Press Release

March 19, 2025

Eli Lilly Japan K.K.
Mitsubishi Tanabe Pharma Corporation

Announcement of NHI Price Listing and Release Date of "Zepbound®", a Long-Acting GIP/GLP-1 Receptor Agonist, for the Chronic Disease of "Obesity Disease*" with Multiple Factors

Eli Lilly Japan K.K. (Head Office: Kobe, Hyogo, Japan; President and Representative Director: Simo-ne Thomsen; hereinafter referred to as "Eli Lilly Japan") and Mitsubishi Tanabe Pharma Corporation (Head Office: Osaka city, Osaka, Japan; Representative Director: Akihiro Tsujimura; hereinafter re-ferred to as "MTPC") announced that the long-acting GIP/GLP-1 receptor agonist "Zepbound® subcu-taneous injec-tion 2.5 mg/5 mg/7.5 mg/10 mg/12.5 mg/15 mg Ateos®" (non-proprietary name: tir-zepatide; hereinafter referred to as "Zepbound") was listed in the National Health Insurance (NHI) price list with the indication "obesity disease*" today on March 19, 2025 and will be released in Japan on April 11, 2025.

* 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 (glucagonlike 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. Zep-bound is administered once weekly by subcutaneous injection with "Ateos®", a single-use autoinjector device. The pre-installed needle is automatically injected subcutaneously by pushing the injection but-

ton and a single dose of medicinal solution filled in the syringe is infused. Patients do not need to handle the needle or set the dose.

In addition, it has six dose standards of 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. For adults, the usual 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 increased or decreased as appropriate, according to the patient's condition; it 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.

"It is estimated that there are approximately 28 million people living with obesity in Japan," said Takahiko Kojima, Head of the Diabetes and Growth hormone Business Unit at Eli Lilly Japan. "And those who have health disorders associated with obesity are people with obesity disease. Obesity disease may not only reduce QOL but also exacerbate existing chronic diseases and further cause other health disorders. Despite these risks, patients with obesity disease have not been treated at the necessary level as those with other chronic diseases. We are very pleased that now this new treatment option can be provided to people with obesity disease in Japan. With Zepbound, we will strive to help people with obesity disease access evidence-based optimal care and lead more fulfilling lives."

"Despite the fact that obesity and obesity disease are caused by multiple factors, including genetic, physical, psychological, and social factors, and is not caused only by lifestyle habits, the prejudice and discrimination against obesity and obesity disease (obesity stigma) remains a social problem," said Yasutaka Kuragaki, Head of the Japan Pharmaceutical Business Division at MTPC. "Now that Zepbound was listed in the NHI price list and will be delivered for clinical use as a new treatment option for obesity disease, we will strive to promote proper use of this medicine by providing information and also help people properly understand the chronic disease of obesity disease to ensure better life for people with obesity disease."

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®.

The safety and efficacy of Zepbound, when used for any purpose other than the indication for which manufacturing and marketing approval has been obtained, have not been confirmed. Zepbound is a medicine requiring proper use in accordance with the package insert provided in Japan, and any use other than that approved in Japan may result in unexpected health problems. Eli Lilly Japan and MTPC will be committed to providing information in accordance with the package insert and the Optimal Clinical Use Guidelines to ensure that people who need Zepbound can use the medicine safely and properly.

Eli Lilly Japan and MTPC will continue to do our best to help people with obesity disease live more fulfilling lives through a variety of research and development and activities with people involved in obesity disease.

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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.
Price	Zepbound® subcutaneous injection 2.5 mg Ateos® 0.5mL 1 kit: 3,067 yen Zepbound® subcutaneous injection 5mg Ateos® 0.5mL 1kit: 5,797 yen Zepbound® subcutaneous injection 7.5mg Ateos® 0.5mL 1kit: 7,721 yen Zepbound® subcutaneous injection 10mg Ateos® 0.5mL 1kit: 8,999 yen Zepbound® subcutaneous injection 12.5mg Ateos® 0.5mL 1kit: 10,180 yen Zepbound® subcutaneous injection 15mg Ateos® 0.5mL 1kit: 11,242 yen
Date of acquisition of manufacturing and marketing approval	December 27, 2024
Date of NHI price listing	March 19, 2025
Date of launch (planning)	April 11, 2025
Manufacturer and distributor	Eli Lilly Japan K.K.
Distributor	Mitsubishi Tanabe Pharma Corporation

About the Optimal Clinical Use Guidelines

Zepbound is a medicine subject to the Optimal Clinical Use Guidelines, and it is required in the use of this medicine to select eligible patients and determine continuous administration/discontinuation and readministration in an appropriate manner. Zepbound should not be used for any purpose other than the indication of obesity disease, such as body weight reduction, and appropriate care should be taken at the onset of any serious adverse reaction after use of this medicine. Therefore, Zepbound should be used at the institutions that meet the conditions described below. For more information, please refer to the Optimal Clinical Use Guidelines for Tirzepatide by the Ministry of Health, Labour and Welfare.

* Excerpt from the Optimal Clinical Use Guidelines for Tirzepatide by the Ministry of Health, Labour and Welfare (p.20)

Institution requirements (Medical institutions should meet the conditions on the right.)	➢ Health insurance-covered medical institution advocating internal medicine, cardiovascular medicine, endocrinology, metabolism, or diabetology. ➢ Medical institution where Zepbound can be prescribed under the direction of a physician, who has an intimate knowledge of the pathogenesis, course and prognosis, diagnosis, and treatment of hypertension, dyslipidemia, or type 2 diabetes mellitus and obesity disease (reference: The Japanese Society of Hypertension Guidelines for the Management of Hypertension, Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases, or Practice Guideline for the Treatment of Diabetes and Guidelines for the Management of Obesity Disease, Comprehensive Treatment Guide for Obesity Disease) and has sufficient knowledge of Zepbound (see the <Physician requirements> below). ➢ Institution to which at least one full-time physician certified as specialist by either of the academic societies described in the <Physician requirements> below belongs and where the system to start treatment with Zepbound is in place. If the specialist certified by either of the academic societies described in the <Physician requirements> below does not belong to the institution, a system should be established to appropriately collaborate with the institution where the specialist physician belongs to. ➢ Institution certified as an educational training institution by either of the academic societies described in the <Physician requirements> below. ➢ Institution where appropriate nutritional guidance can be provided by a full-time nutritionist. The nutritional guidance performed should be recorded on the medical record, etc.
Physician requirements (Physicians meeting the criteria on	➢ Physician with at least 5 years of clinical experience in the treatment of hypertension, dyslipidemia, or type 2 diabetes mellitus and obesity disease following 2 years of residency program after obtaining a medical license; Or, physician with at least 7 years of clinical experience after obtaining a

the right meet the above <Physician requirements>.)	medical license, including at least 5 years of clinical training in hypertension, dyslipidemia, or type 2 diabetes mellitus and obesity disease. ➢ Board certified specialist of either of the academic societies below, which are involved in the treatment of obesity disease with hypertension, dyslipidemia, or type 2 diabetes mellitus. ・ The Japanese Circulation Society* ・ The Japan Diabetes Society* ・ The Japan Endocrine Society The specialist certified by the Japan Society for the Study of Obesity would be desirable. *The specialists certified by the Japan Endocrine Society or the Japan Diabetes Society include specialists certified by both societies (endocrinology, metabolism, and diabetes specialists).

About SURMOUNT-J which is the phase 3 trial of Zepbound

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 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 December of 2023 under the name Zepbound

About Obesity and Obesity Disease[3]

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 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）