

March 29th, 2021

Ohara Pharmaceutical Co., Ltd.

## **Glucarpidase (Genetical Recombination) "OP-07" Application Filed for Marketing Authorization for Methotrexate Intoxication**

Ohara Pharmaceutical Co., Ltd. (Head office: Koga City, Shiga Prefecture; President: Seiji Ohara) has filed an application for marketing authorization to the Ministry of Health, Labour and Welfare (hereinafter, "MHLW") for Glucarpidase (genetical recombination) (hereinafter, "OP-07"), an enzyme that hydrolyzes methotrexate (hereinafter, "MTX"), as a therapeutic agent for MTX intoxication.

This application is filed based on the efficacy and safety results of eight clinical studies conducted in Japan and overseas, including Study CPG2-P11 below.

OP-07 acquired Orphan Drug Designation by the MHLW on August 17, 2020.

### [Study CPG2-P11]

This is a phase II study conducted as an investigator-initiated study in Japan. The purpose of this study was to evaluate the blood MTX level-reducing effect of OP-07 in patients with delayed MTX excretion of high-dose MTX therapy.

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

## [About methotrexate (MTX) intoxication]

High-dose MTX therapy (synonymous to MTX/leucovorin salvage therapy) is one of the important chemotherapy regimens for acute lymphoblastic leukemia, osteosarcoma, malignant lymphoma, etc. As an adverse drug reaction of the high-dose MTX therapy, however, it has been reported that MTX intoxication results from the delayed MTX excretion due to impaired renal function caused by MTX crystals deposited in the kidney tubules. MTX intoxication exposes various organs to high levels of MTX for a long time, which may cause histological damage.

Existing therapies for MTX intoxication include supportive therapy aimed at excreting MTX from the body (high-volume infusion, urine alkalinization and administration of diuretics), as well as leucovorin salvage therapy. However, there have been rare cases with a fatal outcome despite these preventive therapies,<sup>1)</sup> indicating that patients may die if early treatment is not provided. Therefore, there is an unmet medical need for a fast-acting therapeutic drug with a detoxifying effect.

## [What are orphan drugs?]

Orphan drugs refer to drugs designated by the Minister of Health, Labour and Welfare for diseases with less than 50,000 patients in Japan, considered to be of particularly high medical needs through the relevant review.

## [Reference]

- 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-N<sup>10</sup>-methylpteroic acid (DAMPA) and glutamic acid.

OP-07 was approved in January 2012 in the U.S., and it is marketed as Voraxaze® by BTG International Inc. The current indication approved in the U.S. is as follows: "VORAXAZE is a carboxypeptidase 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."

The developer of OP-07, BTG International Inc., licensed Ohara Pharmaceutical, which has filed an application for marketing authorization in Japan.

[About Ohara Pharmaceutical Co., Ltd.]

Ohara Pharmaceutical Co., Ltd. is a pharmaceutical company that discovers and develops orphan drugs and generic drugs as its mainstay business. The company particularly focuses on the development and marketing of orphan drugs for pediatric cancer and other areas, and on the development, manufacturing and marketing of generic drugs that feature the prevention of medical accidents. Ohara Pharmaceutical aims to become a company that provides total healthcare solution by promoting innovations not only in treatment, but also for prevention, diagnosis and aftercare that affect the quality of healthcare, in the substantially changing healthcare environment and improving treatment outcome.