Press Release

December 27, 2024

Eli Lilly Japan K.K.
Mitsubishi Tanabe Pharma Corporation

“Zepbound®”, a Long-Acting GIP/GLP-1 Receptor Agonist, Approved for the Chronic Disease of “Obesity Disease” with Multiple Factors

December 27, 2024--Eli Lilly Japan K.K. (Head Office: Kobe, Hyogo, Japan; President and Representative Director: Simone Thomsen; hereinafter referred to as "Eli Lilly Japan") and Mitsubishi Tanabe Pharma Corporation (Head Office: Osaka city, Osaka, Japan; Representative Director: Akihiro Tsujimura; hereinafter referred to as “MTPC") announced today that Eli Lilly Japan received manufacturing and marketing authorization in Japan from the Japanese Ministry of Health, Labour and Welfare (MHLW) for "Zepbound®” (non-proprietary name: tirzepatide; hereinafter referred to as "Zepbound”), a long-acting GIP/GLP-1 receptor agonist, for the treatment of the chronic disease of “obesity disease*" with multiple factors.

* Zepbound’s approved indication is as below:
“Obesity Disease
However, its use is limited to people with any of hypertension, dyslipidemia, or type 2 diabetes mellitus and do not adequately respond to diet or exercise therapy and meet any of the following conditions:
- BMI of ≥27 kg/m^2 in the presence of at least two obesity-related health conditions
- BMI of ≥35 kg/m^2.”

Zepbound is a long-acting GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptor dual agonist that activates both GIP and GLP-1 receptors. Although the structure of Zepbound is a single molecule based on the native GIP peptide sequences, it has been modified to also bind to the GLP-1 receptor and selectively acts for a long duration, allowing weekly dosing. Tirzeptide is marketed by Eli Lilly Japan and MTPC for the treatment of type 2 diabetes mellitus under the name of Mounjaro®, which contains the same compound as Zepbound. Zepbound is administered once weekly by subcutaneous injection with "ATEOS®”, a single-use autoinjector device, and it has the same dosages as Mounjaro, with six dose standards (2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg), allowing for flexibility in dosing depending on the condition.

“With the current approval of Zepbound, we are very pleased to offer an innovative treatment option for people living with obesity disease in Japan,” said Gary Miles, Chief Officer of the Diabetes and Growth Hormone Division at Eli Lilly Japan. “Obesity disease significantly impacts quality of life and increases the risk of other health complications, including the worsening of existing chronic conditions. However, due to limited treatment options, obesity disease has not been diagnosed or managed with the same priority as other chronic diseases. With the approval of Zepbound, we are committed to providing evidence-based, optimal care to help people living with obesity disease lead healthier, more fulfilling lives.”

"We are very pleased that Zepbound is approved in Japan,” said Yasutaka Kuragaki, Head of the Japan Pharmaceutical Business Division at MTPC. “Despite the fact that obesity is caused by multiple factors, including genetic, physical, psychological, and social factors, and is not caused only by lifestyle habits, the stigma of obesity remains a social problem. We expect that this new treatment option with

Zepbound will help people better understand the chronic condition of obesity disease and lead to a better life for people with obesity disease."

The current approval of Zepbound is based primarily on the efficacy and safety results of tirzepatide in Japanese adults with obesity disease in Study SURMOUNT-J, a Phase 3 clinical trial in Japan. In Study SURMOUNT-J, the mean percent change from baseline in body weight at Week 72 were -17.8% in the tirzepatide 10 mg group (n = 71) and -22.7% in the tirzepatide 15 mg group (n = 76), compared to -1.7% in the placebo group (n = 75), showing superiority of both tirzepatide groups to the placebo group. The proportion of participants who achieved ≥5% body weight reduction was 94.4% in the tirzepatide 10 mg group and 96.1% in the tirzepatide 15 mg group, compared to 20.0% in the placebo group. Both tirzepatide groups showed superiority over the placebo group. Likewise, the secondary endpoints, the proportion of participants who achieved ≥7%, ≥10%, ≥15%, or ≥20% body weight reduction from baseline at Week 72, also demonstrated superiority of both tirzepatide groups over the placebo group.

In Japan, MTPC is responsible for sales and distribution of Zepbound and Eli Lilly Japan and MTPC will jointly provide information, in the same way as Mounjaro. Eli Lilly Japan and MTPC will continue to do our best to support people with obesity disease, so they may live more fulfilling lives, through a variety of research and activities with people involved in obesity disease.

End.

Product Summary

Product Name	Zepbound® subcutaneous injection 2.5 mg Ateos® Zepbound® subcutaneous injection 5 mg Ateos® Zepbound® subcutaneous injection 7.5 mg Ateos® Zepbound® subcutaneous injection 10 mg Ateos® Zepbound® subcutaneous injection 12.5 mg Ateos® Zepbound® subcutaneous injection 15 mg Ateos®
Non-proprietary Name	Tirzepatide
Indications	Obesity Disease However, its use is limited to people with any of hypertension, dyslipidemia, or type 2 diabetes mellitus and do not adequately respond to diet or exercise therapy and meet any of the following conditions: • BMI of ≥27 kg/m^2 in the presence of at least two obesity-related health conditions • BMI of ≥35 kg/m^2.
Dosage and Administration	For adults, the starting dosage of tirzepatide is 2.5 mg injected subcutaneously once weekly and the dosage may be increased by 2.5 mg every 4 weeks to a dose of 10 mg per week. The dosage may be reduced to 5 mg once weekly or increased by 2.5 mg every 4 or more weeks to a maximum dose of 15 mg once weekly, as appropriate, according to the patient's condition.
Date of acquisition of manufacturing and marketing approval	December 27, 2024
Manufacturer and distributor	Eli Lilly Japan K.K.
Distributor	Mitsubishi Tanabe Pharma Corporation

About Obesity and Obesity Disease

In Japan, "obesity" is defined as excessive fat storage in adipose tissue associated with a BMI of ≥25 kg/m^2. Obesity with a BMI of ≥35 kg/m^2 is referred to as "high-degree obesity".
On the other hand, obesity (BMI of ≥25 kg/m^2) is diagnosed as "obesity disease" if it is accompanied by at least one obesity-induced or obesity-associated health disorders (complications) or by possible complication of related health disorders such as visceral fat accumulation, and which from a medical viewpoint requires body weight reduction. "Obesity disease" is a chronic disease that is the target of medical treatment by weight reduction.

Obesity and obesity disease are reported to be related to not only lifestyle habits but also various factors, including genetic and environmental factors, and closely related to various other health disorders.
It is estimated that there are 28 million[1] people living with obesity in Japan. Of those, “obesity disease" which has obesity related disorders is not being actively carried out of the diagnosis and treatment compared to other chronic diseases.

Specific Health Disorders Necessary for the Diagnosis of Obesity Disease
1. Glucose intolerance (including type 2 diabetes mellitus and impaired glucose tolerance)
2. Dyslipidemia
3. Hypertension
4. Hyperuricemia or gout
5. Coronary artery disease
6. Cerebral infarction or transient ischemic attack
7. Non-alcoholic fatty liver disease
8. Menstrual disorder or female infertility
9. Obstructive sleep apnea syndrome or obesity hypoventilation syndrome
10. Musculoskeletal disorders (Osteoarthritis: knee, hip or finger joints, spondylosis deformans)
11. Obesity-related kidney disease

About Tirzepatide
Tirzepatide is a long-acting GIP (glucose-dependent insulinotropic polypeptide) and GLP-1 (glucagon-like peptide-1) receptor dual agonist that activates both GIP and GLP-1 receptors. Although the structure of tirzepatide is a single molecule based on the native GIP peptide sequences, it has been modified to also bind to the GLP-1 receptor and selectively acts for a long time, allowing weekly dosing. Tirzepatide was launched in Japan as Mounjaro in April 2023 for a treatment of type 2 diabetes mellitus, with six dose standards (ranging from 2.5 mg to 15 mg) and has already been used clinically by many people with type 2 diabetes mellitus. It is marketed in many countries around the world as a treatment for type 2 diabetes mellitus and has been approved in the United States and several other countries for the treatment of obesity. In the United States, tirzepatide has been on the market to treat obesity disease since last December under the name Zepbound

About SURMOUNT-J
SURMOUNT-J (NCT04844918) was a phase 3, multi-center, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of tirzepatide 10 mg and 15 mg subcutaneously administered once weekly to Japanese adults with obesity or severe obesity and obesity-related health problems (among impaired glucose tolerance, dyslipidemia, and nonalcoholic steatohepatitis, at least 2 obesity-related health problems in those with obesity and at least one problem in those with severe obesity) in comparison with placebo. Participants were randomly assigned to one of the three groups, i.e., placebo, tirzepatide 10 mg or tirzepatide 15 mg groups. After a 4-week screening period, a dose-escalation period was set in which the treatment was started at a dose of 2.5 mg subcutaneously administered once weekly and the dose was increased by 2.5 mg every 4 weeks. When the dose reached the prescribed level (i.e., tirzepatide 10 mg or 15 mg) in each group, the dosage was fixed at that level and the treatment continued until Week 72 that was the end of the study.
This study was conducted under the low-calorie diet therapy for body weight management and exercise therapy described in the “Guidelines for the Management of Obesity Disease[2]. Throughout the study period, national registered dietitians or those having an equivalent qualification gave counseling about diet and exercise to all participants.
Exclusion criteria were as follows: those with diabetes, those with known clinical laboratory test results as diagnosis criteria for diabetes, those who have undergone or plan to undergo endoscopic and/or device-based therapy for obesity, those with a history of drug therapy for the purpose of reducing body weight within 3 months of randomization, and those with a history of treatment with drugs which may reduce body weight. For more details, please see the press release.

About Eli Lilly Japan
Eli Lilly Japan is the Japanese subsidiary of Eli Lilly and Company based in the United States. We have been developing and supplying world-class, innovative medicines by uniting caring with discovery for 50 years to help patients in Japan achieve healthier and more fulfilling lives. We currently contribute to Japanese medicine in multiple areas, including cancer, diabetes, Alzheimer's disease and other central nervous system diseases, as well as autoimmune diseases, etc. For more details, please visit our website. https://www.lilly.com/jp

About Mitsubishi Tanabe Pharma

Mitsubishi Tanabe Pharma Corporation (MTPC), the pharma arm of Mitsubishi Chemical Group (MCG), is one of the oldest pharmaceutical companies in the world, founded in 1678, and focusing on ethical pharmaceuticals. MTPC is headquartered in Doshomachi, Osaka, the birthplace of Japan's pharmaceutical industry. MTPC sets the MISSION of "Creating hope for all facing illness". To that end, MTPC is working on the disease areas of central nervous system, immuno-inflammation, diabetes and kidney, and cancer. MTPC is focusing on "precision medicine" to provide drugs with high treatment satisfaction by identifying patient populations with high potential for efficacy and safety. In addition, MTPC is working to develop "around the pill solutions" to address specific patient concerns based on therapeutic medicine, including prevention of diseases, pre-symptomatic disease care, prevention of aggravation and prognosis. For more information, go to https://www.mt-pharma.co.jp/e/.

References:

1: The National Health and Nutrition Survey, 2022

2: Guideline for the Management of Obesity Disease 2022, Japan Society for the Study of Obesity（JASSO）