December 17, 2015

Antineoplastic Enzyme Preparation "Crisantaspase"
Submission of a Japan New Drug Application for the Treatment of Diseases including Acute Lymphoblastic Leukemia and Malignant Lymphoma.

We hereby announce that Ohara Pharmaceutical Co., Ltd. (Head office: Shiga, CEO: Seiji Ohara) today submitted a New Drug Application for "Crisantaspase" (Generic name) (Development code: OP-01), an antineoplastic enzyme preparation for patients with acute lymphoblastic leukemia.

In Japan, the medical need for the drug was recognized by the "Evaluation Committee on Unapproved or Off-label Drugs with High Medical Needs" of the Ministry of Health, Labour and Welfare (MHLW). The efficacy and safety data of Crisantaspase has been evaluated by Ohara through a Japanese clinical study in acute lymphoblastic leukemia or Malignant Lymphoma in Japanese patients who experienced allergic reactions to administration of asparaginase preparations derived from *Escherichia coli (E.coli)*.

About Ohara Pharmaceutical Co. Ltd

Ohara is a pharmaceutical manufacturer that develops, produces and sells orphan and generic drugs. For the sake of patients' lives and health, Ohara's mission is always to put itself in the patient's position to help to ensure that patients' needs are met.
In particular, Ohara's primary focus is in the field of childhood cancers, which includes the manufacture and distribution of Leukerin powder 10% (Generic name: mercaptopurine hydrate) and the development of "crisantaspase" expands its product portfolio. Ohara is striving to contribute to the satisfaction of various needs and the improvement of benefits for patients suffering childhood cancers, their families and medical experts.

About Crisantaspase

Erwinaze® / Erwinase® (asparaginase *Erwinia chrysanthemi*) in the rest of the world, Crisantaspase has been approved in 22 countries to date and is sold either on a commercial basis or via named patient basis in over sixty five countries globally.
Erwinaze® / Erwinase® is exclusively licensed to Jazz Pharmaceuticals for worldwide

marketing, sales and distribution by Porton Biopharma Limited (PBL), which also manufactures the product, where it is marketed by Jazz Pharmaceuticals under the name Erwinaze® in the U.S. and Erwinase® (asparaginase *Erwinia chrysanthemi*) in countries outside of the United States (U.S.).
Erwinase® first obtained marketing authorization in the United Kingdom (UK) in 1985. Erwinaze® was approved by the U.S. Food and Drug Administration in November 2011 under a biologics license application, or BLA, for administration via intramuscular injection in conjunction with chemotherapy. In December 2014, the FDA approved a supplemental BLA for administration of Erwinaze® via intravenous infusion in conjunction with chemotherapy.

This agent is an asparaginase isolated from a plant bacterium called *Erwinia chrysanthemi*. The cells of some blood cancers, as typified by childhood acute lymphoblastic leukemia, have few enzymes to synthesize asparagine, one of the amino acids. When asparagine supplied from outside is catabolized by asparaginase, the asparagine required for tumor cells to grow is depleted, making protein synthesis impossible, and resulting in the apoptosis of tumor cells. Therefore, asparaginase agents derived from *E.coli* have already been used concomitantly with other anticancer drugs for the treatment of blood cancers with approval in Japan. Blood cancers respond well to anticancer drugs, and the treatment outcomes have been much improved recently. Meanwhile, many anticancer drugs have very strong adverse effects, which often cause secondary adverse events called late effects when childhood cancer patients grow up, even after complete remission of their cancer. Enhanced treatment efficacy with asparaginase is said to be useful for the prevention of late effects. However, as one of its known potential side effects, asparaginase can induce allergic symptoms, anaphylaxis as well as urticaria, which may force patients to discontinue their treatment. Made from a bacterium other than *E.coli*, the drug (Erwinaze®/Erwinase®) is available for patients who discontinued their treatment due to the development of allergic symptoms caused by asparaginase derived from *E.coli*. There is therefore a high demand for this drug by patients and physicians around the world.

About Porton Biopharma Limited

Porton Biopharma Limited (PBL) is a limited liability company (No 09331560) which

develops and manufactures biopharmaceutical products such as vaccines, therapeutic proteins and enzyme products, including the licensed products Erwinaze® / Erwinase® and the UK's Anthrax Vaccine. PBL also offers specialist expertise in the development of both manufacturing and analytical processes for biological pharmaceutical products, and can undertake contract development leading to manufacture for clinical trial or product launch. For more information please see our website at www.portonbiopharma.com