Dear All,

September 27, 2021

Ohara Pharmaceutical Co., Ltd.

Glucarpidase (Genetical Recombination) "Megludase®"
Marketing Authorization Approval

Ohara Pharmaceutical Co., Ltd. (Head Office: Koka City, Shiga Prefecture; President and CEO: Seiji Ohara; hereinafter, referred to as "our company") has obtained marketing authorization from the Ministry of Health, Labour and Welfare, which granted regulatory approval for "Megludase® injection for intravenous use 1000" (generic name: glucarpidase (genetical recombination); development code: OP-07; hereinafter, referred to as "Megludase") as a therapeutic agent for "detoxication in case of delayed methotrexate elimination with methotrexate-leucovorin rescue therapy," on September 27, 2021.

This authorization has been granted based on the efficacy and safety results of the clinical studies conducted in Japan and overseas, including the investigator-initiated study (herein after, referred to as "CPG2-PII study").

"Megludase" is used as a therapeutic agent in the US. In addition, "Megludase" acquired an Orphan Drug Designation from the Ministry of Health, Labour and Welfare on August 17, 2021.

[About CPG2-PII study]

This phase II study in Japan was conducted as an investigator-initiated study funded by the Japan Medical Association. The purpose of this study was to evaluate the blood MTX level-reducing effect of glucarpidase in the event of delayed MTX excretion, in patients with delayed MTX excretion after methotrexate-leucovorin (hereinafter "MTX-LV") rescue therapy, with the rate of achievement of CIR (Clinically important reduction (of the MTX concentration)) as the primary endpoint. As a result, the CIR achievement rate was 76.9% (10 out of 13 patients evaluated for efficacy). Many of the adverse events recognized in this study appeared to be caused by MTX, and those for which a causal relationship with this agent could not be denied were Grade 3 or lower in 2 patients.

Contact details for inquires regarding this issue:
Ohara Pharmaceutical Co., Ltd.
Representatives: Omori, Ro
TEL: +81-3-6740-7701　FAX: +81-3-6740-7702

[About delayed MTX excretion]

MTX-LV rescue therapy is one of the important chemotherapy regimens for acute lymphoblastic leukemia, osteosarcoma, malignant lymphoma, etc. However, as an adverse drug reaction of MTX-LV therapy, it has been reported that delayed MTX excretion develops due to impaired renal function caused by the deposition of MTX crystals in the kidney tubules. As a result of this delayed MTX excretion, various organs are exposed to high levels of MTX for long periods, which may cause histological damage.

Existing therapies for delayed MTX excretion include a supportive therapy aimed at enhancing excretion of MTX from the body (high-volume infusion, urine alkalinization, and administration of diuretics), an LV administration aimed at reducing MTX toxicity, and a blood purification therapy aimed at directly reducing the blood MTX level. However, in spite of these procedures and treatments, there have been rare cases with a fatal outcome,[1)] indicating that patients may die if early therapeutic intervention is not provided.

[About Megludase]

Megludase (generic name: glucarpidase (genetical recombination)) is a glutamate carboxypeptidase that is derived from the *Variovorax paradoxus* (*Pseudomonas* sp. RS16) strain and is a protein with a molecular weight of approx. 83 kDa, consisting of two sub-units with 390 amino acid residues. It hydrolyzes the C-terminal glutamic acid residue in MTX as a folic acid analog, producing 4-deoxy-4-amino-N^{10}-methylpteroic acid (DAMPA) and glutamic acid.

Megludase was approved in January 2012 in the U.S., and 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.”

In Japan, our company markets this drug under license from Protherics Medicines Development Ltd. (a BTG Company), which developed the drug.

[What are orphan drugs?]

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

[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, manufacturing and marketing of orphan drugs for pediatric cancer and other areas, and on the development, manufacturing and marketing of generic drugs that feature in the prevention of medical accidents. Ohara Pharmaceutical aims to become a company that provides a total healthcare solution by promoting innovations not only in treatment, but also for the prevention, diagnosis and aftercare that affect the quality of healthcare in the substantially changing healthcare environment and improving the treatment outcome.

[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.