started in FY2018, Ohara is committed to addressing medical issues under the theme, "To Challenge unmet medical needs," applying the catch-phrase, "Challenge 2020." Ohara is planning to further expand these activities into emerging countries mainly in Asia as well as other regions.