Dear All,

June 23, 2021

Ohara Pharmaceutical Co., Ltd.

Recombinant Chimeric Monoclonal Antibody "Unituxin®" 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 granted regulatory approval for "Unituxin® injection, for intravenous use 17.5 mg/5 mL" (generic name: dinutuximab [genetical recombination]; development code: OP-08; hereinafter referred to as "Unituxin") as a therapeutic agent for "neuroblastoma after high-dose chemotherapy" on June 23, 2021.

This authorization has been granted based on the outcome of the following two clinical studies conducted in Japan (Study GD2-PI and Study GD2-PII). The Osaka City General Hospital, Osaka City Hospital Organization (principal researcher/coordinating investigator: Junichi Hara) conducted these studies as investigator-initiated studies supported by programs such as the Practical Research for Innovative Cancer Control by the Japan Agency for Medical Research and Development (AMED), and they demonstrated the efficacy and safety of three-drug combination therapy (with filgrastim and teceleukin).

"Unituxin" is used as a standard therapeutic agent for high-risk neuroblastoma in the U.S. and Canada, and there has been a drug lag in Japan for a long time. And "Unituxin" acquired Orphan Drug Designation from the Ministry of Health, Labour and Welfare on August 17, 2020.

[Study GD2-PI]

The phase I/IIa study in Japan was conducted as an investigator-initiated study in patients with relapsed neuroblastoma or high-risk neuroblastoma in remission on treatment and demonstrated the tolerability of three-drug combination therapy.[1)]

[Study GD2-PII]

The phase IIb study in Japan was conducted as an investigator-initiated study in patients with high-risk neuroblastoma in remission on treatment, for the purpose of demonstrating non-inferiority to the U.S. regimen of three-drug combination therapy (a regimen approved in the U.S. that combines sargramostim as a GM-CSF

preparation and aldesleukin and isotretinoin as IL-2 preparations), with two-year EFS (event-free survival) as the primary endpoint. As a result, the non-inferiority of the three-drug combination therapy to the U.S. regimen was demonstrated. There were no substantial differences in safety between the three-combination therapy and the U.S. regimen.

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[About Neuroblastoma]

Neuroblastoma refers to a type of childhood solid tumor where cells become cancerous, originating in neural crest cells in the fetal period. This is the third most frequently observed tumor among childhood cancers after leukemia and brain tumor. The peak age of onset is 0 and 3 years.[2)] It is difficult to detect this disease in the early stage because it remains asymptomatic while the tumor is small. In most patients, it is detected after the tumor has progressed and become metastatic, marked by symptoms such as a head bumps, swollen eyes, pain in the limbs, anemia and/or bruises.[3)]

Up to approximately 160 patients are diagnosed with neuroblastoma every year in Japan.

Neuroblastoma is classified into three risk groups (Low, Intermediate and High), based on the five prognostic factors: staging, age, extra copies of the *MYCN* gene in the tumor cells, International Neuroblastoma Pathology Classification, and the number of chromosomes in the tumor cells. While the cure rate of patients in the Low to Intermediate risk groups exceed 90%, about 40% to 60% of all patients are classified in the High-risk group with a five-year survival rate of 50% or lower. This is why neuroblastoma is considered to have a poor prognosis among other childhood solid tumors.[3–5)] For patients in the Low- to Intermediate-risk groups, a wait and see approach without treatment, chemotherapy, or tumor resection is performed, and for patients in the High-risk group, multimodal treatment is provided including chemotherapy, surgical therapy, radiation therapy, or high-dose chemotherapy with autologous stem cell transplantation.

[About Unituxin]

Unituxin (generic name: dinutuximab [genetical recombination]) is a recombinant

chimeric monoclonal antibody and is a glycoprotein with a molecular weight of approx. 150,000 Da, consisting of a variable region (mouse anti-Ganglioside-GD2 monoclonal antibody) and a constant region (human IgG1).

This drug specifically interacts with the antigen GD2 that is frequently expressed in human neuroectodermal tumor (such as neuroblastoma) and provokes the cytolysis of neuroblastoma cells through the antibody-dependent cell-mediated cytotoxicity (ADCC) effect and the complement-dependent cytotoxicity (CDC) effect.

In the U.S. and Canada, Unituxin is approved for the following indication and marketed as Unituxin® by United Therapeutics Corporation of the U.S. (hereinafter referred to as "UT"): "Unituxin (dinutuximab) is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-2 (IL-2) and 13-cis-retinoic acid (RA), for the treatment of pediatric patients with high-risk neuroblastoma who achieve at least a partial response to prior first-line multiagent, multimodality therapy."*

In Japan, our company markets this drug under license from UT, which developed it.

＊: unapproved in Japan

[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 Osaka City General Hospital]

Osaka City General Hospital is one of Japan's leading hospitals established by integrating two Osaka municipal pediatric hospitals and three other municipal hospitals in 1993. At this hospital, 202 of the 1,063 beds are secured for pediatric patients. It has 18 clinical departments for pediatric diseases and serves as the main hospital for pediatric care in Osaka. In the field of cancer treatment, the hospital is designated as a childhood cancer hub hospital, a regional cancer treatment hospital, and a hub hospital for cancer genomic medicine by the Ministry of Health, Labour and Welfare, and is dedicated to the provision and development of cancer treatment for patients of all generations through various efforts such as the establishment of a special ward for adolescents and young adults.

[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 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.

[About Japan Agency for Medical Research and Development (AMED)]
Please use the link for the AMED website:
https://www.amed.go.jp/en/aboutus/index.html

[About Programs such as the Practical Research for Innovative Cancer Control]
As a novel cancer research strategy based on the "Basic Plan to Promote Cancer Control Programs,"[*1] the "Comprehensive 10-year Strategy for Cancer Control" was enacted in March 2014, with the confirmation of the Minister of Education, Culture, Sports, Science and Technology, the Minister of Health, Labour and Welfare, and the Minister of Economy, Trade and Industry. Based on the strategy, future cancer research will be promoted in cooperation with patients and society, from the viewpoints of complete cure, and prevention of cancer, as well as living together with cancer. Specific research items will also steadily be promoted in consideration of "Recommendations for the Acceleration plan for cancer control" of December 2015 (Cancer Control Promotion Council, the Ministry of Health, Labour and Welfare).[*2]
Under the Practical Research for Innovative Cancer Control initiative, the following programs will be promoted: development of technologies for the prevention and early detection of cancer, development of new drugs and medical devices, development of standard treatments combining various treatments, and development of treatments according to life stages.

[*1] Basic Plan to Promote Cancer Control Programs (Ministry of Health, Labour and Welfare)
[*2] Cancer Control Promotion Council, "Recommendations for Acceleration plan for cancer control" (Ministry of Health, Labour and Welfare)

【参考文献】

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2）日本小児血液・がん学会作成　小児がん診療ガイドライン 2016 年版
3）JCCG 神経芽腫委員会（JNBSG）　URL（2021 年 5 月 28 日現在）
4）七野 他. 神経芽腫に対する集学的治療法：化学療法を中心に. 小児がん. 2010, Vol. 47, No.1, p. 046-052.
5）Cohn SL., et al. The International Neuroblastoma Risk Group (INRG) Classification System: An INRG Task Force Report. J Clin Oncol. 2009, Vol. 27, No. 2, p. 289-297.