ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

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ゼップバウンド皮下注 2.5mg アテオス
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ゼップバウンド皮下注 12.5mg アテオス
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1.5　起原又は発見の経緯及び開発の経緯

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1.5　起原又は発見の経緯及び開発の経緯

チルゼパチドは、グルコース依存性インスリン分泌刺激ポリペプチド（glucose-dependent insulinotropic polypeptide：GIP）受容体及びグルカゴン様ペプチド-1（glucagon-like peptide-1：GLP-1）受容体の両方に結合するアゴニストであり、投与方法は週 1 回である。

消化管ホルモンのインクレチンである GIP 及び GLP-1 は、食後に消化管の内分泌細胞から分泌される。これらのインクレチンは、インクレチン効果（インスリン分泌促進作用）に加えて、満腹感及び栄養素の代謝など、食物に対する生理的反応を促進する。GLP-1 受容体アゴニストによる GLP-1 受容体シグナル伝達の活性化は、脳の食欲抑制経路を活性化することにより食物摂取量と体重を減少させる。

非臨床モデルで、GIP 受容体及び GLP-1 受容体の両方を活性化することにより、GLP-1 受容体を選択的に活性化させた場合よりも優れた摂餌量及び体重の減少作用を示した。GIP 受容体は、GLP-1 受容体と同様にエネルギーバランスの調節に関与する脳の重要な領域に発現している。GIP 及び GLP-1 受容体の多くは、中枢神経系の異なる神経細胞集団で発現している。また、食餌誘発性肥満マウスの食餌制限モデルにおいて、チルゼパチドは脂肪消費量を増加させた。

臨床試験においても、2 型糖尿病患者を対象とした I8F-MC-GPGT 試験では、チルゼパチド投与によりプラセボ群と比較して全体的な食欲、並びに食事及びカロリー摂取量が減少した。GLP-1 受容体アゴニストであるセマグルチド投与でも食事及びカロリー摂取量に対して同様の影響が認められたが、チルゼパチド群でより顕著な体重減少を示した。この臨床試験の結果は、非臨床試験の結果と併せて、チルゼパチドが、食事及びカロリー摂取量の減少以外の作用機序に基づき体重減少を促進している可能性を示している。

結論として、チルゼパチドは、GIP 受容体及び GLP-1 受容体の両方でアゴニストとして機能し、食物及びカロリー摂取量を減少させる。GIP と GLP-1 の既知の生理学と薬理学に基づき、両受容体へのシグナル伝達は、選択的 GLP-1 受容体アゴニスト以上に炭水化物及び脂質の代謝、並びに体重のコントロールを改善すると予想される。これは、2 型糖尿病及び肥満又は過体重に対する体重管理におけるチルゼパチドの非臨床及び臨床研究の両方の結果により支持される。

チルゼパチドは、国内では、2022 年 9 月に「2 型糖尿病」を効能又は効果として承認されている（販売名：マンジャロ皮下注）。チルゼパチドの肥満症を適応とする開発を目標として、以下に示す肥満症診療ガイドライン 2016 に準じて肥満症患者を対象とした国内第 3 相試験、及び日本人を含む肥満又は過体重の被験者を対象とした国際共同第 3 相試験を実施し、チルゼパチドの肥満症に対する有効性及び安全性を評価した。

- 国内第 3 相試験
  - I8F-JE-GPHZ 試験（以下、GPHZ 試験）
- 国際共同第 3 相試験
  - I8F-MC-GPHK 試験（以下、GPHK 試験）
  - I8F-MC-GPHL 試験（以下、GPHL 試験）

試験の結果から、チルゼパチドは、肥満症、肥満、又は過体重の様々な臨床的症状を呈する被験者集団に対して、臨床的に意味のある体重減少をもたらし、肥満症の治療に対して承認されているインクレチン関連薬と同様の安全性プロファイルを有していることが示された。

今般、これらの試験成績に基づくベネフィット・リスク評価の結果から、当該疾患に対するチルゼパチドの高い有用性が示され、新たなより良い治療の選択肢となり得ると考えられることから、肥満症の治療薬として、販売名をゼップバウンド皮下注（以下、本剤）として製造販売承認申請を行うこととした。

本剤は、2 型糖尿病治療薬として既に承認されているマンジャロ皮下注との識別を可能にするため、ラベル及び個装箱のデザインを変更する。原薬及び製剤は、ラベル及び個装箱のデザイン以外は、製造所も含めてすべてマンジャロ皮下注と同一である。

本剤における起原又は発見の経緯及び開発の経緯は主に第 2.3、2.4 及び 2.5 項に記載した。表 1.5-1 に第 2 部での当該内容の記載場所を示す。また開発の経緯図を図 1.5-1 に示す。

表 1.5-1　起原又は発見の経緯及び開発の経緯

第 1.5 項に記載する内容	第 2 部での記載場所	
起原又は発見の経緯	2.5.1	製品開発の根拠
非臨床試験の概略	2.4	非臨床試験の概括評価
臨床開発の経緯、臨床データパッケージ、治験相談	2.5.1.4 2.5.1.5	臨床開発の経緯 規制当局への相談
臨床試験の概略	2.5.2 2.5.3 2.5.4 2.5.5	生物薬剤学に関する概括評価 臨床薬理に関する概括評価 有効性の概括評価 安全性の概括評価
本剤の有効性及び安全性に基づく有用性に関する記載	2.5.6	ベネフィットとリスクに関する結論

試験項目		20[redacted]年	20[redacted]年	20[redacted]年	20[redacted]年	20[redacted]年	20[redacted]年
品質に関する試験		[redacted]					
非臨床試験	薬理						
臨床試験	第 3 相試験						

[redacted]

[redacted]

図 1.5-1　チルゼパチドの開発の経緯図

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ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

1.6　外国における使用状況等に関する資料

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1.6　外国における使用状況等に関する資料

1.6.1　外国における申請・承認状況

チルゼパチド製剤は、2022 年 5 月に米国で 2 型糖尿病に対して世界で最初に承認され、2024 年 10 月現在、欧米等主要国（米国、EU、英国、カナダ、及びオーストラリア）を含む 50 以上の国又は地域で承認を取得している。国内においては、2022 年 9 月に「2 型糖尿病」を効能又は効果として承認された（国内販売名：マンジャロ皮下注）。

また、チルゼパチド製剤は肥満又は過体重に対する体重管理を適応として、2023 年 11 月に米国、英国、及びアラブ首長国連邦で、2023 年 12 月に EU 及びサウジアラビアで承認を取得している。2024 年 10 月現在、40 以上の国又は地域で承認を取得している。

1.6.2　外国における添付文書

本剤の米国における添付文書及び欧州における Summary of product characteristics（SmPC）の原文、並びに企業中核データシートの原文を添付する。

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPBOUND safely and effectively. See full prescribing information for ZEPBOUND.

ZEPBOUND® (tirzepatide) Injection, for subcutaneous use
Initial U.S. Approval: 2022

WARNING: RISK OF THYROID C-CELL TUMORS

See full prescribing information for complete boxed warning.

- **In rats, tirzepatide causes thyroid C-cell tumors. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as the human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined (5.1, 13.1).**
- **ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). Counsel patients regarding the potential risk of MTC and symptoms of thyroid tumors (4, 5.1).**

---------- RECENT MAJOR CHANGES ----------

Warnings and Precautions

Pulmonary Aspiration During General Anesthesia or Deep Sedation (5.10)	10/2024

---------- INDICATIONS AND USAGE ----------

ZEPBOUND® is a glucose-dependent insulinotropic polypeptide (GIP) receptor and glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition. (1)

Limitations of Use:

- Coadministration with other tirzepatide-containing products or with any GLP-1 receptor agonist is not recommended. (1)

----------DOSAGE AND ADMINISTRATION----------

- The recommended starting dosage is 2.5 mg injected subcutaneously once weekly. (2.1)
- After 4 weeks, increase to 5 mg injected subcutaneously once weekly. (2.1)
- Increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose. (2.1)
- The recommended maintenance dosages are 5 mg, 10 mg, or 15 mg injected subcutaneously once weekly. (2.1)
- Consider treatment response and tolerability when selecting the maintenance dosage. (2.1)
- The maximum dosage is 15 mg subcutaneously once weekly. (2.1)
- Administer in combination with a reduced-calorie diet and increased physical activity. (2.3)
- Administer once weekly at any time of day, with or without meals. (2.3)
- Inject subcutaneously in the abdomen, thigh, or upper arm. (2.3)
- Rotate injection sites with each dose. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg per 0.5 mL in single-dose pen or single-dose vial (3)

---------- CONTRAINDICATIONS ----------

- Personal or family history of medullary thyroid carcinoma or in patients with Multiple Endocrine Neoplasia syndrome type 2 (4)
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND (4)

----------WARNINGS AND PRECAUTIONS----------

- *Severe Gastrointestinal Adverse Reactions:* Use has been associated with gastrointestinal adverse reactions, sometimes severe. Has not been studied in patients with severe gastrointestinal disease and is not recommended in these patients. (5.2)
- *Acute Kidney Injury:* Monitor renal function in patients reporting adverse reactions that could lead to volume depletion. (5.3)
- *Acute Gallbladder Disease:* Has been reported in clinical trials. If cholecystitis is suspected, gallbladder studies and clinical follow-up are indicated. (5.4)
- *Acute Pancreatitis:* Has been reported in clinical trials. Discontinue promptly if pancreatitis is suspected. Do not restart if pancreatitis is confirmed. (5.5)
- *Hypersensitivity Reactions:* Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported postmarketing with tirzepatide. If suspected, advise patients to promptly seek medical attention and discontinue ZEPBOUND. (5.6)
- *Hypoglycemia:* Concomitant use with insulin or an insulin secretagogue may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin or insulin secretagogue may be necessary. Inform all patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. (5.7)
- *Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus:* Has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Monitor patients with a history of diabetic retinopathy for progression. (5.8)
- *Suicidal Behavior and Ideation:* Monitor for depression or suicidal thoughts. Discontinue ZEPBOUND if symptoms develop. (5.9)
- *Pulmonary Aspiration During General Anesthesia or Deep Sedation:* Has been reported in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures. Instruct patients to inform healthcare providers of any planned surgeries or procedures. (5.10)

----------ADVERSE REACTIONS----------

The most common adverse reactions, reported in ≥5% of patients treated with ZEPBOUND are: nausea, diarrhea, vomiting, constipation, abdominal pain, dyspepsia, injection site reactions, fatigue, hypersensitivity reactions, eructation, hair loss, gastroesophageal reflux disease. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---------- DRUG INTERACTIONS ----------

ZEPBOUND delays gastric emptying and has the potential to impact the absorption of concomitantly administered oral medications. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* May cause fetal harm. When pregnancy is recognized, discontinue ZEPBOUND. (8.1)
- *Females of Reproductive Potential:* Advise females using oral contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation. (8.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved Medication Guide.

Revised: 10/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: RISK OF THYROID C-CELL TUMORS

- **In rats, tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined *[see Warnings and Precautions (5.1) and Nonclinical Toxicology (13.1)]*.**
- **ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2) *[see Contraindications (4)]*. Counsel patients regarding the potential risk for MTC with the use of ZEPBOUND and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness). Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with ZEPBOUND *[see Contraindications (4) and Warnings and Precautions (5.1)]*.**

1 INDICATIONS AND USAGE

ZEPBOUND® is indicated in combination with a reduced-calorie diet and increased physical activity to reduce excess body weight and maintain weight reduction long term in adults with obesity or adults with overweight in the presence of at least one weight-related comorbid condition.

Limitations of Use

- ZEPBOUND contains tirzepatide. Coadministration with other tirzepatide-containing products or with any glucagon-like peptide-1 (GLP-1) receptor agonist is not recommended.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

- The recommended starting dosage of ZEPBOUND is 2.5 mg injected subcutaneously once weekly. Follow the dosage escalation below to reduce the risk of gastrointestinal adverse reactions *[see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]*. The 2.5 mg dosage is for treatment initiation and is not approved as a maintenance dosage.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly. The dosage may be increased in 2.5 mg increments, after at least 4 weeks on the current dose.
- The recommended maintenance dosages of ZEPBOUND in adults are 5 mg, 10 mg, or 15 mg, injected subcutaneously once weekly.
- Consider treatment response and tolerability when selecting the maintenance dosage *[see Adverse Reactions (6.1) and Clinical Studies (14.1)]*. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.
- The maximum dosage of ZEPBOUND is 15 mg injected subcutaneously once weekly.

2.2 Recommendations Regarding Missed Dose

- If a dose is missed, instruct patients to administer ZEPBOUND as soon as possible within 4 days (96 hours) after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.
- The day of weekly administration can be changed, if necessary, as long as the time between the two doses is at least 3 days (72 hours).

2.3 Important Administration Instructions

- Prior to initiation of ZEPBOUND, train patients and caregivers on proper injection technique. Refer to the accompanying Instructions for Use for complete administration instructions with illustrations.
- Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose).
- Inspect ZEPBOUND visually before use. It should appear clear and colorless to slightly yellow. Do not use ZEPBOUND if particulate matter or discoloration is seen.
- Administer ZEPBOUND in combination with a reduced-calorie diet and increased physical activity.
- Administer ZEPBOUND once weekly at any time of day, with or without meals.

- Inject ZEPBOUND subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.

3 DOSAGE FORMS AND STRENGTHS

Injection: Clear, colorless to slightly yellow solution in pre-filled single-dose pens or single-dose vials, each available in the following strengths:

- 2.5 mg/0.5 mL
- 5 mg/0.5 mL
- 7.5 mg/0.5 mL
- 10 mg/0.5 mL
- 12.5 mg/0.5 mL
- 15 mg/0.5 mL

4 CONTRAINDICATIONS

ZEPBOUND is contraindicated in patients with:

- A personal or family history of MTC or in patients with MEN 2 *[see Warnings and Precautions (5.1)]*.
- Known serious hypersensitivity to tirzepatide or any of the excipients in ZEPBOUND. Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with tirzepatide *[see Warnings and Precautions (5.6) and Adverse Reactions (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Thyroid C-Cell Tumors

In rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma exposures *[see Nonclinical Toxicology (13.1)]*. It is unknown whether ZEPBOUND causes thyroid C-cell tumors, including MTC, in humans as human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined.

ZEPBOUND is contraindicated in patients with a personal or family history of MTC or in patients with MEN 2. Counsel patients regarding the potential risk for MTC with the use of ZEPBOUND and inform them of symptoms of thyroid tumors (e.g., a mass in the neck, dysphagia, dyspnea, persistent hoarseness).

Routine monitoring of serum calcitonin or using thyroid ultrasound is of uncertain value for early detection of MTC in patients treated with ZEPBOUND. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

5.2 Severe Gastrointestinal Adverse Reactions

Use of ZEPBOUND has been associated with gastrointestinal adverse reactions, sometimes severe *[see Adverse Reactions (6.1)]*. In a pool of two ZEPBOUND clinical trials (Studies 1 and 2), severe gastrointestinal adverse reactions were reported more frequently among patients receiving ZEPBOUND (5 mg 1.7%, 10 mg 2.5%, 15 mg 3.1%) than placebo (1%).

ZEPBOUND has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and is therefore not recommended in these patients.

5.3 Acute Kidney Injury

Use of ZEPBOUND has been associated with acute kidney injury, which can result from dehydration due to gastrointestinal adverse reactions to ZEPBOUND, including nausea, vomiting, and diarrhea *[see Adverse Reactions (6.1)]*.

In patients treated with GLP-1 receptor agonists, there have been postmarketing reports of acute kidney injury and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events have been reported in patients without known underlying renal disease. A majority of the reported events occurred in patients who had

experienced nausea, vomiting, diarrhea, or dehydration. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion.

5.4 Acute Gallbladder Disease

Treatment with ZEPBOUND and GLP-1 receptor agonists is associated with an increased occurrence of acute gallbladder disease.

In a pool of two ZEPBOUND clinical trials (Studies 1 and 2), cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients. Acute gallbladder events were associated with weight reduction. If cholecystitis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

5.5 Acute Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists or tirzepatide.

In clinical trials of tirzepatide for a different indication, 14 events of acute pancreatitis were confirmed by adjudication in 13 tirzepatide-treated patients (0.23 patients per 100 years of exposure) versus 3 events in 3 comparator-treated patients (0.11 patients per 100 years of exposure). In a pool of two ZEPBOUND clinical trials (Studies 1 and 2), 0.2% of ZEPBOUND-treated patients had acute pancreatitis confirmed by adjudication (0.14 patients per 100 years of exposure) versus 0.2% of placebo-treated patients (0.15 patients per 100 years of exposure). ZEPBOUND has not been studied in patients with a prior history of pancreatitis. It is unknown if patients with a history of pancreatitis are at higher risk for development of pancreatitis on ZEPBOUND.

After initiation of ZEPBOUND, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue ZEPBOUND and initiate appropriate management. If the diagnosis of pancreatitis is confirmed, ZEPBOUND should not be restarted.

5.6 Hypersensitivity Reactions

There have been postmarketing reports of serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) in patients treated with tirzepatide. In a pool of two ZEPBOUND clinical trials (Studies 1 and 2), 0.1% of ZEPBOUND-treated patients had severe hypersensitivity reactions compared to no placebo-treated patients. If hypersensitivity reactions occur, advise patients to promptly seek medical attention and discontinue use of ZEPBOUND. Do not use in patients with a previous serious hypersensitivity reaction to tirzepatide or any of the excipients in ZEPBOUND *[see Contraindications (4) and Adverse Reactions (6.2)]*.

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with ZEPBOUND.

5.7 Hypoglycemia

ZEPBOUND lowers blood glucose and can cause hypoglycemia.

In a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2 (Study 2), hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients. In this trial, patients taking ZEPBOUND in combination with an insulin secretagogue (e.g., sulfonylurea) had increased risk of hypoglycemia (10.3%) compared to ZEPBOUND-treated patients not taking a sulfonylurea (2.1%). There is also increased risk of hypoglycemia in patients treated with tirzepatide in combination with insulin *[see Drug Interactions (7.1)]*.

Hypoglycemia has also been associated with ZEPBOUND and GLP-1 receptor agonists in adults without type 2 diabetes mellitus *[see Adverse Reactions (6.1)]*.

Inform patients of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia. In patients with diabetes mellitus, monitor blood glucose prior to starting ZEPBOUND and during ZEPBOUND treatment. The risk of hypoglycemia may be lowered by a reduction in the dose of insulin or sulfonylurea (or other concomitantly administered insulin secretagogue).

5.8 Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

5.9 Suicidal Behavior and Ideation

Suicidal behavior and ideation have been reported in clinical trials with other weight management products. Monitor patients treated with ZEPBOUND for the emergence or worsening of depression, suicidal thoughts or behaviors, and/or any unusual changes in mood or behavior. Discontinue ZEPBOUND in patients who experience suicidal thoughts or behaviors. Avoid ZEPBOUND in patients with a history of suicidal attempts or active suicidal ideation.

5.10 Pulmonary Aspiration During General Anesthesia or Deep Sedation

ZEPBOUND delays gastric emptying *[see Clinical Pharmacology (12.2)]*. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.

Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking ZEPBOUND, including whether modifying preoperative fasting recommendations or temporarily discontinuing ZEPBOUND could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ZEPBOUND.

6 ADVERSE REACTIONS

The following serious adverse reactions are described below or elsewhere in the prescribing information:

- Risk of Thyroid C-cell Tumors *[see Warnings and Precautions (5.1)]*
- Severe Gastrointestinal Adverse Reactions *[see Warnings and Precautions (5.2)]*
- Acute Kidney Injury *[see Warnings and Precautions (5.3)]*
- Acute Gallbladder Disease *[see Warnings and Precautions (5.4)]*
- Acute Pancreatitis *[see Warnings and Precautions (5.5)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.6)]*
- Hypoglycemia *[see Warnings and Precautions (5.7)]*
- Diabetic Retinopathy Complications in Patients with Type 2 Diabetes Mellitus *[see Warnings and Precautions (5.8)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.9)]*
- Pulmonary Aspiration During General Anesthesia or Deep Sedation *[see Warnings and Precautions (5.10)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Pool of Placebo-Controlled Weight Reduction Trials in Adults with Obesity or Overweight, with or without Type 2 Diabetes (Study 1 and Study 2)

ZEPBOUND was evaluated for safety in a pool of two randomized, double-blind, placebo-controlled trials that included 2,519 adult patients with obesity or overweight treated with ZEPBOUND for up to 72 weeks and a 4-week off drug follow-up period (Study 1 and Study 2) *[see Clinical Studies (14.1)]*. The mean age of patients was 47 years and 37% were male. The population was 72% White, 12% Asian, 8% Black or African American, and 7% American Indian or Alaska Native; 51% identified as Hispanic or Latino ethnicity. Baseline characteristics included an average BMI of 37.4 kg/m^2, 29% with a BMI ≥40 kg/m^2, 41% with hypertension, 37% with dyslipidemia, 25% with type 2 diabetes mellitus, 7% with obstructive sleep apnea, and 4% with cardiovascular disease.

Across both trials, 4.8%, 6.3%, and 6.7% of patients treated with 5 mg, 10 mg, and 15 mg of ZEPBOUND, respectively, permanently discontinued treatment as a result of adverse reactions compared to 3.4% of patients treated with placebo. The majority of patients who discontinued ZEPBOUND due to adverse reactions did so during the first few months of treatment due to gastrointestinal adverse reactions.

Common Adverse Reactions

Table 1 shows common adverse reactions associated with the use of ZEPBOUND in the pool of two placebo-controlled trials for weight reduction (Study 1 and Study 2). These adverse reactions occurred more commonly with ZEPBOUND than with placebo and occurred in at least 2% of patients treated with ZEPBOUND.

Table 1: Adverse Reactions (≥2% and Greater than Placebo) in ZEPBOUND-Treated Adults with Obesity or Overweight (Study 1 and Study 2)

Adverse Reaction	Placebo (N=958) %	ZEPBOUND 5 mg (N=630) %	ZEPBOUND 10 mg (N=948) %	ZEPBOUND 15 mg (N=941) %
Nausea	8	25	29	28
Diarrhea[a]	8	19	21	23
Vomiting	2	8	11	13
Constipation[b]	5	17	14	11
Abdominal Pain[c]	5	9	9	10
Dyspepsia	4	9	9	10
Injection Site Reactions[d]	2	6	8	8
Fatigue[e]	3	5	6	7
Hypersensitivity Reactions	3	5	5	5
Eructation	1	4	5	5
Hair Loss	1	5	4	5
Gastroesophageal Reflux Disease	2	4	4	5
Flatulence	2	3	3	4
Abdominal Distension	2	3	3	4
Dizziness	2	4	5	4
Hypotension[f]	0	1	1	2

[a] Includes diarrhea, frequent bowel movements.

[b] Includes constipation, feces hard.

[c] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, abdominal tenderness.

[d] Includes multiple related adverse event terms, such as injection site bruising, injection site erythema, injection site pruritus, injection site pain, injection site rash, injection site reaction.

[e] Includes asthenia, fatigue, lethargy, malaise.

[f] Includes blood pressure decreased, hypotension, orthostatic hypotension.

In a clinical trial that included an intensive lifestyle intervention lead-in period (Study 3), 287 patients were treated with ZEPBOUND for up to 72 weeks. In a randomized withdrawal trial (Study 4), 783 patients were treated with ZEPBOUND for up to 36 weeks, and 335 of these patients were treated for up to 88 weeks *[see Clinical Studies (14.1)]*. In Study 3, 10% of ZEPBOUND-treated patients and 2% of placebo-treated patients discontinued drug due to adverse reactions. In Study 4, 7% of patients discontinued ZEPBOUND treatment before randomized withdrawal at Week 36 due to adverse reactions. In Study 3 and Study 4, adverse reactions were similar to those reported in the two pooled ZEPBOUND clinical trials (Study 1 and Study 2).

Gastrointestinal Adverse Reactions

In a pool of Study 1 and 2, gastrointestinal adverse reactions occurred more frequently among patients receiving ZEPBOUND (5 mg 56%, 10 mg 56%, 15 mg 56%) than placebo (30%). More patients receiving ZEPBOUND 5 mg (1.9%), ZEPBOUND 10 mg (3.3%), and ZEPBOUND 15 mg (4.3%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.5%). The majority of nausea, vomiting, and/or diarrhea events occurred during dose escalation and decreased over time.

Hypotension

In a pool of Study 1 and 2, hypotension occurred more frequently among patients taking ZEPBOUND (1.6%) than patients taking placebo (0.1%). Hypotension was more frequently seen in ZEPBOUND-treated patients on concomitant antihypertensive therapy (2.2%) compared to ZEPBOUND-treated patients not on antihypertensive therapy (1.2%). Hypotension also occurred in association with gastrointestinal adverse events and dehydration.

Hypersensitivity Reactions

In a pool of Study 1 and 2, immediate hypersensitivity reactions (within one day after drug administration) occurred in 2.1% of ZEPBOUND-treated patients compared to 0.4% of placebo-treated patients, while non-immediate hypersensitivity reactions occurred in 3.5% of ZEPBOUND-treated patients compared to 2.7% of placebo-treated patients. Among ZEPBOUND-treated patients, hypersensitivity reactions were more frequent in those with anti-tirzepatide antibodies (6.2%) compared to those who did not develop anti-tirzepatide antibodies (3%) *[see Clinical Pharmacology (12.6)]*. The majority of the hypersensitivity reactions in trials were skin reactions (e.g., rash, itching).

Injection Site Reactions

In ZEPBOUND-treated patients in a pool of Study 1 and 2, injection site reactions were more frequent in those with anti-tirzepatide antibodies (11.3%) compared to those who did not develop anti-tirzepatide antibodies (1%) *[see Clinical Pharmacology (12.6)]*.

Hair Loss

Hair loss adverse reactions in ZEPBOUND-treated patients were associated with weight reduction. In a pool of Study 1 and 2, hair loss was reported more frequently in female than male patients in the ZEPBOUND (7.1% female versus 0.5% male) and placebo (1.3% female versus 0% male) treatment groups. No ZEPBOUND-treated patients and one placebo-treated patient discontinued study treatment due to hair loss.

Other Adverse Reactions

Acute Kidney Injury

In a pool of Study 1 and 2, acute kidney injury was reported in 0.5% of ZEPBOUND-treated patients compared to 0.2% of placebo-treated patients.

Acute Gallbladder Disease

In a pool of Study 1 and 2, cholelithiasis was reported in 1.1% of ZEPBOUND-treated patients and 1% of placebo-treated patients, cholecystitis was reported in 0.7% of ZEPBOUND-treated patients and 0.2% of placebo-treated patients, and cholecystectomy was reported in 0.2% of ZEPBOUND-treated patients and no placebo-treated patients.

Hypoglycemia

In Study 2, a trial of patients with type 2 diabetes mellitus and BMI ≥27 kg/m^2, hypoglycemia (plasma glucose <54 mg/dL) was reported in 4.2% of ZEPBOUND-treated patients versus 1.3% of placebo-treated patients.

In Study 1, a trial of ZEPBOUND in adults with obesity/overweight without type 2 diabetes mellitus, there was no systematic capturing of hypoglycemia, but plasma glucose <54 mg/dL was reported in 0.3% of ZEPBOUND-treated patients versus no placebo-treated patients.

Heart Rate Increase

In a pool of Study 1 and 2, treatment with ZEPBOUND resulted in a mean increase in heart rate of 1 to 3 beats per minute compared to no increase in placebo-treated patients.

Dysesthesia

In a pool of Study 1 and 2, dysesthesia occurred more frequently among patients receiving ZEPBOUND (5 mg 0.2%, 10 mg 0.2%, 15 mg 0.4%) than placebo (0.1%).

Dysgeusia

In a pool of Study 1 and 2, dysgeusia was reported by 0.4% of ZEPBOUND-treated patients and no placebo-treated patients.

Dry Mouth

In a pool of Study 1 and 2, dry mouth or dry throat was reported by 1% of ZEPBOUND-treated patients and 0.1% of placebo-treated patients.

Laboratory Abnormalities

Amylase and Lipase Increase

In a pool of Study 1 and 2, treatment with ZEPBOUND resulted in mean increases from baseline in serum pancreatic amylase concentrations of 20% to 25% and serum lipase concentrations of 28% to 35%, compared to mean increases

from baseline in pancreatic amylase of 2.1% and serum lipase of 5.8% in placebo-treated patients. The clinical significance of elevations in amylase or lipase with ZEPBOUND is unknown in the absence of other signs and symptoms of pancreatitis.

6.2 Postmarketing Experience

The following adverse reactions have been reported during post-approval use of tirzepatide, the active ingredient in ZEPBOUND. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure.

Hypersensitivity: anaphylaxis, angioedema

Gastrointestinal: ileus

Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation.

7 DRUG INTERACTIONS

7.1 Concomitant Use with Insulin or an Insulin Secretagogue (e.g., Sulfonylurea)

ZEPBOUND lowers blood glucose. When initiating ZEPBOUND, consider reducing the dose of concomitantly administered insulin or insulin secretagogues (e.g., sulfonylureas) to reduce the risk of hypoglycemia *[see Warnings and Precautions (5.7)]*.

7.2 Oral Medications

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications. Caution should be exercised when oral medications are concomitantly administered with ZEPBOUND.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin) when concomitantly administered with ZEPBOUND.

Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation. Hormonal contraceptives that are not administered orally should not be affected *[see Use in Specific Populations (8.3) and Clinical Pharmacology (12.2, 12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND (tirzepatide) during pregnancy. Pregnant patients exposed to ZEPBOUND and healthcare providers are encouraged to contact Eli Lilly and Company at 1-800-LillyRx (1-800-545-5979).

Risk Summary

Weight loss offers no benefit to a pregnant patient and may cause fetal harm. Advise pregnant patients that weight loss is not recommended during pregnancy and to discontinue ZEPBOUND when a pregnancy is recognized *(see Clinical Considerations)*. Available data with tirzepatide in pregnant patients are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption *(see Data)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is increased when compared to the general population. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Disease-Associated Maternal and/or Embryo/Fetal Risk

Appropriate weight gain based on pre-pregnancy weight is currently recommended for all pregnant patients, including those with obesity or overweight, due to the obligatory weight gain that occurs in maternal tissues during pregnancy.

Data

Animal Data

In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide [0.03-, 0.07-, and 0.5-fold the maximum recommended human dose (MRHD) of 15 mg once weekly based on AUC] during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically mediated effects on the gastrointestinal system resulting in maternal mortality or abortion in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F_1 pups from F_0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

8.2 Lactation

Risk Summary

There are no data on the presence of tirzepatide or its metabolites in animal or human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPBOUND and any potential adverse effects on the breastfed infant from ZEPBOUND or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is largest after the first dose and diminishes over time. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception, for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation *[see Drug Interactions (7.2) and Clinical Pharmacology (12.2, 12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of ZEPBOUND have not been established in pediatric patients.

8.5 Geriatric Use

In a pool of two fixed dose ZEPBOUND clinical trials (Study 1 and Study 2), 226 (9%) ZEPBOUND-treated patients were 65 years of age or older, and 13 (0.5%) ZEPBOUND-treated patients were 75 years of age or older at baseline.

No overall differences in safety or effectiveness of ZEPBOUND have been observed between patients 65 years of age and older and younger adult patients.

8.6 Renal Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with renal impairment. In subjects with renal impairment including end-stage renal disease (ESRD), no change in tirzepatide pharmacokinetics (PK) was observed *[see Clinical Pharmacology (12.3)]*. Monitor renal function in patients reporting adverse reactions to ZEPBOUND that could lead to volume depletion *[see Warnings and Precautions (5.3)]*.

8.7 Hepatic Impairment

No dosage adjustment of ZEPBOUND is recommended for patients with hepatic impairment. In a clinical pharmacology study in subjects with varying degrees of hepatic impairment, no change in tirzepatide PK was observed *[see Clinical Pharmacology (12.3)]*.

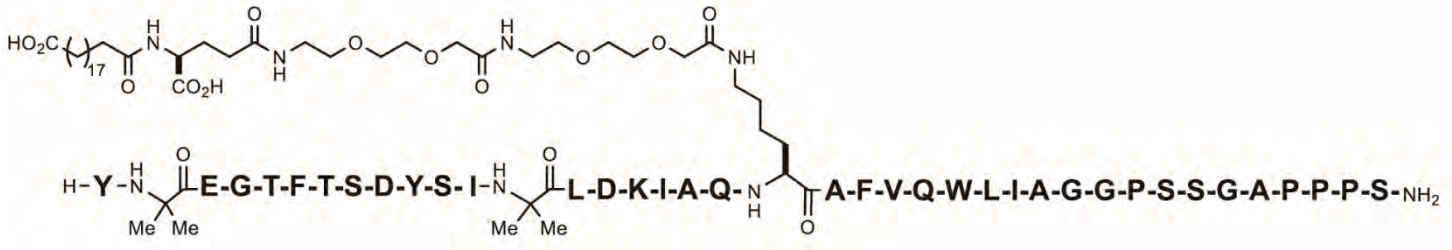
10 OVERDOSAGE

In the event of an overdosage, contact the Poison Help Line (1-800-222-1222) or a medical toxicologist for additional overdosage management recommendations. Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A period of observation and treatment for these symptoms may be necessary, taking into account the half-life of tirzepatide of approximately 5 days.

11 DESCRIPTION

ZEPBOUND (tirzepatide) injection, for subcutaneous use, contains tirzepatide, a GIP receptor and GLP-1 receptor agonist. Tirzepatide is based on the GIP sequence and contains aminoisobutyric acid (Aib) in positions 2 and 13, a C-terminal amide, and Lys residue at position 20 that is attached to 1,20-eicosanedioic acid via a linker. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Structural formula:



ZEPBOUND is a clear, colorless to slightly yellow, sterile solution for subcutaneous use. Each single-dose pen or single-dose vial contains preservative-free 0.5 mL solution of 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg of tirzepatide and the following excipients: sodium chloride (4.1 mg), sodium phosphate dibasic heptahydrate (0.7 mg), and water for injection. Hydrochloric acid solution and/or sodium hydroxide solution may have been added to adjust the pH. ZEPBOUND has a pH of 6.5 – 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It contains a C20 fatty diacid that enables albumin binding and prolongs the half-life. Tirzepatide selectively binds to and activates both the GIP and GLP-1 receptors, the targets for native GIP and GLP-1.

GLP-1 is a physiological regulator of appetite and caloric intake. Nonclinical studies suggest the addition of GIP may further contribute to the regulation of food intake.

Both GIP receptors and GLP-1 receptors are found in areas of the brain involved in appetite regulation. Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake.

12.2 Pharmacodynamics

Tirzepatide lowers body weight with greater fat mass loss than lean mass loss.

Tirzepatide decreases calorie intake. The effects are likely mediated by affecting appetite.

Tirzepatide stimulates insulin secretion in a glucose-dependent manner and reduces glucagon secretion. Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study in patients with type 2 diabetes mellitus after 28 weeks of treatment. These effects can lead to a reduction of blood glucose.

Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time.

12.3 Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with overweight or obesity. Steady-state plasma tirzepatide concentrations were achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose-proportional manner.

Absorption

Following subcutaneous administration, the median time (range) to maximum plasma concentration of tirzepatide is 24 hours (8 to 72 hours). The mean absolute bioavailability of tirzepatide following subcutaneous administration is 80%. Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Distribution

The mean [coefficient of variation (CV)%] apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with overweight or obesity is approximately 9.7 L (28.5%). Tirzepatide is highly bound to plasma albumin (99%).

Elimination

The apparent population mean clearance (CV%) of tirzepatide in patients with overweight or obesity is 0.056 L/h (20.9%) with an elimination half-life of approximately 5 days.

Metabolism

Tirzepatide is metabolized by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid, and amide hydrolysis.

Excretion

The primary excretion routes of tirzepatide metabolites are via urine and feces. Intact tirzepatide is not observed in urine or feces.

Specific Populations

The intrinsic factors of age (18 to 84 years), sex, race (71% White, 11% Asian, 9% American Indian or Alaska Native, and 8% Black or African American), ethnicity, or body weight do not have a clinically relevant effect on the PK of tirzepatide.

Patients with Renal Impairment

Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function. Data from clinical studies have also shown that renal impairment in patients with overweight or obesity does not impact the pharmacokinetics of tirzepatide *[see Use in Specific Populations (8.6)]*.

Patients with Hepatic Impairment

Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5 mg dose were evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function *[see Use in Specific Populations (8.7)]*.

Drug Interaction Studies

Potential for Tirzepatide to Influence the Pharmacokinetics of Other Drugs

In vitro studies have shown low potential for tirzepatide to inhibit or induce CYP enzymes, and to inhibit drug transporters.

ZEPBOUND delays gastric emptying and thereby has the potential to impact the absorption of concomitantly administered oral medications *[see Drug Interactions (7.2)]*.

The impact of tirzepatide on gastric emptying was greatest after a single dose of 5 mg and diminished after subsequent doses.

Following a first dose of tirzepatide 5 mg, acetaminophen maximum concentration (C_{max}) was reduced by 55%, and the median peak plasma concentration (t_{max}) occurred 1 hour later. After coadministration at Week 6 with tirzepatide 15 mg, there was no meaningful impact on acetaminophen C_{max} and t_{max}. Overall acetaminophen exposure ($AUC_{0\text{-}24hr}$) was not influenced.

Following administration of a combined oral contraceptive (0.035 mg ethinyl estradiol and 0.25 mg norgestimate) in the presence of a single dose of tirzepatide 5 mg, mean C_{max} of ethinyl estradiol, norgestimate, and norelgestromin was reduced by 59%, 66%, and 55%, while mean AUC was reduced by 20%, 21%, and 23%, respectively. A delay in t_{max} of 2.5 to 4.5 hours was observed.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials.

During the 72-week treatment period with anti-drug antibodies (ADA) sampling in Studies 1 and 2 *[see Clinical Studies (14)]*, 64.5% (1591/2467) of ZEPBOUND-treated patients developed anti-tirzepatide antibodies. In these trials, anti-tirzepatide antibody formation in 40% and 16.5% of ZEPBOUND-treated patients showed cross-reactivity to native GIP or native GLP-1, respectively.

Of the ZEPBOUND-treated patients, 2.8% and 2.7% developed neutralizing antibodies against tirzepatide activity on the GIP or GLP-1 receptors, respectively, and 0.8% and 0.1% developed neutralizing antibodies against native GIP or GLP-1, respectively.

There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of ZEPBOUND. More ZEPBOUND-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity reactions or injection site reactions than those who did not develop these antibodies *[see Adverse Reactions (6.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.1-, 0.4-, and 1-fold the MRHD of 15 mg once weekly based on AUC) administered by subcutaneous injection twice weekly. A statistically significant increase in thyroid C-cell adenomas was observed in male rats (≥0.5 mg/kg) and female rats (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in male and female rats at all doses examined. In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly was not tumorigenic.

Tirzepatide was not genotoxic in a rat bone marrow micronucleus assay.

In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15 mg once weekly based on AUC). No effects of tirzepatide were observed on sperm morphology, mating, fertility, and conception. In female rats, an increase in the number of females with prolonged diestrus and a decrease in the mean number of corpora lutea resulting in a decrease in the mean number of implantation sites and viable embryos was observed at all dose levels. These effects were considered secondary to the pharmacological effects of tirzepatide on food consumption and body weight.

14 CLINICAL STUDIES

14.1 Weight Reduction and Long-term Maintenance Studies in Adults with Obesity or Overweight

Weight Reduction in Adults with Obesity or Overweight, with or without Type 2 Diabetes Mellitus (Study 1 and Study 2)

Overview of Study 1 and Study 2

The efficacy of ZEPBOUND for weight reduction in conjunction with a reduced-calorie diet and increased physical activity was studied in two randomized, double-blind, placebo-controlled fixed-dosage trials (Study 1 and Study 2) in adults aged 18 years and older. In Studies 1 and 2, all patients received a standard lifestyle intervention which included instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) that began with the first dose of study medication or placebo and continued throughout the trial. Patients also received counseling on behavior modification strategies to adhere to diet and exercise recommendations. In both trials, weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

Study 1 (NCT04184622) was a 72-week trial that enrolled 2,539 adult patients with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1:1 ratio to once weekly fixed dosage of ZEPBOUND 5 mg, ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo, with an escalation period of up to 20 weeks followed by the maintenance period. At baseline, mean age was 45 years (range 18-84 years), 68% were female, 71% were White, 11% were Asian, 9% were American Indian/Alaska Native, and 8% were Black or African American. A total of 48% were Hispanic or Latino ethnicity. Mean baseline body weight was 104.8 kg and mean BMI was 38 kg/m^2. Baseline characteristics included 32% with hypertension, 30% with dyslipidemia, 8% with obstructive sleep apnea, and 3% with cardiovascular disease.

Study 2 (NCT04657003) was a 72-week trial that enrolled 938 adult patients with BMI ≥27 kg/m^2 and type 2 diabetes mellitus. Patients included in the trial had HbA1c 7-10% and were treated with either diet and exercise alone, or any oral anti-hyperglycemic agent except dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1 receptor agonists. Patients who were

taking insulin or injectable GLP-1 receptor agonists for type 2 diabetes mellitus were excluded. Patients were randomized in a 1:1:1 ratio to once weekly fixed dosage of ZEPBOUND 10 mg, ZEPBOUND 15 mg, or placebo with an escalation period of up to 20 weeks followed by the maintenance period. At baseline, mean age was 54 years (range 18-85 years), 51% were female, 76% were White, 13% were Asian, and 8% were Black or African American. A total of 60% were Hispanic or Latino ethnicity. Mean baseline body weight was 100.7 kg and mean BMI was 36.1 kg/m^2. Baseline characteristics included 66% with hypertension, 61% with dyslipidemia, 8% with obstructive sleep apnea, and 10% with cardiovascular disease.

Results for Study 1 and Study 2

The proportions of patients who discontinued study drug in Study 1 were 14.3%, 16.4%, and 15.1% for the 5 mg, 10 mg, and 15 mg ZEPBOUND-treated groups, respectively, and 26.4% for the placebo-treated group. The proportions of patients who discontinued study drug in Study 2 were 9.3% and 13.8% for the 10 mg and 15 mg ZEPBOUND-treated groups, respectively, and 14.9% for the placebo-treated group.

For Studies 1 and 2, weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose). In both studies, the primary efficacy parameters were mean percent change in body weight and the percentage of patients achieving ≥5% weight reduction from baseline to Week 72 (see Table 3).

After 72 weeks of treatment, ZEPBOUND resulted in a statistically significant reduction in body weight compared with placebo, and greater proportions of patients treated with ZEPBOUND 5 mg, 10 mg, and 15 mg achieved at least 5% weight reduction compared to placebo. Among patients treated with ZEPBOUND 10 mg and 15 mg, greater proportions of patients achieved at least 10%, 15%, and 20% weight reduction compared to placebo (see Table 3). A reduction in body weight was observed with ZEPBOUND irrespective of age, sex, race, ethnicity, baseline BMI, and glycemic status.

Table 3: Changes in Body Weight at Week 72 in Studies 1 and 2 in Patients with Obesity or Overweight

	Study 1				**Study 2**		
Intention-to-Treat (ITT) Population[a]	**Placebo N = 643**	**ZEPBOUND 5 mg N = 630**	**ZEPBOUND 10 mg N = 636**	**ZEPBOUND 15 mg N = 630**	**Placebo N = 315**	**ZEPBOUND 10 mg N = 312**	**ZEPBOUND 15 mg N = 311**
Body Weight							
Baseline mean (kg)	104.8	102.9	105.8	105.6	101.7	100.9	99.6
% Change from baseline[b]	-3.1	-15.0	-19.5	-20.9	-3.2	-12.8	-14.7
% Difference from placebo[b] (95% CI)		-11.9 (-13.4, –10.4)[d]	-16.4 (–17.9, -14.8)[d]	-17.8 (–19.3, -16.3)[d]		-9.6 (-11.1, -8.1)[d]	-11.6 (-13.0, -10.1)[d]
% of Patients losing ≥5% body weight	34.5	85.1	88.9	90.9	32.5	79.2	82.8
% Difference from placebo (95% CI)		50.3 (44.3, 56.2)[c,d]	54.6 (49.1, 60.0)[c,d]	56.4 (50.9, 62.0)[c,d]		46.8 (39.5, 54.1)[c,d]	50.4 (43.1, 57.8)[c,d]
% of Patients losing ≥10% body weight	18.8	68.5	78.1	83.5	9.5	60.5	64.8
% Difference from placebo (95% CI)		49.3 (43.6, 54.9)[c,e]	59.5 (54.2, 64.9)[c,d]	64.8 (59.6, 70.1)[c,d]		51.0 (44.4, 57.7)[c,d]	55.3 (48.6, 62.0)[c,d]
% of Patients losing ≥15% body weight	8.8	48.0	66.6	70.6	2.7	39.7	48.0
% Difference from placebo (95% CI)		38.7 (33.6, 43.7)[c,e]	58.1 (53.2, 63.0)[c,d]	62.0 (57.2, 66.8)[c,d]		37.0 (31.1, 42.9)[c,d]	45.4 (39.4, 51.4)[c,d]
% of Patients losing ≥20% body weight	3.1	30.0	50.1	56.7	1.0	21.5	30.8
% Difference from placebo (95% CI)		26.6 (22.4, 30.7)[c,e]	47.3 (42.7, 51.9)[c,d]	53.8 (49.3, 58.3)[c,d]		20.5 (15.7, 25.4)[c,d]	29.7 (24.3, 35.0)[c,d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intention-to-treat population includes all randomly assigned patients. For Study 1 at Week 72, body weight was missing for 21.6%, 10.2%, 10.5%, and 9.4% of patients randomly assigned to placebo, ZEPBOUND 5 mg, 10 mg, and 15 mg, respectively. For Study 2 at

Week 72, body weight was missing for 11.1%, 4.8%, and 8.4% of patients randomly assigned to placebo, ZEPBOUND 10 mg, and 15 mg, respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

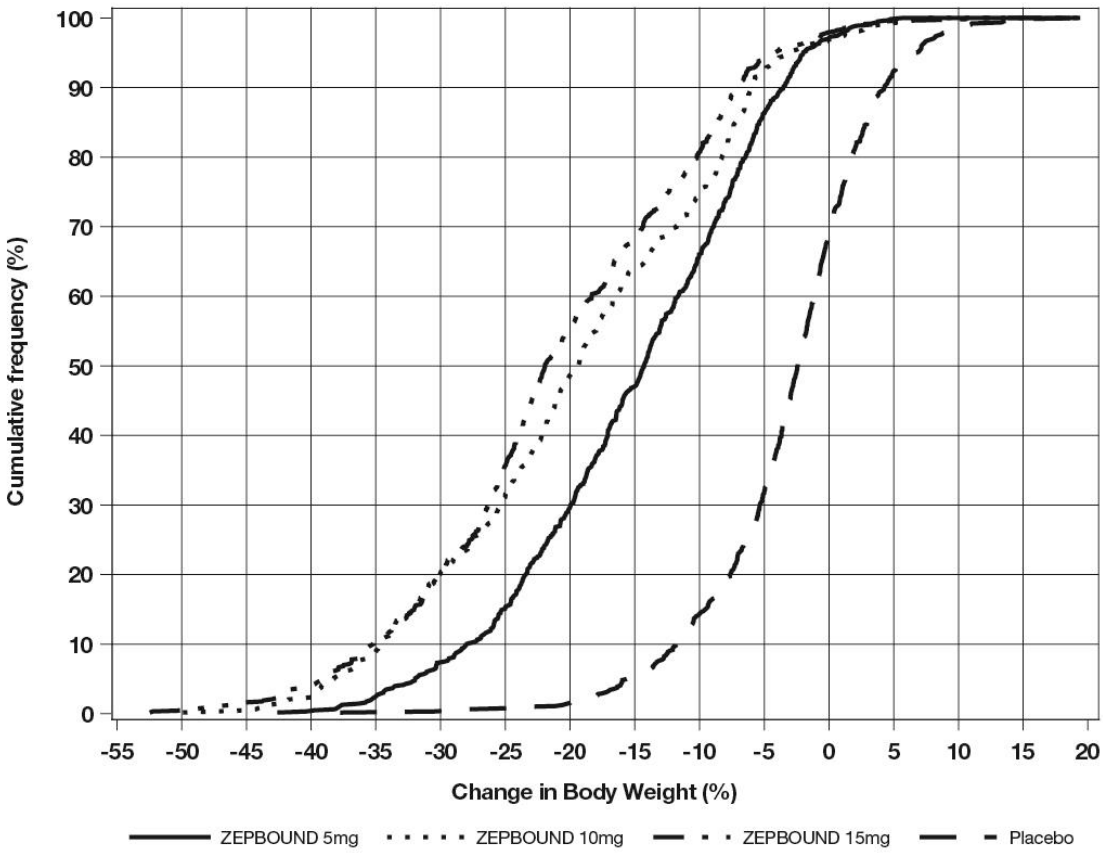
[c] Analyzed using logistic regression adjusted for baseline value.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Not controlled for type I error rate.

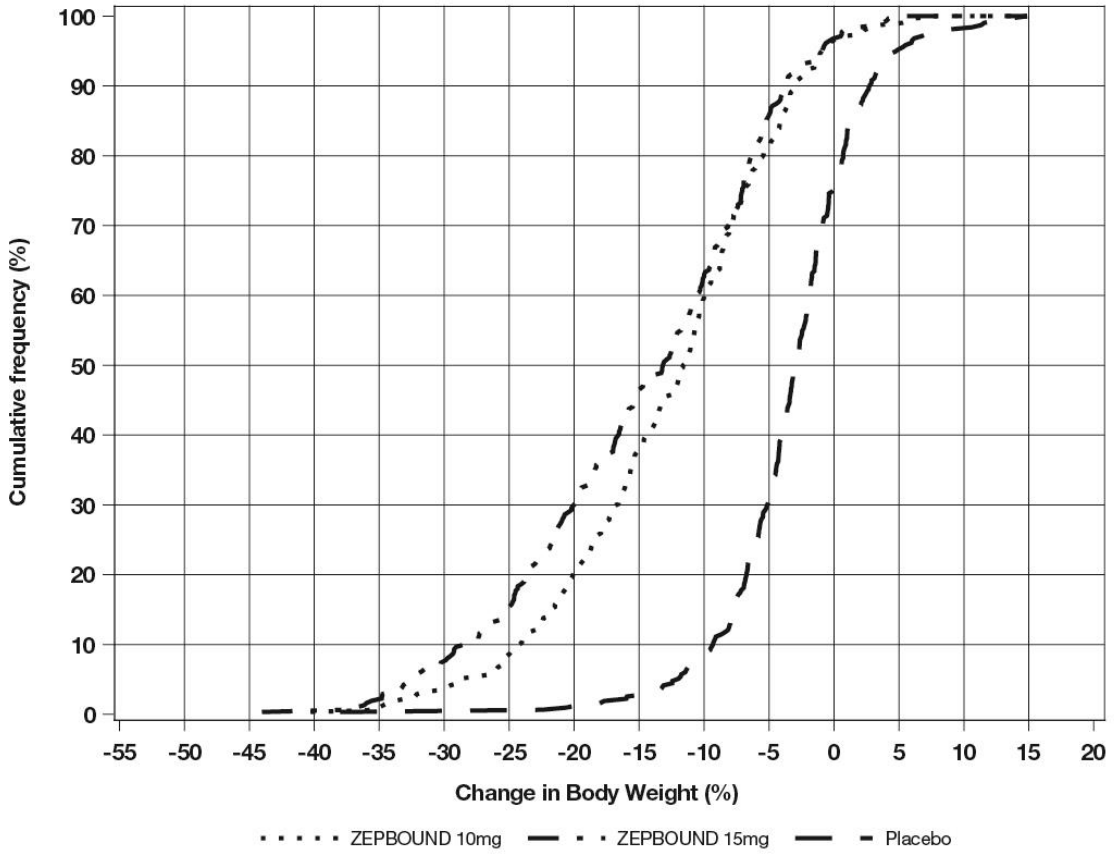
The cumulative frequency distributions of change in body weight are shown in Figure 1 for Study 1 and Figure 2 for Study 2. One way to interpret this figure is to select a change in body weight of interest on the horizontal axis and note the corresponding proportions of patients (vertical axis) in each treatment group who achieved at least that degree of weight reduction. For example, note that the vertical line arising from -10% in Figure 1 intersects the ZEPBOUND 15 mg and placebo curves at approximately 83.5%, and 18.8%, respectively, which correspond to the values shown in Table 3.

Figure 1: Changes in Body Weight (%) from Baseline to Week 72 in Study 1 in Patients with Obesity or Overweight (without Type 2 Diabetes)



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

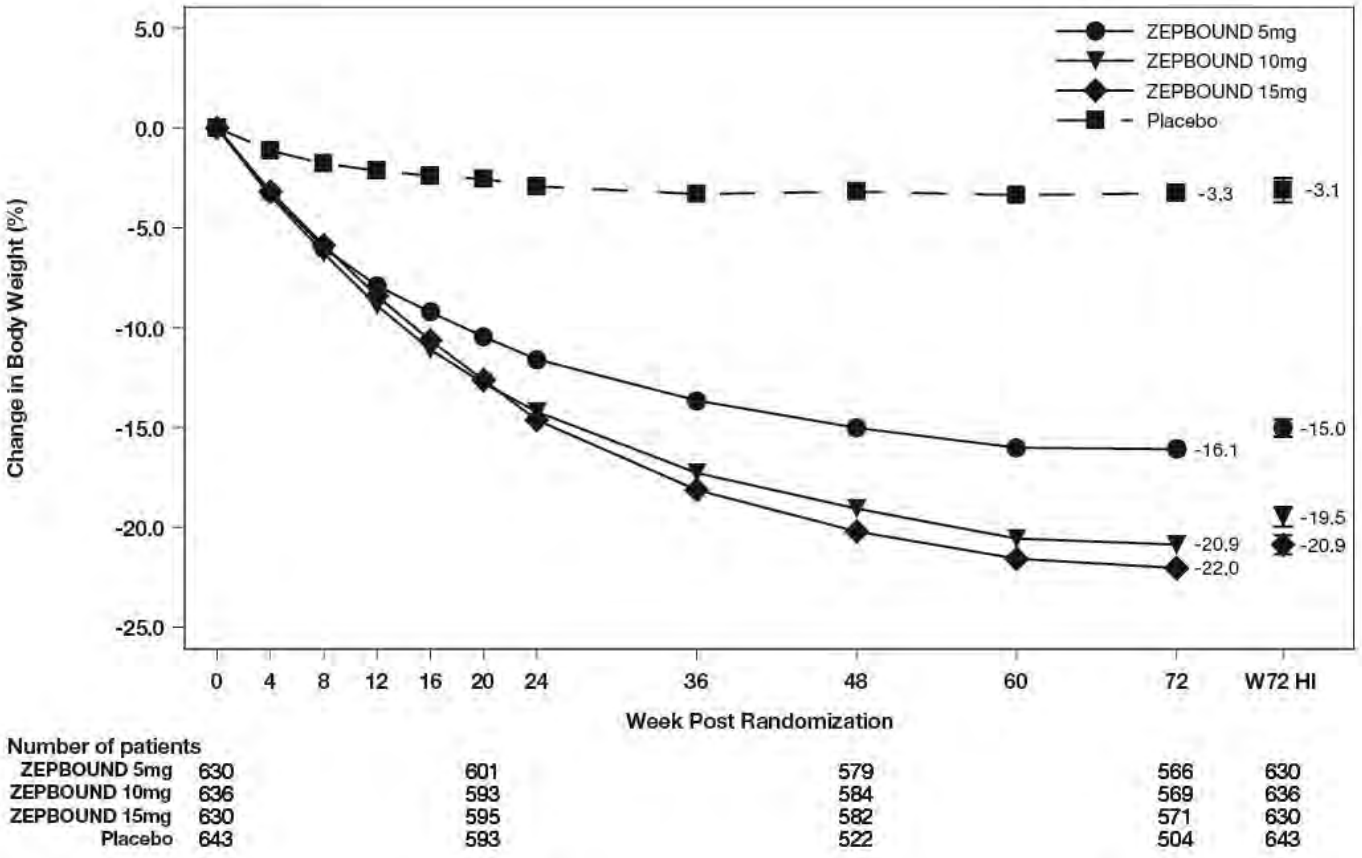
Figure 2: Changes in Body Weight (%) from Baseline to Week 72 in Study 2 in Patients with Obesity or Overweight and Type 2 Diabetes



Note: Based on average percent weight change of each randomized patient within each specific treatment arm from 100 imputed datasets including observed data and imputed data using hybrid approach for missing values.

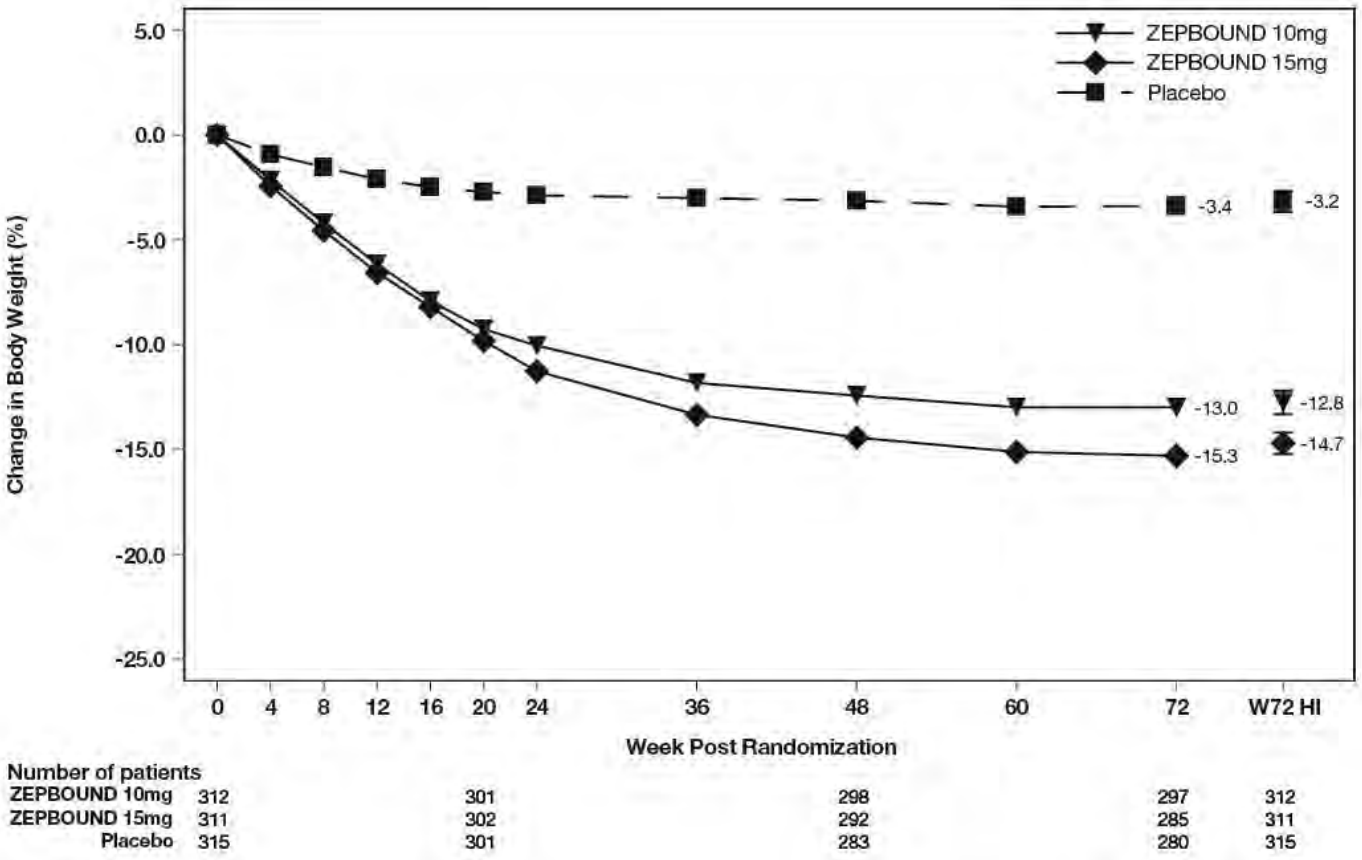
The time courses of weight reduction with ZEPBOUND and placebo from baseline through Week 72 are depicted in Figure 3 for Study 1 and Figure 4 for Study 2.

Figure 3: Change from Baseline (%) in Body Weight in Study 1 in Patients with Obesity or Overweight (without Type 2 Diabetes)



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least-squares mean ± standard error at Week 72 hybrid imputation (HI).

Figure 4: Change from Baseline (%) in Body Weight in Study 2 in Patients with Obesity or Overweight and Type 2 Diabetes



Note: Displayed results are from the Intent-to-Treat Population. (1) Observed mean value from Week 0 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI).

Changes in waist circumference and cardiometabolic parameters with ZEPBOUND are shown in Table 4 for Study 1 and Study 2.

Table 4: Changes in Anthropometry and Cardiometabolic Parameters at Week 72 in Studies 1 and 2 in Patients with Obesity or Overweight

	Study 1				Study 2		
Intention-to-Treat (ITT) Population[a]	**Placebo N = 643**	**ZEPBOUND 5 mg N = 630**	**ZEPBOUND 10 mg N = 636**	**ZEPBOUND 15 mg N = 630**	**Placebo N = 315**	**ZEPBOUND 10 mg N = 312**	**ZEPBOUND 15 mg N = 311**
Waist Circumference (cm)							
Baseline mean	114.0	113.2	114.8	114.4	116.0	114.2	114.6
Change from baseline[b]	-4.0	-14.0	-17.7	-18.5	-3.3	-10.8	-13.1
Difference from placebo[b] (95% CI)		-10.1 (-11.6, -8.6)[e]	-13.8 (-15.2, -12.3)[d]	-14.5 (-15.9, -13.0)[d]		-7.4 (-9.0, -5.9)[d]	-9.8 (-11.2, -8.3)[d]
Systolic Blood Pressure (mmHg)							
Baseline mean	122.9	123.6	123.8	123.0	131.0	130.6	130.0
Change from baseline[b]	-1.0	-6.6	-7.7	-7.4	-1.2	-5.6	-7.1
Difference from placebo[b] (95% CI)		-5.6 (-7.2, -3.9)[e]	-6.7 (-8.4, -5.0)[e]	-6.4 (-8.0, -4.8)[e]		-4.4 (-6.7, -2.1)[e]	-5.9 (-8.3, -3.6)[e]

Diastolic Blood Pressure (mmHg)							
Baseline mean	79.6	79.3	79.9	79.3	79.4	80.2	79.7
Change from baseline[b]	-0.8	-4.9	-5.0	-4.5	-0.3	-2.1	-2.9
Difference from placebo[b] (95% CI)		-4.1 (-5.2, -3.0)[e]	-4.2 (-5.3, -3.0)[e]	-3.7 (-4.8, -2.7)[e]		-1.8 (-3.3, -0.4)[e]	-2.7 (-4.2, -1.2)[e]
Pulse Rate (beats per minute)							
Baseline mean	72.9	72.4	71.8	72.4	74.8	75.9	75.6
Change from baseline[f]	0.1	0.6	2.3	2.6	-0.5	0.6	1.0
Difference from placebo[f] (95% CI)		0.5 (-0.5, 1.5)[e]	2.2 (1.2, 3.2)[e]	2.5 (1.5, 3.4)[e]		1.2 (-0.1, 2.5)[e]	1.5 (0.2, 2.8)[e]
Total Cholesterol (mg/dL)							
Baseline mean[g]	187.5	187.1	190.6	187.5	174.9	173.9	167.0
% change from baseline[b]	-1.8	-3.8	-4.4	-6.3	2.8	-2.8	-1.0
Relative difference from placebo[b] (95% CI)		-2.1 (-4.5, 0.4)[c,e]	-2.7 (-5.1, -0.2)[c,e]	-4.6 (-6.8, -2.2)[c,e]		-5.5 (-8.7, -2.2)[c,e]	-3.8 (-7.1, -0.3)[c,e]
LDL Cholesterol (mg/dL)							
Baseline mean[g]	109.4	108.7	112.3	109.3	92.4	90.5	85.7
% change from baseline[b]	-1.7	-4.6	-5.6	-7.1	7.4	1.8	4.1
Relative difference from placebo[b] (95% CI)		-2.9 (-6.6, 0.9)[c,e]	-4.0 (-7.5, -0.5)[c,e]	-5.5 (-8.9, -2.0)[c,e]		-5.2 (-10.1, 0.1)[c,e]	-3.0 (-8.4, 2.6)[c,e]
HDL Cholesterol (mg/dL)							
Baseline mean[g]	46.6	47.6	47.6	47.6	42.7	43.8	42.2
% change from baseline[b]	-0.7	6.9	9.2	8.0	0.2	8.2	9.7
Relative difference from placebo[b] (95% CI)		7.7 (4.6, 10.8)[c,e]	9.9 (6.7, 13.2)[c,e]	8.7 (5.7, 11.8)[c,e]		8.0 (4.2, 11.8)[c,e]	9.5 (5.6, 13.5)[c,e]
Non-HDL Cholesterol (mg/dL)							
Baseline mean[g]	138.3	137.0	140.4	137.5	129.6	127.2	121.9
% change from baseline[b]	-2.3	-8.0	-9.4	-11.7	3.7	-6.6	-5.2
Relative difference from placebo[b] (95% CI)		-5.8 (-8.9, -2.6)[c,e]	-7.2 (-10.3, -4.1)[c,e]	-9.6 (-12.4, -6.6)[c,e]		-9.9 (-14.1, -5.6)[c,e]	-8.5 (-12.9, -4.0)[c,e]
Triglycerides (mg/dL)							
Baseline mean[g]	130.8	128.7	125.7	128.1	165.0	158.8	158.5
% change from baseline[b]	-5.6	-21.2	-23.8	-29.1	-3.3	-27.1	-27.3
Relative difference from placebo[b] (95% CI)		-16.5 (-21.2, -11.4)[c,e]	-19.3 (-23.9, -14.4)[c,e]	-24.9 (-29.1, -20.4)[c,e]		-24.6 (-30.0, -18.7)[c,e]	-24.8 (-30.3, -18.9)[c,e]
HbA1c (%)							
Baseline mean	5.6	5.6	5.5	5.6	8.0	8.0	8.1
Change from baseline[b]	-0.1	-0.4	-0.4	-0.4	-0.5	-2.1	-2.1
Difference from placebo[b] (95% CI)		-0.3 (-0.3, -0.2)[e]	-0.4 (-0.4, -0.3)[e]	-0.4 (-0.4, -0.3)[e]		-1.6 (-1.7, -1.4)[d]	-1.6 (-1.8, -1.4)[d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intention-to-treat population includes all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using log-transformed data.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline value is the geometric mean.

Weight Reduction Following Intensive Lifestyle Intervention in Adults with Obesity or Overweight (Study 3)

Overview of Study 3

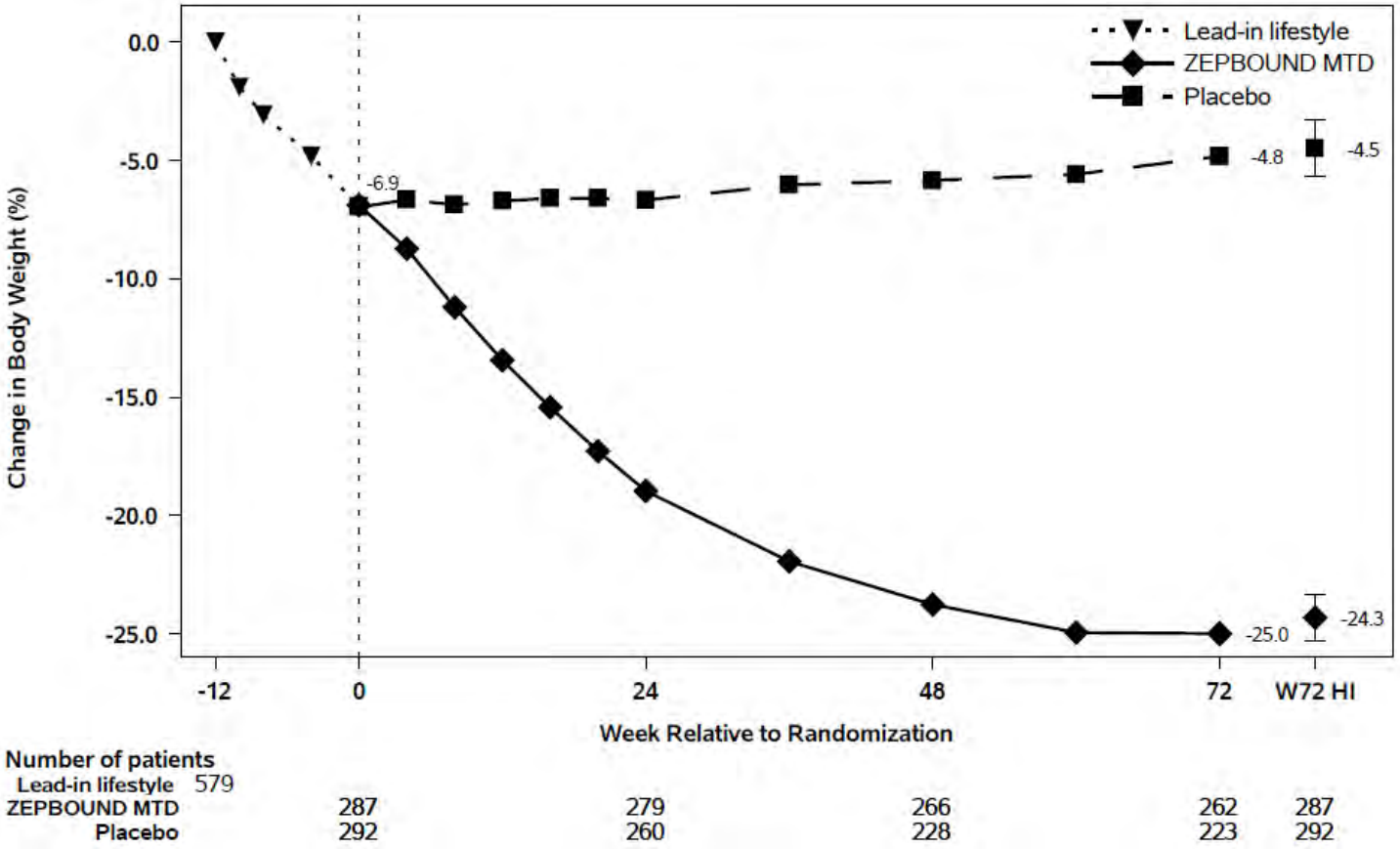
Study 3 (NCT04657016) was an 84-week trial with a 12-week intensive lifestyle intervention lead-in period (Week -12 to Week 0), followed by a 72-week randomized treatment period of ZEPBOUND versus placebo (Week 0 to Week 72) with a standard lifestyle intervention. Only patients who lost ≥5% body weight during the 12-week intensive lifestyle lead-in period entered the 72-week randomized treatment period. The trial initially enrolled 806 adult patients (aged 18 years and older) with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. During the intensive lifestyle intervention lead-in period, lifestyle instruction was delivered 8 times over 12 weeks by a dietician or dietician-equivalent, with all patients receiving instruction to exercise for at least 150 minutes per week and to reduce their caloric intake to approximately 1,200 kcal/day (females) or 1,500 kcal/day (males). Patients also received counseling on behavior modification strategies to adhere to diet and exercise recommendations. At the end of the 12-week intensive lifestyle intervention lead-in period, 579 patients who achieved ≥5% weight reduction were randomized in a 1:1 ratio to ZEPBOUND or placebo for 72 weeks. ZEPBOUND dosages were escalated over a period of up to 20 weeks to a maximum tolerated dosage (MTD) of 10 mg or 15 mg subcutaneous once weekly. During the randomized treatment period, patients received a standard lifestyle instruction every 12 weeks on reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity (recommended minimum of 150 min/week) that began with the first dose of ZEPBOUND or placebo and continued throughout the 72-week treatment period; behavior modification strategies were recommended as needed. Weight reduction was assessed after 72 weeks of treatment (at least 52 weeks at maintenance dose).

For the 579 patients who were randomized, mean body weight at enrollment prior to entering the 12-week lifestyle lead-in period (Week -12) was 109.5 kg and mean BMI was 38.6 kg/m^2. At randomization (Week 0), after the 12-week intensive lifestyle lead-in period, mean body weight was 101.9 kg and mean BMI was 35.9 kg/m^2. The mean age of patients randomized to treatment was 46 years (range 18-77 years), 63% were female, 86% were White, 11% were Black or African American, and 1% were Asian. A total of 54% were Hispanic or Latino ethnicity. Baseline characteristics for the 579 randomized patients included 34% with hypertension, 26% with dyslipidemia, 10% with obstructive sleep apnea, and 2% with cardiovascular disease.

Results for Study 3

At the end of the 12-week intensive lifestyle intervention lead-in, for patients who subsequently entered the randomized treatment period (n=579), the average body weight loss due to lifestyle was 6.9% (Week -12 to Week 0). Eighty-six percent (86%) of ZEPBOUND-treated patients had a maximum tolerated dosage of 15 mg weekly based on their final dose during the double-blind treatment period. The time course of weight reduction during the lead-in and from Week 0 to Week 72 with ZEPBOUND and placebo are depicted in Figure 5.

Figure 5: Change in Body Weight (%) After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight



Note: Displayed results are from the randomized Population. (1) Observed mean value from Week -12 to Week 72, and (2) least squares mean ± standard error at Week 72 hybrid imputation (HI). Change from Week -12 is not a primary endpoint in Study 3.

The proportions of patients who discontinued study drug after randomization were 21.3% for the ZEPBOUND-treated group and 30.5% for the placebo-treated group.

For Study 3, the primary efficacy parameters were mean percent change in body weight from randomization (Week 0) to Week 72 and the percentage of patients achieving ≥5% weight reduction from randomization (Week 0) to Week 72. Amongst randomized patients who already lost ≥5% body weight during the 12-week intensive lifestyle lead-in period, subsequent treatment with ZEPBOUND resulted in a statistically significant reduction in body weight compared to placebo from randomization (Week 0) to Week 72. A greater proportion of patients treated with ZEPBOUND achieved at least 5%, 10%, 15%, and 20% weight reduction from Week 0 to Week 72 compared to placebo (see Table 5).

Table 5: Changes in Body Weight After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight

	Study 3 N = 579[a]	
Body weight		
Mean (kg) at Week -12	109.5	
Intention-to-Treat (ITT) Population[a,b]	**Placebo N = 292**	**ZEPBOUND MTD (10 mg or 15 mg) N = 287**
Body Weight		
Mean (kg) at Week 0	101.3	102.5

% Change from randomization at Week 72[c]	2.5	-18.4
% Difference from placebo, at Week 72[c] (95% CI)		-20.8 (-23.2, -18.5)[e]
% of Patients losing ≥5% body weight	16.5	87.5
% Difference from placebo (95% CI)		71.1 (63.6, 78.5)[d,e]
% of Patients losing ≥10% body weight	8.9	76.7
% Difference from placebo (95% CI)		67.9 (60.7, 75.1)[d,e]
% of Patients losing ≥15% body weight	4.2	65.4
% Difference from placebo (95% CI)		61.3 (54.5, 68.1)[d,e]
% of Patients losing ≥20% body weight	2.2	44.7
% Difference from placebo (95% CI)		42.6 (36.0, 49.1)[d,e]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; MTD = maximum tolerated dose; N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population included only randomized patients with ≥5% weight loss at Week 0 after 12 weeks of intensive lifestyle intervention. During the 12-week lead-in period, 227 of 806 patients (28.2%) discontinued from the study. Of these 141 (17.5%) discontinued due to not achieving the randomization criteria of ≥5% weight reduction.

[b] The intent-to-treat population includes all randomly assigned patients. For Study 3 at Week 72, body weight was missing for 23.6% and 8.7% of patients randomly assigned to placebo and ZEPBOUND MTD (10 or 15 mg). The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[c] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[d] Analyzed using logistic regression adjusted for baseline value.

[e] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

Changes in waist circumference and cardiometabolic parameters are shown in Table 6.

Table 6: Changes in Anthropometry and Cardiometabolic Parameters After 12-Week Intensive Lifestyle Intervention Lead-In Followed by Randomized Treatment and a Standard Lifestyle Intervention (Study 3) in Patients with Obesity or Overweight

	All Randomized Patients N=579		**Placebo N=292**		**ZEPBOUND MTD (10 mg or 15 mg) N=287**		
Intention-to-Treat (ITT) Population[a]	**Baseline (Week -12)**	**Change from Week -12 to Week 0**	**Randomization (Week 0)**	**Change from Week 0 to Week 72**	**Randomization (Week 0)**	**Change from Week 0 to Week 72**	**Difference from placebo, Week 0 to Week 72 (95% CI)**
Waist circumference (cm)[h]	116.1	-6.7	109.6	0.2[b]	109.3	-14.6[b]	-14.8[b] (-17.2, -12.5)[d]
Systolic Blood Pressure (mmHg)[h]	126.2	-5.0	120.8	3.5[b]	121.7	-5.1[b]	-8.6[b] (-11.3, -6.0)[e]
Diastolic Blood Pressure (mmHg)[h]	81.7	-2.9	78.3	2.1[b]	79.3	-3.2[b]	-5.3[b] (-6.9, -3.7)[e]
Pulse Rate (beats per minute)[h]	73.0	-1.6	70.7	0.9[f]	72.2	2.7[f]	1.8[f] (0.3, 3.4)[e]
HbA1c (%)[h]	5.5	-0.1	5.4	0.0[b]	5.3	-0.4[b]	-0.4[b] (-0.5, -0.3)[e]

Total Cholesterol (mg/dL)[g,h]	190.2	-8.6	181.6	4.3	181.7	-2.4	-6.4[b] (-9.0, -3.6)[c,e]
LDL Cholesterol (mg/dL)[g,h]	111.6	-3.5	107.5	4.4	108.0	-5.6	-9.6[b] (-13.7, -5.4)[c,e]
HDL Cholesterol (mg/dL)[g,h]	48.4	-1.2	47.8	5.4	46.9	15.2	9.3[b] (4.5, 14.2)[c,e]
Non-HDL Cholesterol (mg/dL)[g,h]	139.2	-7.4	131.5	4.4	132.4	-8.8	-12.6[b] (-15.9, -9.3)[c,e]
Triglycerides (mg/dL)[g,h]	123.1	-19.8	108.8	2.1	111.7	-23.5	-25.1[b] (-30.9, -18.9)[c,e]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population included all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using log-transformed data.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline and randomization values are the geometric mean.

[h] Observed means are shown for change from Week -12 to Week 0. Least-square means are shown for change from Week 0 to Week 72.

Weight Reduction Following Randomized Withdrawal in Adults with Obesity or Overweight (Study 4)

Overview of Study 4

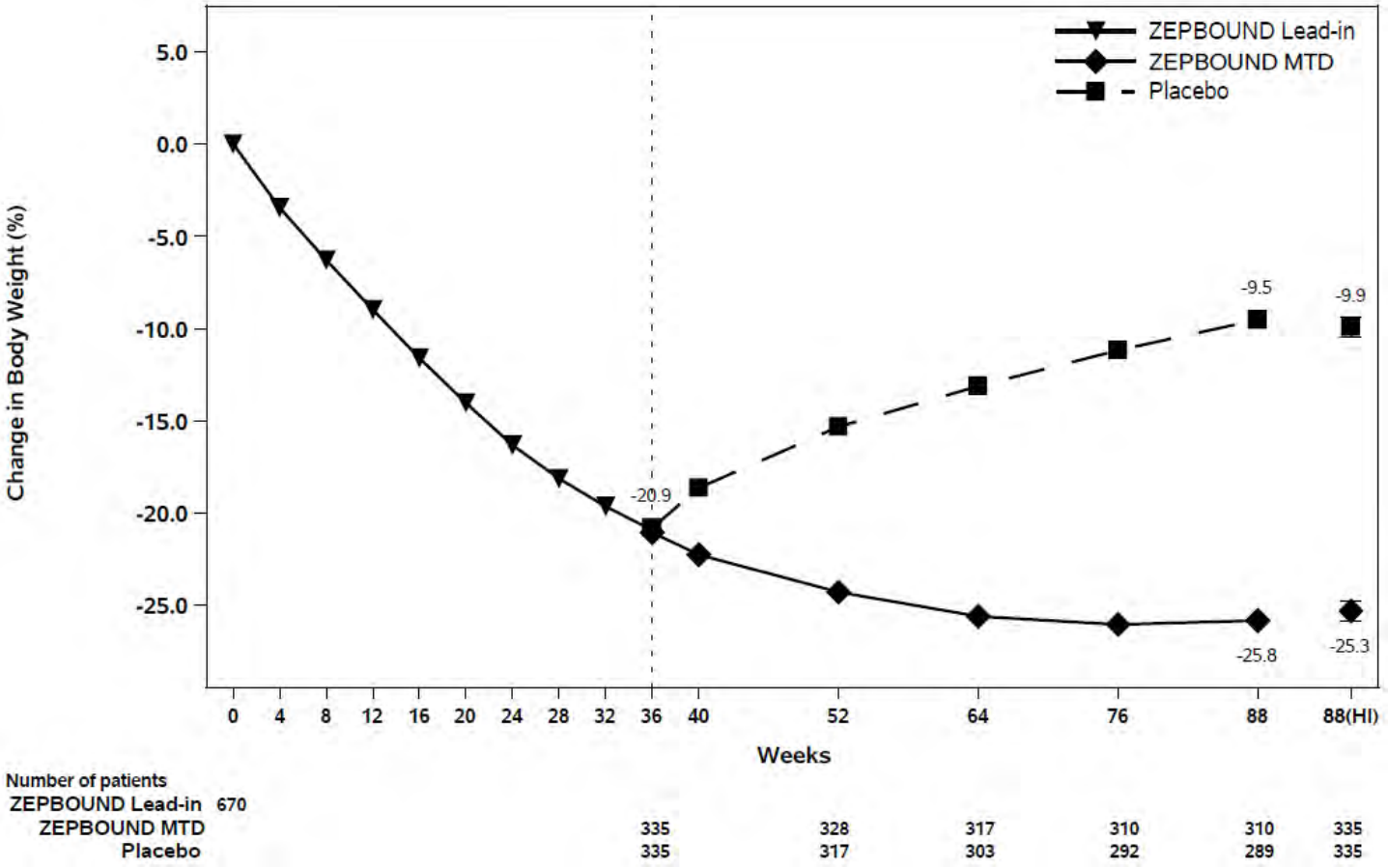
Study 4 (NCT04660643) was an 88-week randomized withdrawal trial in which all patients received open-label ZEPBOUND during a 36-week lead-in period, followed by randomization to either continue ZEPBOUND or switch to placebo for 52 weeks. The trial enrolled 783 adult patients (aged 18 years and older) with obesity (BMI ≥30 kg/m^2), or with overweight (BMI 27 to <30 kg/m^2) and at least one weight-related comorbid condition, such as dyslipidemia, hypertension, obstructive sleep apnea, or cardiovascular disease; patients with type 2 diabetes mellitus were excluded. All patients received a standard lifestyle intervention which included instruction on a reduced-calorie diet (approximately 500 kcal/day deficit) and increased physical activity counseling (recommended minimum of 150 min/week) that began with the first dose of ZEPBOUND, during the lead-in period, and continued throughout the trial. During the 36-week open-label ZEPBOUND lead-in period, ZEPBOUND dosages were escalated over a period of up to 20 weeks to an MTD of 10 mg or 15 mg subcutaneous once weekly. After the lead-in period, patients were randomized at Week 36 to continue ZEPBOUND or switch to placebo for 52 weeks.

Of the 783 patients who started ZEPBOUND at Week 0, 14.4% discontinued treatment before randomization at Week 36, and adverse events were the most common reason for discontinuation (6.8%). At Week 36, a total of 670 patients were randomized in a 1:1 ratio to ZEPBOUND MTD or placebo for 52 weeks. For the 670 randomized patients, at study entry (Week 0) mean body weight was 107.3 kg and mean BMI was 38.4 kg/m^2, and at randomization (Week 36, after the open-label ZEPBOUND lead-in period) mean body weight was 85.2 kg and mean BMI was 30.5 kg/m^2. Among the randomized patients, the mean age was 49 years (range 19-81 years), 71% were female, 80% were White, 11% were Black or African American, and 7% were Asian. A total of 44% were Hispanic or Latino ethnicity. Baseline characteristics for the 670 randomized patients included 35% with hypertension, 32% with dyslipidemia, 12% with obstructive sleep apnea, and 6% with cardiovascular disease.

Results for Study 4

At the end of the 36-week open-label ZEPBOUND lead-in period, of the 670 randomized patients, 93% were on ZEPBOUND MTD of 15 mg weekly and 7% were on MTD of 10 mg weekly. After open-label ZEPBOUND treatment, randomized patients (n=670) had an average body weight loss of 20.9% (Week 0 to Week 36). The time course of weight reduction from Week 0 through Week 88 is depicted in Figure 6.

Figure 6: Change in Body Weight (%) After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight



Note: Displayed results are from the randomized population. (1) Displayed results are observed mean value from Week 0 to Week 88 and (2) least squares mean ± standard error at Week 88 hybrid imputation (HI). Change from Week 0 was not a primary endpoint in Study 4.

The proportions of patients who discontinued study drug after randomization at Week 36 were 10.4% for the ZEPBOUND-treated group and 17.9% for the placebo-treated group.

For Study 4, the primary efficacy parameter was mean percent change in body weight from randomization (Week 36) to Week 88. After weight loss with ZEPBOUND treatment during the open-label lead-in period (Week 0 to Week 36), continued treatment with ZEPBOUND from randomization (Week 36) to Week 88 resulted in a statistically significant reduction in body weight compared with placebo (see Table 7).

Table 7: Changes in Body Weight After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight

	Study 4 N=670[a]	
Body weight		
Mean at Week 0 (kg)	107.3	
Intention-to-Treat (ITT) Population[a]	**Placebo N=335**	**ZEPBOUND (MTD 10 mg or 15 mg) N=335**
Body Weight		
Mean at Week 36 (kg)	85.8	84.6

% change from Week 36 at Week 88[b]	14.0	-5.5
% difference from placebo at Week 88 (95% CI)[b]		-19.4 (-21.2, -17.7)[d]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; MTD = maximum tolerated dose; N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population included all randomly assigned patients and did not include 113 patients who were enrolled but not randomized. At Week 88, body weight was missing for 13.7% and 7.5% of patients randomly assigned to placebo and ZEPBOUND MTD (10 or 15 mg), respectively. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using logistic regression adjusted for baseline value.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

Changes in waist circumference and cardiometabolic parameters in Study 4 are shown in Table 8.

Table 8: Mean Changes in Anthropometry and Cardiometabolic Parameters After 36-Week Open-Label Treatment Followed by Randomized Withdrawal (Study 4) in Patients with Obesity or Overweight

	All Randomized Patients N=670		**Placebo N=335**		**ZEPBOUND MTD (10 mg or 15 mg) N=335**		
Intention-to-Treat (ITT) Population[a]	**Baseline (Week 0)**	**Change from Week 0 to Week 36**	**Randomization (Week 36)**	**Change from Week 36 to Week 88**	**Randomization (Week 36)**	**Change from Week 36 to Week 88**	**Difference from placebo, Week 36 to Week 88 (95% CI)**
Waist circumference (cm)[h]	115.2	-17.8	98.2	7.8[b]	96.8	-4.3[b]	-12.1[b] (-13.5, -10.6)[d]
Systolic Blood Pressure (mmHg)[h]	126.1	-11.2	114.8	8.2[b]	115.0	2.0[b]	-6.2[b] (-8.2, -4.3)[e]
Diastolic Blood Pressure (mmHg)[h]	80.9	-5.1	76.2	3.2[b]	75.4	-0.7[b]	-3.8[b] (-5.2, -2.4)[e]
Pulse Rate (beats per minute)[h]	72.5	5.0	77.8	-5.2[f]	77.1	-2.1[f]	3.1[f] (1.9, 4.3)[e]
HbA1c (%)[h]	5.5	-0.5	5.0	0.3[b]	5.1	-0.0[b]	-0.3[b] (-0.3, -0.2)[e]
Total Cholesterol (mg/dL)[g,h]	188.3	-12.4	176.1	8.0	175.9	2.7	-4.9[b] (-7.4, -2.4)[c,e]
LDL Cholesterol (mg/dL)[g,h]	108.6	-1.9	107.6	3.2	105.9	-3.5	-6.5[b] (-10.0, -2.9)[c,e]
HDL Cholesterol (mg/dL)[g,h]	49.9	-2.7	47.3	14.8	47.7	18.7	3.4[b] (0.2, 6.6)[c,e]
Non-HDL Cholesterol (mg/dL)[g,h]	135.8	-9.8	126.3	5.1	126.0	-3.4	-8.1[b] (-11.3, -4.8)[c,e]
Triglycerides (mg/dL)[g,h]	121.4	-40.4	85.5	13.5	90.9	-4.8	-16.1[b] (-21.7, -10.0)[c,e]

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; N = number of patients randomly assigned to study drug.

[a] The intent-to-treat population included all randomly assigned patients. The missing values were imputed by a hybrid approach using retrieved dropouts from the same treatment group (if missing not due to COVID-19) or using all non-missing data assuming missing at random (for missing solely due to COVID-19).

[b] Least-squares mean from ANCOVA adjusted for baseline value and other stratification factors.

[c] Analyzed using log-transformed data.

[d] p-value<0.001 (unadjusted 2-sided) for superiority, controlled for type I error rate.

[e] Not controlled for type I error rate.

[f] Least-squares mean from mixed model for repeated measures adjusted for baseline value and other stratification factors.

[g] Baseline and randomization values are the geometric mean.

[h] Observed means are shown for change from Week 0 to Week 36. Least-square means are shown for change from Week 36 to Week 88.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ZEPBOUND is a clear, colorless to slightly yellow solution available in cartons containing 4 pre-filled single-dose pens or 1 single-dose vial as follows:

Total Strength per Total Volume	Pen NDC	Vial NDC
2.5 mg/0.5 mL	0002-2506-80	0002-0152-01
5 mg/0.5 mL	0002-2495-80	0002-0243-01
7.5 mg/0.5 mL	0002-2484-80	0002-1214-01
10 mg/0.5 mL	0002-2471-80	0002-1340-01
12.5 mg/0.5 mL	0002-2460-80	0002-1423-01
15 mg/0.5 mL	0002-2457-80	0002-2002-01

16.2 Storage and Handling

- Store ZEPBOUND in a refrigerator at 2°C to 8°C (36°F to 46°F).
- If needed, each single-dose pen or single-dose vial can be stored unrefrigerated at temperatures not to exceed 30°C (86°F) for up to 21 days. If ZEPBOUND is stored at room temperature, it should not be returned to the refrigerator.
- Discard if not used within 21 days after removing from the refrigerator.
- Do not freeze ZEPBOUND. Do not use ZEPBOUND if frozen.
- Store ZEPBOUND in the original carton to protect from light.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling *(Medication Guide and Instructions for Use)*.

Risk of Thyroid C-Cell Tumors

Inform patients that ZEPBOUND causes thyroid C-cell tumors in rats and that the human relevance of this finding has not been determined. Counsel patients to report symptoms of thyroid tumors (e.g., a lump in the neck, persistent hoarseness, dysphagia, or dyspnea) to their healthcare provider *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Severe Gastrointestinal Adverse Reactions

Inform patients of the potential risk of severe gastrointestinal adverse reactions. Instruct patients to contact their healthcare provider if they have severe or persistent gastrointestinal symptoms *[see Warnings and Precautions (5.2)]*.

Acute Kidney Injury

Advise patients treated with ZEPBOUND of the potential risk of dehydration due to gastrointestinal adverse reactions and take precautions to avoid fluid depletion. Inform patients of the potential risk for worsening renal function and explain the associated signs and symptoms of renal impairment, as well as the possibility of dialysis as a medical intervention if renal failure occurs *[see Warnings and Precautions (5.3)]*.

Acute Gallbladder Disease

Inform patients of the risk of acute gallbladder disease. Instruct patients to contact their healthcare provider for appropriate clinical follow-up if gallbladder disease is suspected *[see Warnings and Precautions (5.4)]*.

Acute Pancreatitis

Inform patients of the potential risk for pancreatitis. Instruct patients to discontinue ZEPBOUND promptly and contact their healthcare provider if pancreatitis is suspected (severe abdominal pain that may radiate to the back, and which may or may not be accompanied by vomiting) *[see Warnings and Precautions (5.5)]*.

Hypersensitivity Reactions

Inform patients that serious hypersensitivity reactions have been reported with use of tirzepatide. Advise patients on the symptoms of hypersensitivity reactions and instruct them to stop taking ZEPBOUND and seek medical advice promptly if such symptoms occur *[see Warnings and Precautions (5.6)]*.

Hypoglycemia

Inform patients of the risk of hypoglycemia and educate patients on the signs and symptoms of hypoglycemia. Advise patients on insulin or insulin secretagogue therapy that they may have an increased risk of hypoglycemia when using ZEPBOUND and to report signs and/or symptoms of hypoglycemia to their healthcare provider *[see Warnings and Precautions (5.7)]*.

Diabetic Retinopathy Complications

Inform patients with type 2 diabetes mellitus to contact their healthcare provider if changes in vision are experienced during treatment with ZEPBOUND *[see Warnings and Precautions (5.8)]*.

Suicidal Behavior and Ideation

Advise patients to report emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Inform patients that if they experience suicidal thoughts or behaviors, they should stop taking ZEPBOUND *[see Warnings and Precautions (5.9)]*.

Pulmonary Aspiration During General Anesthesia or Deep Sedation

Inform patients that ZEPBOUND may cause their stomach to empty more slowly which may lead to complications with anesthesia or deep sedation during planned surgeries or procedures. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking ZEPBOUND *[see Warnings and Precautions (5.10)]*.

Pregnancy

Advise a pregnant patient of the potential risk to a fetus. Advise patients to inform their healthcare provider if they are pregnant or intend to become pregnant during treatment with ZEPBOUND. Advise patients that there will be a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ZEPBOUND during pregnancy *[see Use in Specific Populations (8.1)]*.

Contraception

Use of ZEPBOUND may reduce the efficacy of oral hormonal contraceptives. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method or add a barrier method of contraception for 4 weeks after initiation with ZEPBOUND and for 4 weeks after each dose escalation *[see Drug Interactions (7.2), Use in Specific Populations (8.3), and Clinical Pharmacology (12.3)]*.

Administration

Instruct patients how to prepare and administer the correct dose of ZEPBOUND and assess their ability to inject subcutaneously to ensure the proper administration of ZEPBOUND. Instruct patients using the single-dose vial to use a syringe appropriate for dose administration (e.g., a 1 mL syringe capable of measuring a 0.5 mL dose) *[see Dosage and Administration (2.3)]*.

Missed Doses

Inform patients if a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, the missed dose should be skipped and the next dose should be administered on the regularly scheduled day. In each case, inform patients to resume their regular once weekly dosing schedule *[see Dosage and Administration (2.2)]*.

Marketed by: Lilly USA, LLC, Indianapolis, IN 46285, USA

C4.0-NL-ZEP-0003-USPI-YYYYMMDD

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in pre-filled pen
Mounjaro 5 mg solution for injection in pre-filled pen
Mounjaro 7.5 mg solution for injection in pre-filled pen
Mounjaro 10 mg solution for injection in pre-filled pen
Mounjaro 12.5 mg solution for injection in pre-filled pen
Mounjaro 15 mg solution for injection in pre-filled pen
Mounjaro 2.5 mg solution for injection in vial
Mounjaro 5 mg solution for injection in vial
Mounjaro 7.5 mg solution for injection in vial
Mounjaro 10 mg solution for injection in vial
Mounjaro 12.5 mg solution for injection in vial
Mounjaro 15 mg solution for injection in vial
Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Pre-filled pen, single-dose

Mounjaro 2.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).

Mounjaro 5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).

Mounjaro 7.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).

Mounjaro 10 mg solution for injection in pre-filled pen
Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).

Mounjaro 12.5 mg solution for injection in pre-filled pen
Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).

Mounjaro 15 mg solution for injection in pre-filled pen
Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

Vial, single-dose

Mounjaro 2.5 mg solution for injection in vial
Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).

Mounjaro 5 mg solution for injection in vial
Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).

Mounjaro 7.5 mg solution for injection in vial
Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).

Mounjaro 10 mg solution for injection in vial
Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).

Mounjaro 12.5 mg solution for injection in vial
Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).

Mounjaro 15 mg solution for injection in vial
Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

Pre-filled pen (KwikPen), multi-dose

Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 2.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 10 mg of tirzepatide in 2.4 ml (4.17 mg/ml). Each pen delivers 4 doses of 2.5 mg.

Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 20 mg of tirzepatide in 2.4 ml (8.33 mg/ml). Each pen delivers 4 doses of 5 mg.

Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 7.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 30 mg of tirzepatide in 2.4 ml (12.5 mg/ml). Each pen delivers 4 doses of 7.5 mg.

Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 10 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 40 mg of tirzepatide in 2.4 ml (16.7 mg/ml). Each pen delivers 4 doses of 10 mg.

Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 12.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 50 mg of tirzepatide in 2.4 ml (20.8 mg/ml). Each pen delivers 4 doses of 12.5 mg.

Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen
Each dose contains 15 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 60 mg of tirzepatide in 2.4 ml (25 mg/ml). Each pen delivers 4 doses of 15 mg.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection (injection).

Clear, colourless to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Type 2 diabetes mellitus

Mounjaro is indicated for the treatment of adults with insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance or contraindications
- in addition to other medicinal products for the treatment of diabetes.

For study results with respect to combinations, effects on glycaemic control and the populations studied, see sections 4.4, 4.5 and 5.1.

Weight management

Mounjaro is indicated as an adjunct to a reduced-calorie diet and increased physical activity for weight management, including weight loss and weight maintenance, in adults with an initial Body Mass Index (BMI) of

- ≥ 30 kg/m^2 (obesity) or
- ≥ 27 kg/m^2 to < 30 kg/m^2 (overweight) in the presence of at least one weight-related comorbid condition (e.g., hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease, prediabetes, or type 2 diabetes mellitus).

4.2 Posology and method of administration

Posology

The starting dose of tirzepatide is 2.5 mg once weekly. After 4 weeks, the dose should be increased to 5 mg once weekly. If needed, dose increases can be made in 2.5 mg increments after a minimum of 4 weeks on the current dose.

The recommended maintenance doses are 5 mg, 10 mg and 15 mg.

The maximum dose is 15 mg once weekly.

When tirzepatide is added to existing metformin and/or sodium-glucose co-transporter 2 inhibitor (SGLT2i) therapy, the current dose of metformin and/or SGLT2i can be continued.

When tirzepatide is added to existing therapy of a sulphonylurea and/or insulin, a reduction in the dose of sulphonylurea or insulin may be considered to reduce the risk of hypoglycaemia. Blood glucose self-monitoring is necessary to adjust the dose of sulphonylurea and insulin. A stepwise approach to insulin reduction is recommended (see sections 4.4 and 4.8).

Missed doses

If a dose is missed, it should be administered as soon as possible within 4 days after the missed dose. If more than 4 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Changing the dosing schedule

The day of weekly administration can be changed, if necessary, as long as the time between two doses is at least 3 days.

Special populations

Elderly, gender, race, ethnicity or body weight
No dose adjustment is needed based on age, gender, race, ethnicity or body weight (see sections 5.1 and 5.2). Only very limited data are available from patients aged ≥ 85 years.

Renal impairment
No dose adjustment is required for patients with renal impairment including end stage renal disease (ESRD). Experience with the use of tirzepatide in patients with severe renal impairment and ESRD is limited. Caution should be exercised when treating these patients with tirzepatide (see section 5.2).

Hepatic impairment
No dose adjustment is required for patients with hepatic impairment. Experience with the use of tirzepatide in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with tirzepatide (see section 5.2).

Paediatric population
The safety and efficacy of tirzepatide in children aged less than 18 years have not yet been established. No data are available.

Method of administration

Mounjaro is to be injected subcutaneously in the abdomen, thigh or upper arm.

The dose can be administered at any time of day, with or without meals.

Injection sites should be rotated with each dose. If a patient also injects insulin, they should inject Mounjaro into a different injection site.

Patients should be advised to carefully read the instructions for use included with the package leaflet before administering the medicinal product.

Vial

Patients and their caregivers should be trained in subcutaneous injection technique before administering Mounjaro.

For further information before administration see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Acute pancreatitis

Tirzepatide has not been studied in patients with a history of pancreatitis, and should be used with caution in these patients.

Acute pancreatitis has been reported in patients treated with tirzepatide.

Patients should be informed of the symptoms of acute pancreatitis. If pancreatitis is suspected, tirzepatide should be discontinued. If the diagnosis of pancreatitis is confirmed, tirzepatide should not be restarted. In the absence of other signs and symptoms of acute pancreatitis, elevations in pancreatic enzymes alone are not predictive of acute pancreatitis (see section 4.8).

Hypoglycaemia

Patients receiving tirzepatide in combination with an insulin secretagogue (for example, a sulphonylurea) or insulin may have an increased risk of hypoglycaemia. The risk of hypoglycaemia may be lowered by a reduction in the dose of the insulin secretagogue or insulin (see sections 4.2 and 4.8).

Gastrointestinal effects

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhoea (see section 4.8). These adverse reactions may lead to dehydration, which could lead to a deterioration in renal function including acute renal failure. Patients treated with tirzepatide should be advised of the potential risk of dehydration, due to the gastrointestinal adverse reactions and take precautions to avoid fluid depletion and electrolyte disturbances. This should particularly be considered in the elderly, who may be more susceptible to such complications.

Severe gastrointestinal disease

Tirzepatide has not been studied in patients with severe gastrointestinal disease, including severe gastroparesis, and should be used with caution in these patients.

Diabetic retinopathy

Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy or diabetic macular oedema, and should be used with caution in these patients with appropriate monitoring.

Aspiration in association with general anaesthesia or deep sedation

Cases of pulmonary aspiration have been reported in patients receiving GLP-1 receptor agonists undergoing general anaesthesia or deep sedation. Therefore, the increased risk of residual gastric content due to delayed gastric emptying (see section 5.1) should be considered prior to performing procedures with general anaesthesia or deep sedation.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

Benzyl alcohol

This medicinal product contains 5.4 mg benzyl alcohol in each 0.6 ml dose of Mounjaro KwikPen.

4.5 Interaction with other medicinal products and other forms of interaction

Tirzepatide delays gastric emptying and thereby has the potential to impact the rate of absorption of concomitantly administered oral medicinal products. This effect, resulting in decreased C_{max} and a delayed t_{max}, is most pronounced at the time of tirzepatide treatment initiation.

Based on the results from a study with paracetamol, which was used as a model medicinal product to evaluate the effect of tirzepatide on gastric emptying, no dose adjustments are expected to be required for most concomitantly administered oral medicinal products. However, it is recommended to monitor patients on oral medicinal products with a narrow therapeutic index (e.g., warfarin, digoxin), especially at initiation of tirzepatide treatment and following dose increase. The risk of delayed effect should also be considered for oral medicinal products for which a rapid onset of effect is of importance.

Paracetamol

Following a 5 mg single dose of tirzepatide, the maximum plasma concentration (C_{max}) of paracetamol was reduced by 50 %, and the median (t_{max}) was delayed by 1 hour. The effect of tirzepatide on the oral absorption of paracetamol is dose and time dependent. At low doses (0.5 and 1.5 mg), there was only a minor change in paracetamol exposure. After four consecutive weekly doses of tirzepatide (5/5/8/10 mg), no effect on the paracetamol C_{max} and t_{max} was observed. The overall exposure (AUC) was not influenced. No dose adjustment of paracetamol is necessary when administered with tirzepatide.

Oral contraceptives

Administration of a combination oral contraceptive (0.035 mg ethinyl estradiol plus 0.25 mg norgestimate, a prodrug of norelgestromin) in the presence of a single dose of tirzepatide (5 mg) resulted in a reduction of oral contraceptive C_{max} and area under the curve (AUC). Ethinyl estradiol C_{max} was reduced by 59 % and AUC by 20 % with a delay in t_{max} of 4 hours. Norelgestromin C_{max} was reduced by 55 % and AUC by 23 % with a delay in t_{max} of 4.5 hours. Norgestimate C_{max} was reduced by 66 %, and AUC by 20 % with a delay in t_{max} of 2.5 hours. This reduction in exposure after a single dose of tirzepatide is not considered clinically relevant. No dose adjustment of oral contraceptives is required.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential are recommended to use contraception when treated with tirzepatide.

Pregnancy

There are no or a limited amount of data from the use of tirzepatide in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. If a patient wishes to become pregnant, or pregnancy occurs, tirzepatide should be discontinued. Tirzepatide should be discontinued at least 1 month before a planned pregnancy due to the long half-life (see section 5.2).

Breast-feeding

It is unknown whether tirzepatide is excreted in human milk. A risk to the newborn/infant cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from tirzepatide therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The effect of tirzepatide on fertility in humans is unknown.

Animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Tirzepatide has no or negligible influence on the ability to drive or use machines. When tirzepatide is used in combination with a sulphonylurea or insulin, patients should be advised to take precautions to avoid hypoglycaemia while driving and using machines (see section 4.4).

4.8 Undesirable effects

Summary of safety profile

In 10 completed phase 3 studies, 7 925 patients were exposed to tirzepatide alone or in combination with other glucose lowering medicinal products. The most frequently reported adverse reactions were gastrointestinal disorders and these were mostly mild or moderate in severity. The incidence of nausea, diarrhoea and vomiting was higher during the dose escalation period and decreased over time (see sections 4.2, and 4.4).

Tabulated list of adverse reactions

The following related adverse reactions from clinical studies are listed below by system organ class and in order of decreasing incidence (very common: ≥ 1/10; common: ≥ 1/100 to < 1/10; uncommon: ≥ 1/1 000 to < 1/100; rare: ≥ 1/10 000 to < 1/1 000; very rare: < 1/10 000). Within each incidence grouping, adverse reactions are presented in order of decreasing frequency.

Table 1. Adverse reactions

System organ class	Very common	Common	Uncommon	Rare
Immune system disorders		Hypersensitivity reactions		Anaphylactic reaction[#], Angioedema[#]
Metabolism and nutrition disorders	Hypoglycaemia[1]* when used with sulphonylurea or insulin	Hypoglycaemia[1]* when used with metformin and SGLT2i, Decreased appetite[1]	Hypoglycaemia[1]* when used with metformin, Weight decreased[1]	
Nervous system disorders		Dizziness[2]	Dysgeusia	
Vascular disorders		Hypotension[2]		
Gastrointestinal disorders	Nausea, Diarrhoea, Vomiting[3], Abdominal pain[3], Constipation[3]	Dyspepsia, Abdominal distention, Eructation, Flatulence, Gastroesophageal reflux disease	Cholelithiasis, Cholecystitis, Acute pancreatitis	
Skin and subcutaneous tissue disorders		Hair loss[2]		
General disorders and administration site conditions		Fatigue[†], Injection site reactions	Injection site pain	
Investigations		Heart rate increased, Lipase increased, Amylase increased, Blood calcitonin increased[4]		

[#]From post-marketing reports
*Hypoglycaemia defined below.
[†]Fatigue includes the terms fatigue, asthenia, malaise, and lethargy.
[1] Adverse reaction that only applies to patients with type 2 diabetes mellitus (T2DM).
[2] Adverse reaction that mainly applies to patients with overweight or obesity, with or without T2DM.
[3] Frequency was very common in weight management trials, and common in T2DM trials.
[4] Frequency was common in weight management trials, and uncommon in T2DM trials.

Description of selected adverse reactions

Hypersensitivity reactions

Hypersensitivity reactions have been reported with tirzepatide in the pool of T2DM placebo-controlled trials, sometimes severe (e.g., urticaria and eczema); hypersensitivity reactions were reported in 3.2 % of tirzepatide-treated patients compared to 1.7 % of placebo-treated patients. Cases of anaphylactic reaction and angioedema have been rarely reported with marketed use of tirzepatide.

Hypersensitivity reactions have been reported with tirzepatide in a pool of 3 placebo-controlled weight management trials, sometimes severe (e.g., rash and dermatitis); hypersensitivity reactions were reported in 5.0 % of tirzepatide-treated patients compared to 3.8 % of placebo-treated patients.

Hypoglycaemia in patients with type 2 diabetes mellitus

Type 2 diabetes studies
Clinically significant hypoglycaemia (blood glucose < 3.0 mmol/L (< 54 mg/dL)) or severe hypoglycaemia (requiring the assistance of another person) occurred in 10 to 14 % (0.14 to 0.16 events/patient year) of patients when tirzepatide was added to sulphonylurea and in 14 to 19 % (0.43 to 0.64 events/patient year) of patients when tirzepatide was added to basal insulin.

The rate of clinically significant hypoglycaemia when tirzepatide was used as monotherapy or when added to other oral antidiabetic medicinal products was up to 0.04 events/patient year (see table 1 and sections 4.2, 4.4 and 5.1).

In phase 3 clinical studies, 10 (0.2 %) patients reported 12 episodes of severe hypoglycaemia. Of these 10 patients, 5 (0.1 %) were on a background of insulin glargine or sulphonylurea who reported 1 episode each.

Weight management study
In a placebo-controlled weight management phase 3 trial in patients with T2DM, hypoglycaemia (blood glucose < 3.0 mmol/L (< 54 mg/dL)) was reported in 4.2 % of tirzepatide-treated patients versus 1.3 % of placebo-treated patients. In this trial, patients taking tirzepatide in combination with an insulin secretagogue (e.g., sulfonylurea) had a higher incidence of hypoglycaemia (10.3 %) compared to tirzepatide-treated patients not taking a sulfonylurea (2.1 %). No severe hypoglycaemia episodes were reported.

Gastrointestinal adverse reactions

In the placebo-controlled T2DM phase 3 studies, gastrointestinal disorders were dose-dependently increased for tirzepatide 5 mg (37.1 %), 10 mg (39.6 %) and 15 mg (43.6 %) compared with placebo (20.4 %). Nausea occurred in 12.2 %, 15.4 % and 18.3 % versus 4.3 % and diarrhoea in 11.8 %, 13.3 % and 16.2 % versus 8.9 % for tirzepatide 5 mg, 10 mg and 15 mg versus placebo. Gastrointestinal adverse reactions were mostly mild (74 %) or moderate (23.3 %) in severity. The

incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time.

More patients in the tirzepatide 5 mg (3.0 %), 10 mg (5.4 %) and 15 mg (6.6 %) groups compared to the placebo group (0.4 %) discontinued permanently due to the gastrointestinal event.

In a placebo-controlled weight management phase 3 study in patients without T2DM, gastrointestinal disorders were increased for tirzepatide 5 mg (55.6 %), 10 mg (60.8 %) and 15 mg (59.2 %) compared with placebo (30.3 %). Nausea occurred in 24.6 %, 33.3 % and 31.0 % versus 9.5 % and diarrhoea in 18.7 %, 21.2 % and 23.0 % versus 7.3 % for tirzepatide 5 mg, 10 mg and 15 mg respectively versus placebo. Gastrointestinal adverse reactions were mostly mild (60.8 %) or moderate (34.6 %) in severity. The incidence of nausea, vomiting, and diarrhoea was higher during the dose escalation period and decreased over time.

More patients in the tirzepatide 5 mg (1.9 %), 10 mg (4.4 %) and 15 mg (4.1 %) groups compared to the placebo group (0.5 %) discontinued study treatment permanently due to the gastrointestinal event.

Gallbladder-related events

In a pool of 3 placebo-controlled weight management phase 3 studies, the overall incidence of cholecystitis and cholecystitis acute was 0.6 % and 0.2 % for tirzepatide- and placebo-treated patients, respectively.

In a pool of 3 placebo-controlled weight management phase 3 studies , acute gallbladder disease was reported by 2.0 % of tirzepatide-treated patients and 1.6 % of placebo-treated patients. These acute gallbladder events were positively associated with weight reduction.

Immunogenicity

5 025 tirzepatide-treated patients in the T2DM phase 3 clinical studies were assessed for anti-drug antibodies (ADAs). Of these, 51.1 % developed treatment-emergent (TE) ADAs during the on-treatment period. In 38.3 % of the assessed patients, TE ADAs were persistent (ADAs present for a period of 16-weeks or greater). 1.9 % and 2.1 % had neutralizing antibodies against tirzepatide activity on the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, respectively and 0.9 % and 0.4 % had neutralising antibodies against native GIP and GLP-1, respectively. There was no evidence of an altered pharmacokinetic profile or an impact on efficacy of tirzepatide associated with the development of ADAs.

3 484 tirzepatide-treated patients in the 4 phase 3 weight management studies were assessed for anti-drug antibodies (ADAs). Of these, 65.1 % developed treatment-emergent (TE) ADAs during the on-treatment period. In 51.3 % of the assessed patients, TE ADAs were persistent (ADAs present for a period of 16 weeks or greater). 2.3 % and 2.3 % had neutralising antibodies against tirzepatide activity on the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, respectively and 0.7 % and 0.1 % had neutralising antibodies against native GIP and GLP-1, respectively.

Heart rate

In the placebo-controlled T2DM phase 3 studies, treatment with tirzepatide resulted in a maximum mean increase in heart rate of 3 to 5 beats per minute. The maximum mean increase in heart rate in placebo-treated patients was 1 beat per minute.

The percentage of patients who had a change of baseline heart rate of > 20 bpm for 2 or more consecutive visits was 2.1 %, 3.8 % and 2.9 %, for tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared with 2.1 % for placebo.

Small mean increases in PR interval were observed with tirzepatide when compared to placebo (mean increase of 1.4 to 3.2 msec and mean decrease of 1.4 msec respectively). No difference in arrhythmia and cardiac conduction disorder treatment emergent events were observed between tirzepatide 5 mg, 10 mg, 15 mg and placebo (3.8 %, 2.1 %, 3.7 % and 3 % respectively).

In 3 placebo-controlled weight management phase 3 studies, treatment with tirzepatide resulted in a mean increase in heart rate of 3 beats per minute. There was no mean increase in heart rate in the placebo treated patients.

In a placebo-controlled weight management study in patients without T2DM, the percentage of patients who had a change in baseline heart rate of > 20 bpm for 2 or more consecutive visits was 2.4 %, 4.9 % and 6.3 %, for tirzepatide 5 mg, 10 mg and 15 mg, respectively, compared with 1.2 % for placebo. Small mean increases in PR interval were observed with tirzepatide and placebo (mean increase of 0.3 to 1.4 msec and of 0.5 msec respectively). No difference in arrhythmia and cardiac conduction disorder treatment emergent events were observed between tirzepatide 5 mg, 10 mg, 15 mg and placebo (3.7 %, 3.3 %, 3.3 % and 3.6 % respectively).

Injection site reactions

In the placebo-controlled T2DM phase 3 studies, injection site reactions were increased for tirzepatide (3.2 %) compared with placebo (0.4 %).

In 3 placebo-controlled weight management phase 3 studies, injection site reactions were increased for tirzepatide (8.0 %) compared with placebo (1.8 %).

Overall, in phase 3 studies, the most common signs and symptoms of injection site reactions were erythema and pruritus. The maximum severity of injection site reactions for patients was mild (91 %) or moderate (9 %). No injection site reactions were serious.

Pancreatic enzymes

In the placebo-controlled T2DM phase 3 studies, treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 33 % to 38 % and lipase of 31 % to 42 %. Placebo treated patients had an increase from baseline in amylase of 4 % and no changes were observed in lipase.

In 3 placebo-controlled weight management phase 3 studies , treatment with tirzepatide resulted in mean increases from baseline in pancreatic amylase of 23 % and lipase of 34 %. Placebo treated patients had an increase from baseline in amylase of 1.8 % and in lipase of 5.7 %.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. Patients may experience gastrointestinal adverse reactions including nausea. There is no specific antidote for overdose of tirzepatide. A prolonged period of observation and treatment of these symptoms may be necessary, taking into account the half-life of tirzepatide (approximately 5 days).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins, ATC code: A10BX16

Mechanism of action

Tirzepatide is a long acting GIP and GLP-1 receptor agonist, highly selective to human GIP and GLP-1 receptors. Tirzepatide has high affinity to both the GIP and GLP-1 receptors. The activity of tirzepatide on the GIP receptor is similar to native GIP hormone. The activity of tirzepatide on the GLP-1 receptor is lower compared to native GLP-1 hormone. Both receptors are present on the pancreatic α and β endocrine cells, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes.

In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important to appetite regulation. Animal studies show that tirzepatide distributes to and activates neurons in brain regions involved in regulation of appetite and food intake. Animal studies show that tirzepatide can modulate fat utilization through the GIP receptor. In human adipocytes cultured in vitro, tirzepatide acts on GIP receptors to regulate glucose uptake and modulate lipid uptake and lipolysis.

Glycaemic control

Tirzepatide improves glycaemic control by lowering fasting and postprandial glucose concentrations in patients with type 2 diabetes through several mechanisms.

Appetite regulation and energy metabolism

Tirzepatide lowers body weight and body fat mass. The body weight reduction is mostly due to reduced fat mass. The mechanisms associated with body weight and body fat mass reduction involve decreased food intake through the regulation of appetite. Clinical studies show that tirzepatide reduces energy intake and appetite by increasing feelings of satiety and fullness, and decreasing feelings of hunger. Tirzepatide also reduces the intensity of food cravings and preferences for high sugar and high fat foods. Tirzepatide modulates fat utilisation.

Pharmacodynamic effects

Insulin secretion

Tirzepatide increases pancreatic β-cell glucose sensitivity. It enhances first- and second-phase insulin secretion in a glucose dependent manner.

In a hyperglycaemic clamp study in patients with type 2 diabetes, tirzepatide was compared to placebo and the selective GLP-1 receptor agonist semaglutide 1 mg for insulin secretion. Tirzepatide 15 mg enhanced the first and second-phase insulin secretion rate by 466 % and 302 % from baseline, respectively. There was no change in first- and second-phase insulin secretion rate for placebo.

Insulin sensitivity

Tirzepatide improves insulin sensitivity.

Tirzepatide 15 mg improved whole body insulin sensitivity by 63 %, as measured by M-value, a measure of glucose tissue uptake using hyperinsulinemic euglycaemic clamp. The M-value was unchanged for placebo.

Tirzepatide lowers body weight in patients with obesity and overweight, and in patients with type 2 diabetes (irrespective of body weight), which may contribute to improvement in insulin sensitivity.

Glucagon concentration

Tirzepatide reduced the fasting and postprandial glucagon concentrations in a glucose dependent manner. Tirzepatide 15 mg reduced fasting glucagon concentration by 28 % and glucagon AUC after a mixed meal by 43 %, compared with no change for placebo.

Gastric emptying

Tirzepatide delays gastric emptying which may slow post meal glucose absorption and can lead to a beneficial effect on postprandial glycaemia. Tirzepatide induced delay in gastric emptying diminishes over time.

Clinical efficacy and safety

Type 2 diabetes mellitus

The safety and efficacy of tirzepatide were evaluated in five global randomised, controlled, phase 3 studies (SURPASS 1-5) assessing glycaemic control as the primary objective. The studies involved 6 263 treated patients with type 2 diabetes (4 199 treated with tirzepatide). The secondary objectives included body weight, percentage of patients achieving weight reduction targets, fasting serum glucose (FSG) and percentage of patients reaching target HbA1c. All five phase 3 studies assessed tirzepatide 5 mg, 10 mg and 15 mg. All patients treated with tirzepatide started with 2.5 mg for 4 weeks. Then the dose of tirzepatide was increased by 2.5 mg every 4 weeks until they reached their assigned dose.

Across all studies, treatment with tirzepatide demonstrated sustained, statistically significant and clinically meaningful reductions from baseline in HbA1c as the primary objective compared to either placebo or active control treatment (semaglutide, insulin degludec and insulin glargine) for up to 1 year. In 1 study these effects were sustained for up to 2 years. Statistically significant and clinically meaningful reductions from baseline in body weight were also demonstrated. Results from the phase 3 studies are presented below based on the on-treatment data without rescue therapy in the modified intent-to-treat (mITT) population consisting of all randomly assigned patients who were exposed to at least 1 dose of study treatment, excluding patients discontinuing study treatment due to inadvertent enrolment.

SURPASS-1 – Monotherapy

In a 40 week double-blind placebo-controlled study, 478 patients with inadequate glycaemic control with diet and exercise, were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. Patients had a mean age of 54 years and 52 % were men. At baseline the patients had a mean duration of diabetes of 5 years and the mean BMI was 32 kg/m^2.

Table 2. SURPASS-1: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)		121	121	120	113
HbA_{1c} (%)	Baseline (mean)	7.97	7.88	7.88	8.08
	Change from baseline	-1.87##	-1.89##	-2.07##	+0.04
	Difference from placebo [95 % CI]	-1.91** [-2.18, -1.63]	-1.93** [-2.21, -1.65]	-2.11** [-2.39, -1.83]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	63.6	62.6	62.6	64.8
	Change from baseline	-20.4##	-20.7##	-22.7##	+0.4
	Difference from placebo [95 % CI]	-20.8** [-23.9, -17.8]	-21.1** [-24.1, -18.0]	-23.1** [-26.2, -20.0]	-
Patients (%) achieving HbA_{1c}	< 7 %	86.8**	91.5**	87.9**	19.6
	≤ 6.5 %	81.8††	81.4††	86.2††	9.8
	< 5.7 %	33.9**	30.5**	51.7**	0.9
FSG (mmol/L)	Baseline (mean)	8.5	8.5	8.6	8.6
	Change from baseline	-2.4##	-2.6##	-2.7##	+0.7#
	Difference from placebo [95 % CI]	-3.13** [-3.71, -2.56]	-3.26** [-3.84, -2.69]	-3.45** [-4.04, -2.86]	-
FSG (mg/dL)	Baseline (mean)	153.7	152.6	154.6	155.2
	Change from baseline	-43.6##	-45.9##	-49.3##	+12.9#
	Difference from placebo [95 % CI]	-56.5** [-66.8, -46.1]	-58.8** [-69.2, -48.4]	-62.1** [-72.7, -51.5]	-
Body weight (kg)	Baseline (mean)	87.0	85.7	85.9	84.4
	Change from baseline	-7.0##	-7.8##	-9.5##	-0.7
	Difference from placebo [95 % CI]	-6.3** [-7.8, -4.7]	-7.1** [-8.6, -5.5]	-8.8** [-10.3, -7.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.9††	78.0††	76.7††	14.3
	≥ 10 %	30.6††	39.8††	47.4††	0.9
	≥ 15 %	13.2†	17.0†	26.7†	0.0

*p < 0.05, ** p < 0.001 for superiority, adjusted for multiplicity.
†p < 0.05, ††p < 0.001 compared to placebo, not adjusted for multiplicity.
#p < 0.05, ## p < 0.001 compared to baseline, not adjusted for multiplicity.

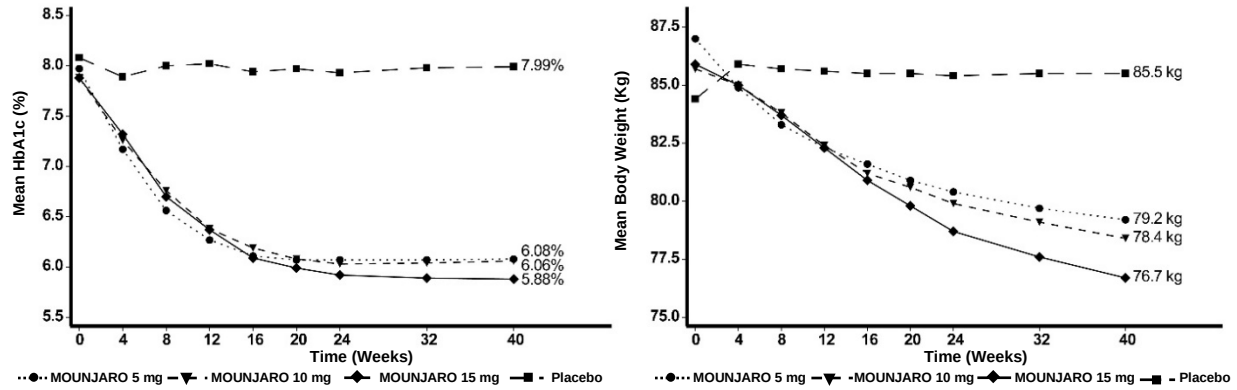


Figure 1. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

SURPASS-2 – Combination therapy with metformin

In a 40 week active-controlled open-label study, (double-blind with respect to tirzepatide dose assignment) 1 879 patients were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or

semaglutide 1 mg once weekly, all in combination with metformin. Patients had a mean age of 57 years and 47 % were men. At baseline the patients had a mean duration of diabetes of 9 years and the mean BMI was 34 kg/m^2.

Table 3. SURPASS-2: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Semaglutide 1 mg
mITT population (n)		470	469	469	468
HbA_{1c} (%)	Baseline (mean)	8.33	8.31	8.25	8.24
	Change from baseline	-2.09$^{\#\#}$	-2.37$^{\#\#}$	-2.46$^{\#\#}$	-1.86$^{\#\#}$
	Difference from semaglutide [95 % CI]	-0.23** [-0.36, -0.10]	-0.51** [-0.64, -0.38]	-0.60** [-0.73, -0.47]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.5	67.3	66.7	66.6
	Change from baseline	-22.8$^{\#\#}$	-25.9$^{\#\#}$	-26.9$^{\#\#}$	-20.3$^{\#\#}$
	Difference from semaglutide [95 % CI]	-2.5** [-3.9, -1.1]	-5.6** [-7.0, -4.1]	-6.6** [-8.0, -5.1]	N/A
Patients (%) achieving HbA_{1c}	< 7 %	85.5*	88.9**	92.2**	81.1
	≤ 6.5 %	74.0†	82.1††	87.1††	66.2
	< 5.7 %	29.3††	44.7**	50.9**	19.7
FSG (mmol/L)	Baseline (mean)	9.67	9.69	9.56	9.49
	Change from baseline	-3.11$^{\#\#}$	-3.42$^{\#\#}$	-3.52$^{\#\#}$	-2.70$^{\#\#}$
	Difference from semaglutide [95 % CI]	-0.41† [-0.65, -0.16]	-0.72†† [-0.97, -0.48]	-0.82†† [-1.06, -0.57]	-
FSG (mg/dL)	Baseline (mean)	174.2	174.6	172.3	170.9
	Change from baseline	-56.0$^{\#\#}$	-61.6$^{\#\#}$	-63.4$^{\#\#}$	-48.6$^{\#\#}$
	Difference from semaglutide [95 % CI]	-7.3† [-11.7, -3.0]	-13.0†† [-17.4, -8.6]	-14.7†† [-19.1, -10.3]	-
Body weight (kg)	Baseline (mean)	92.6	94.9	93.9	93.8
	Change from baseline	-7.8$^{\#\#}$	-10.3$^{\#\#}$	-12.4$^{\#\#}$	-6.2$^{\#\#}$
	Difference from semaglutide [95 % CI]	-1.7** [-2.6, -0.7]	-4.1** [-5.0, -3.2]	-6.2** [-7.1, -5.3]	-
Patients (%) achieving weight loss	≥ 5 %	68.6†	82.4††	86.2††	58.4
	≥ 10 %	35.8††	52.9††	64.9††	25.3
	≥ 15 %	15.2†	27.7††	39.9††	8.7

$^{*}p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ compared to semaglutide 1 mg, not adjusted for multiplicity.

$^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared to baseline, not adjusted for multiplicity.

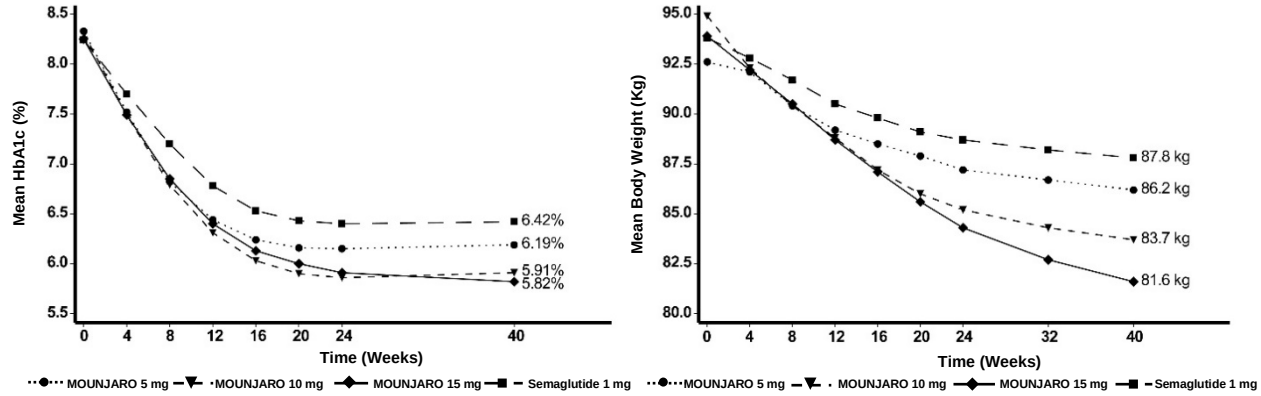


Figure 2. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

SURPASS-3 – Combination therapy with metformin, with or without SGLT2i

In a 52 week active-controlled open-label study, 1 444 patients were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or insulin degludec, all in combination with metformin with or without a SGLT2i. 32 % of patients were using SGLT2i at baseline. At baseline the patients had a mean duration of diabetes of 8 years, a mean BMI of 34 kg/m^2, a mean age of 57 years and 56 % were men.

Patients treated with insulin degludec started at a dose of 10 U/day which was adjusted using an algorithm for a target fasting blood glucose of < 5 mmol/L. The mean dose of insulin degludec at week 52 was 49 units/day.

Table 4. SURPASS-3: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin degludec
mITT population (n)		358	360	358	359
HbA_{1c} (%)	Baseline (mean)	8.17	8.19	8.21	8.13
	Change from baseline	-1.93##	-2.20##	-2.37##	-1.34##
	Difference from insulin degludec [95 % CI]	-0.59** [-0.73, -0.45]	-0.86** [-1.00, -0.72]	-1.04** [-1.17, -0.90]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	65.8	66.0	66.3	65.4
	Change from baseline	-21.1##	-24.0##	-26.0##	-14.6##
	Difference from insulin degludec [95 % CI]	-6.4** [-7.9, -4.9]	-9.4** [-10.9, -7.9]	-11.3** [-12.8, -9.8]	-
Patients (%) achieving HbA_{1c}	< 7 %	82.4**	89.7**	92.6**	61.3
	≤ 6.5 %	71.4††	80.3††	85.3††	44.4
	< 5.7 %	25.8††	38.6††	48.4††	5.4
FSG (mmol/L)	Baseline (mean)	9.54	9.48	9.35	9.24
	Change from baseline	-2.68##	-3.04##	-3.29##	-3.09##
	Difference from insulin degludec [95 % CI]	0.41† [0.14, 0.69]	0.05 [-0.24, 0.33]	-0.20 [-0.48, 0.08]	-
FSG (mg/dL)	Baseline (mean)	171.8	170.7	168.4	166.4
	Change from baseline	-48.2##	-54.8##	-59.2##	-55.7##
	Difference from insulin degludec [95 % CI]	7.5† [2.4, 12.5]	0.8 [-4.3, 5.9]	-3.6 [-8.7, 1.5]	-
Body weight (kg)	Baseline (mean)	94.5	94.3	94.9	94.2
	Change from baseline	-7.5##	-10.7##	-12.9##	+2.3##
	Difference from insulin degludec [95 % CI]	-9.8** [-10.8, -8.8]	-13.0** [-14.0, -11.9]	-15.2** [-16.2, -14.2]	-
Patients (%) achieving weight loss	≥ 5 %	66.0††	83.7††	87.8††	6.3
	≥ 10 %	37.4††	55.7††	69.4††	2.9
	≥ 15 %	12.5††	28.3††	42.5††	0.0

*p < 0.05, **p < 0.001 for superiority, adjusted for multiplicity.
†p < 0.05, ††p < 0.001 compared to insulin degludec, not adjusted for multiplicity.
#p < 0.05, ## p < 0.001 compared to baseline, not adjusted for multiplicity.

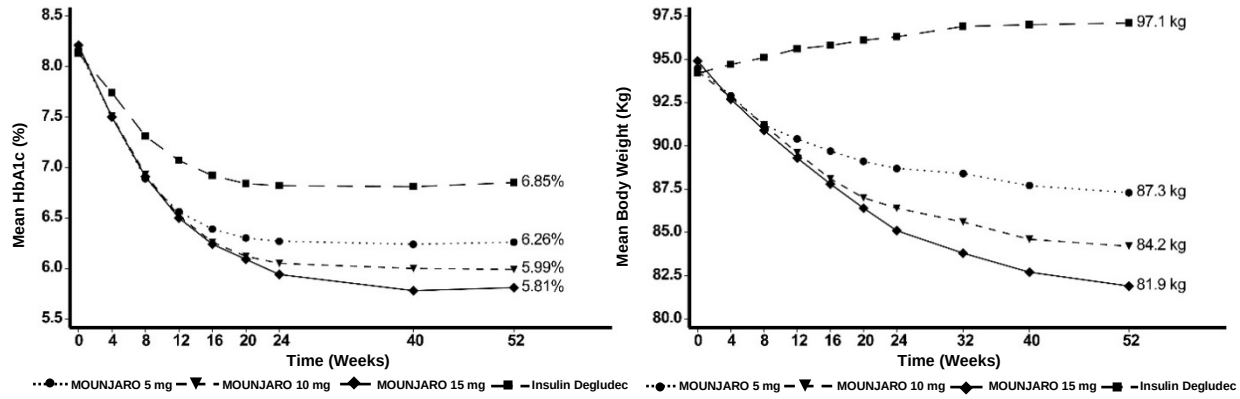


Figure 3. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

Continuous glucose monitoring (CGM)
A subset of patients (N = 243) participated in an evaluation of the 24 hour glucose profiles captured with blinded CGM. At 52 weeks, patients treated with tirzepatide (10 mg and 15 mg pooled) spent significantly more time with glucose values in the euglycaemic range defined as 71 to 140 mg/dL (3.9

to 7.8 mmol/L) compared to patients treated with insulin degludec, with 73 % and 48 % of the 24 hour period in range, respectively.

SURPASS-4 – Combination therapy with 1-3 oral antidiabetic medicinal products: metformin, sulphonylureas or SGLT2i

In an active-controlled open-label study of up to 104 weeks (primary endpoint at 52 weeks), 2 002 patients with type 2 diabetes and increased cardiovascular risk were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or insulin glargine once daily on a background of metformin (95 %) and/or sulphonylureas (54 %) and/or SGLT2i (25 %). At baseline the patients had a mean duration of diabetes of 12 years, a mean BMI of 33 kg/m^2, a mean age of 64 years and 63 % were men. Patients treated with insulin glargine started at a dose of 10 U/day which was adjusted using an algorithm with a fasting blood glucose target of < 5.6 mmol/L. The mean dose of insulin glargine at week 52 was 44 units/day.

Table 5. SURPASS-4: Results at week 52

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Titrated insulin glargine
mITT population (n)		328	326	337	998
52 weeks					
HbA_{1c} (%)	Baseline (mean)	8.52	8.60	8.52	8.51
	Change from baseline	-2.24$^{\#\#}$	-2.43$^{\#\#}$	-2.58$^{\#\#}$	-1.44$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-0.80** [-0.92, -0.68]	-0.99** [-1.11, -0.87]	-1.14** [-1.26, -1.02]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	69.6	70.5	69.6	69.5
	Change from baseline	-24.5$^{\#\#}$	-26.6$^{\#\#}$	-28.2$^{\#\#}$	-15.7$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-8.8** [-10.1, -7.4]	-10.9** [-12.3, -9.6]	-12.5** [-13.8, -11.2]	-
Patients (%) achieving HbA_{1c}	< 7 %	81.0**	88.2**	90.7**	50.7
	≤ 6.5 %	66.0††	76.0††	81.1††	31.7
	< 5.7 %	23.0††	32.7††	43.1††	3.4
FSG (mmol/L)	Baseline (mean)	9.57	9.75	9.67	9.37
	Change from baseline	-2.80$^{\#\#}$	-3.06$^{\#\#}$	-3.29$^{\#\#}$	-2.84$^{\#\#}$
	Difference from insulin glargine [95 % CI]	0.04 [-0.22, 0.30]	-0.21 [-0.48, 0.05]	-0.44†† [-0.71, -0.18]	-
FSG (mg/dL)	Baseline (mean)	172.3	175.7	174.2	168.7
	Change from baseline	-50.4$^{\#\#}$	-54.9$^{\#\#}$	-59.3$^{\#\#}$	-51.4$^{\#\#}$
	Difference from insulin glargine [95 % CI]	1.0 [-3.7, 5.7]	-3.6 [-8.2, 1.1]	-8.0†† [-12.6, -3.4]	-
Body weight (kg)	Baseline (mean)	90.3	90.7	90.0	90.3
	Change from baseline	-7.1$^{\#\#}$	-9.5$^{\#\#}$	-11.7$^{\#\#}$	+1.9$^{\#\#}$
	Difference from insulin glargine [95 % CI]	-9.0** [-9.8, -8.3]	-11.4** [-12.1, -10.6]	-13.5** [-14.3, -12.8]	-
Patients (%) achieving weight loss	≥ 5 %	62.9††	77.6††	85.3††	8.0
	≥ 10 %	35.9††	53.0††	65.6††	1.5
	≥ 15 %	13.8††	24.0††	36.5††	0.5

* $p < 0.05$, ** $p < 0.001$ for superiority, adjusted for multiplicity.

$^{\dagger}p < 0.05$, $^{\dagger\dagger}p < 0.001$ compared to insulin glargine, not adjusted for multiplicity.

$^{\#}p < 0.05$, $^{\#\#}p < 0.001$ compared to baseline, not adjusted for multiplicity.

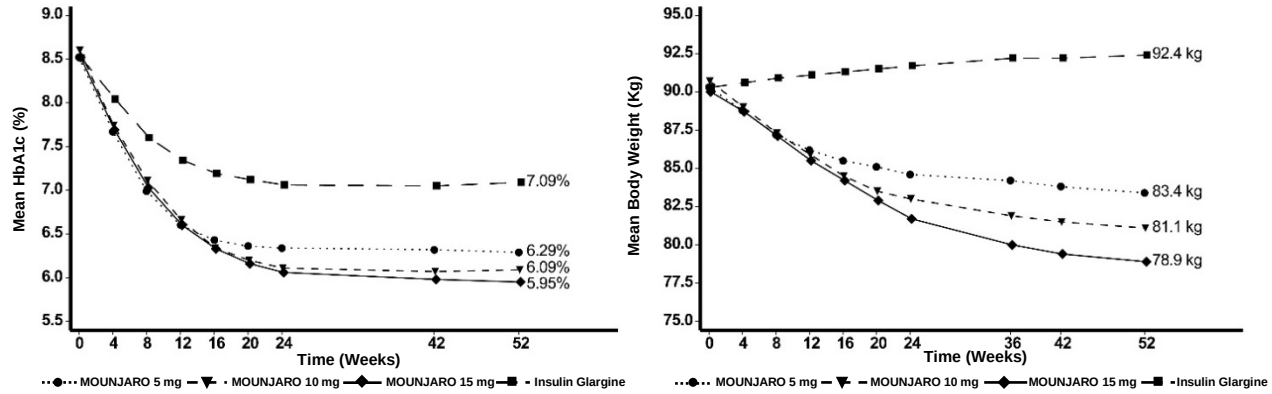


Figure 4. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 52

SURPASS-5 – Combination therapy with titrated basal insulin, with or without metformin

In a 40 week double-blind placebo-controlled study, 475 patients with inadequate glycaemic control using insulin glargine with or without metformin were randomised to tirzepatide 5 mg, 10 mg or

15 mg once weekly or placebo. Insulin glargine doses were adjusted utilizing an algorithm with a fasting blood glucose target of < 5.6 mmol/L. At baseline the patients had a mean duration of diabetes of 13 years, a mean BMI of 33 kg/m^2, a mean age of 61 years and 56 % were men. The overall estimated median dose of insulin glargine at baseline was 34 units/day. The median dose of insulin glargine at week 40 was 38, 36, 29 and 59 units/day for tirzepatide 5 mg, 10 mg, 15 mg and placebo respectively.

Table 6. SURPASS-5: Results at week 40

		Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)		116	118	118	119
HbA_{1c} (%)	Baseline (mean)	8.29	8.34	8.22	8.39
	Change from baseline	-2.23##	-2.59##	-2.59##	-0.93##
	Difference from placebo [95 % CI]	-1.30** [-1.52, -1.07]	-1.66** [-1.88, -1.43]	-1.65** [-1.88, -1.43]	-
HbA_{1c} (mmol/mol)	Baseline (mean)	67.1	67.7	66.4	68.2
	Change from baseline	-24.4##	-28.3##	-28.3##	-10.2##
	Difference from placebo [95 % CI]	-14.2** [-16.6, -11.7]	-18.1** [-20.6, -15.7]	-18.1** [-20.5, -15.6]	-
Patients (%) achieving HbA_{1c}	< 7 %	93.0**	97.4**	94.0**	33.9
	≤ 6.5 %	80.0††	94.7††	92.3††	17.0
	< 5.7 %	26.1††	47.8††	62.4††	2.5
FSG (mmol/L)	Baseline (mean)	9.00	9.04	8.91	9.13
	Change from baseline	-3.41##	-3.77##	-3.76##	-2.16##
	Difference from placebo [95 % CI]	-1.25** [-1.64, -0.86]	-1.61** [-2.00, -1.22]	-1.60** [-1.99, -1.20]	-
FSG (mg/dL)	Baseline (mean)	162.2	162.9	160.4	164.4
	Change from baseline	-61.4##	-67.9##	-67.7##	-38.9##
	Difference from placebo [95 % CI]	-22.5** [-29.5, -15.4]	-29.0** [-36.0, -22.0]	-28.8** [-35.9, -21.6]	-
Body weight (kg)	Baseline (mean)	95.5	95.4	96.2	94.1
	Change from baseline	-6.2##	-8.2##	-10.9##	+1.7#
	Difference from placebo [95 % CI]	-7.8** [-9.4, -6.3]	-9.9** [-11.5, -8.3]	-12.6** [-14.2, -11.0]	-
Patients (%) achieving weight loss	≥ 5 %	53.9††	64.6††	84.6††	5.9
	≥ 10 %	22.6††	46.9††	51.3††	0.9
	≥ 15 %	7.0†	26.6†	31.6††	0.0

*p < 0.05, ** p < 0.001 for superiority, adjusted for multiplicity.

†p < 0.05, ††p < 0.001 compared to placebo, not adjusted for multiplicity.

#p < 0.05, ## p < 0.001 compared to baseline, not adjusted for multiplicity.

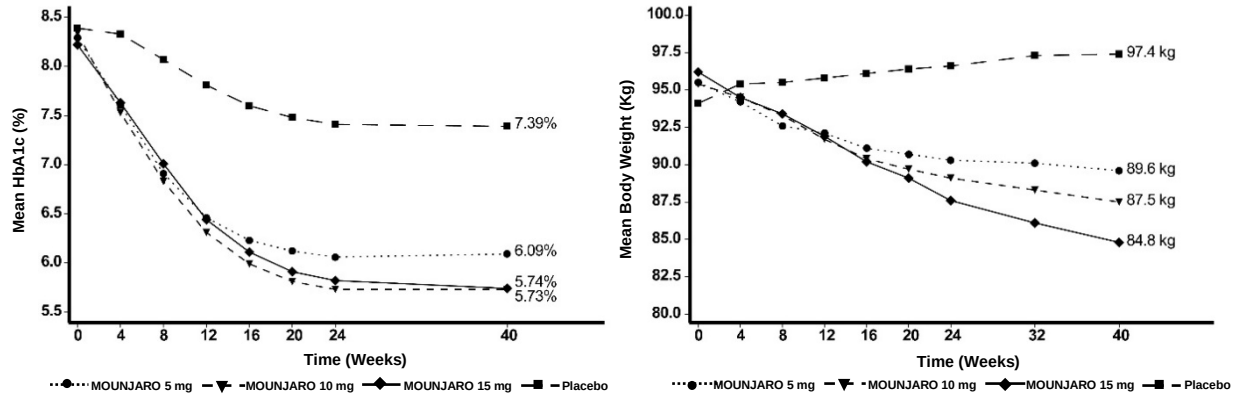


Figure 5. Mean HbA_{1c} (%) and mean body weight (kg) from baseline to week 40

Weight management

The efficacy and safety of tirzepatide for weight management, in combination with a reduced calorie intake and increased physical activity, in patients with obesity (BMI ≥ 30 kg/m^2), or overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbidity (such as treated or untreated dyslipidaemia, hypertension, obstructive sleep apnoea, or cardiovascular disease), and with prediabetes or normoglycemia, but without type 2 diabetes mellitus, were evaluated in three randomised double-blinded, placebo-controlled phase 3 studies (SURMOUNT-1, SURMOUNT-3, SURMOUNT-4). A total of 3 900 adult patients (2 518 randomised to tirzepatide) were included in these studies.

Treatment with tirzepatide demonstrated clinically meaningful and sustained weight reduction compared with placebo. Furthermore, a higher percentage of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight loss with tirzepatide compared with placebo.

The efficacy and safety of tirzepatide for weight management in patients with type 2 diabetes were evaluated in a randomised double-blinded, placebo-controlled phase 3 study (SURMOUNT-2), and in a subpopulation of patients with BMI ≥ 27 kg/m^2 in five randomised phase 3 studies (SURPASS-1 to -5). A total of 6 330 patients with BMI ≥ 27 kg/m^2 (4 249 randomised to treatment with tirzepatide) were included in these studies. In SURMOUNT-2 treatment with tirzepatide demonstrated clinically meaningful and sustained weight reduction compared with placebo. Furthermore, a higher percentage of patients achieved ≥ 5 %, ≥ 10 %, ≥ 15 % and ≥ 20 % weight loss with tirzepatide compared with placebo. Subgroup analyses of patients with obesity or overweight in the SURPASS studies (amounting to 86 % of the overall SURPASS-1 to -5 population) showed sustained weight reduction, and a higher percentage of patients achieving weight reduction targets compared to active comparator/placebo.

In all SURMOUNT studies, the same tirzepatide dose escalation scheme was used as in the SURPASS programme (starting with 2.5 mg for 4 weeks, followed by increases in 2.5 mg increments every 4 weeks until the assigned dose was reached).

SURMOUNT-1

In a 72 week double-blind placebo-controlled study, 2 539 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight-related comorbid condition, were randomised to tirzepatide 5 mg, 10 mg or 15 mg once weekly or placebo. All patients were counselled on a reduced-calorie diet and increased physical activity throughout the trial. At baseline, patients had a mean age of 45 years, 67.5 % were women and 40.6 % of patients had prediabetes. Mean BMI at baseline was 38 kg/m^2.

Table 7. SURMOUNT-1: Results at week 72

	Tirzepatide 5 mg	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)	630	636	630	643
Body weight				
Baseline (kg)	102.9	105.9	105.5	104.8
Change (%) from baseline	-16.0††	-21.4††	-22.5††	-2.4
Difference (%) from placebo [95 % CI]	-13.5** [-14.6, -12.5]	-18.9** [-20.0, -17.8]	-20.1** [-21.2, -19.0]	-
Change (kg) from baseline	-16.1††	-22.2††	-23.6††	-2.4††
Difference (kg) from placebo [95 % CI]	-13.8## [-15.0, -12.6]	-19.8## [-21.0, -18.6]	-21.2## [-22.4, -20.0]	-
Patients (%) achieving body weight reduction				
≥ 5 %	89.4**	96.2**	96.3**	27.9
≥ 10 %	73.4##	85.9**	90.1**	13.5
≥ 15 %	50.2##	73.6**	78.2**	6.0
≥ 20 %	31.6##	55.5**	62.9**	1.3
Waist circumference (cm)				
Baseline	113.2	114.9	114.4	114.0
Change from baseline	-14.6††	-19.4††	-19.9††	-3.4††
Difference from placebo [95 % CI]	-11.2## [-12.3, -10.0]	-16.0** [-17.2, -14.9]	-16.5** [-17.7, -15.4]	-

††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

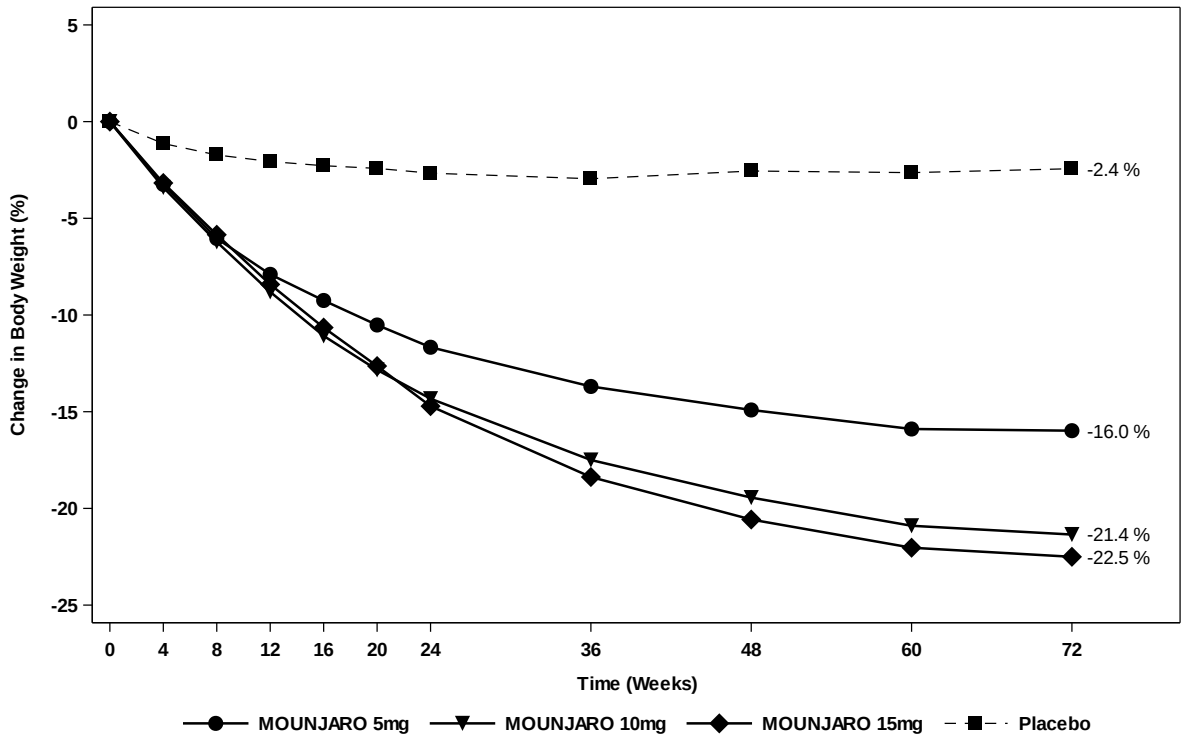


Figure 6. Mean change in body weight (%) from baseline to week 72

In SURMOUNT-1, pooled doses of tirzepatide 5 mg, 10 mg, and 15 mg led to a significant improvement compared to placebo in systolic blood pressure (-8.1 mmHg vs. -1.3 mmHg), triglycerides (-27.6 % vs. -6.3 %), non-HDL-C (-11.3 % vs. -1.8 %), HDL-C (7.9 % vs. 0.3 %), and fasting insulin (-46.9 % vs. -9.7 %).

Among the patients in SURMOUNT-1 with prediabetes at baseline (N = 1032), 95.3 % patients treated with tirzepatide reverted to normoglycemia at week 72, as compared with 61.9 % of patients in the placebo group.

SURMOUNT-2

In a 72 week double-blind placebo-controlled study, 938 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and type 2 diabetes, were randomised to tirzepatide 10 mg or 15 mg once weekly or placebo. Patients included in the trial had HbA1c 7-10 % and were treated with either diet and exercise alone, or with one or more oral anti-hyperglycemic agent . All patients were counselled on a reduced calorie diet and increased physical activity throughout the trial. Patients had a mean age of 54 years and 51 % were women.Mean BMI at baseline was 36.1 kg/m^2.

Table 8. SURMOUNT-2: Results at week 72

	Tirzepatide 10 mg	Tirzepatide 15 mg	Placebo
mITT population (n)	312	311	315
Body weight			
Baseline (kg)	101.1	99.5	101.7
Change (%) from baseline	-13.4††	-15.7††	-3.3††
Difference (%) from placebo [95 % CI]	-10.1** [-11.5, -8.8]	-12.4** [-13.7, -11.0]	-
Change (kg) from baseline	-13.5††	-15.6††	-3.2
Difference (kg) from placebo [95 % CI]	-10.3## [-11.7, -8.8]	-12.4## [-13.8,-11.0]	-
Patients (%) achieving body weight reduction			
≥ 5 %	81.6**	86.4**	30.5
≥ 10 %	63.4**	69.6**	8.7
≥ 15 %	41.4**	51.8**	2.6
≥ 20 %	23.0**	34.0**	1.0
Waist circumference (cm)			
Baseline	114.3	114.6	116.1
Change from baseline	-11.2††	-13.8††	-3.4††
Difference from placebo [95 % CI]	-7.8** [-9.2, -6.4]	-10.4** [-11.8, -8.9]	-
HbA_{1c} (mmol/mol)			
Baseline	64.1	64.7	63.4
Change from baseline	-23.4††	-24.3††	-1.8†
Difference from placebo [95 % CI]	-21.6** [-23.5, -19.6]	-22.5** [-24.4, -20.6]	-
HbA_{1c} (%)			
Baseline	8.0	8.1	8.0
Change from baseline	-2.1††	-2.2††	-0.2†
Difference from placebo [95 % CI]	-2.0** [-2.2, -1.8]	-2.1** [-2.2, -1.9]	-
Patients (%) achieving HbA1c			
< 7 %	90.0**	90.7**	29.3
≤ 6.5 %	84.1**	86.7**	15.5
< 5.7 %	50.2**	55.3**	2.8
FSG (mmol/L)			
Baseline	8.8	9.0	8.7
Change from baseline	-2.7††	-2.9††	-0.1
Difference from placebo [95 % CI]	-2.6** [-2.9, -2.3]	-2.7** [-3.1, -2.4]	-
FSG (mg/dL)			
Baseline	157.8	161.5	156.7
Change from baseline	-49.2††	-51.7††	-2.4
Difference from placebo [95 % CI]	-46.8** [-52.7, -40.9]	-49.3** [-55.2, -43.3]	-

†p< 0.05 versus baseline
††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

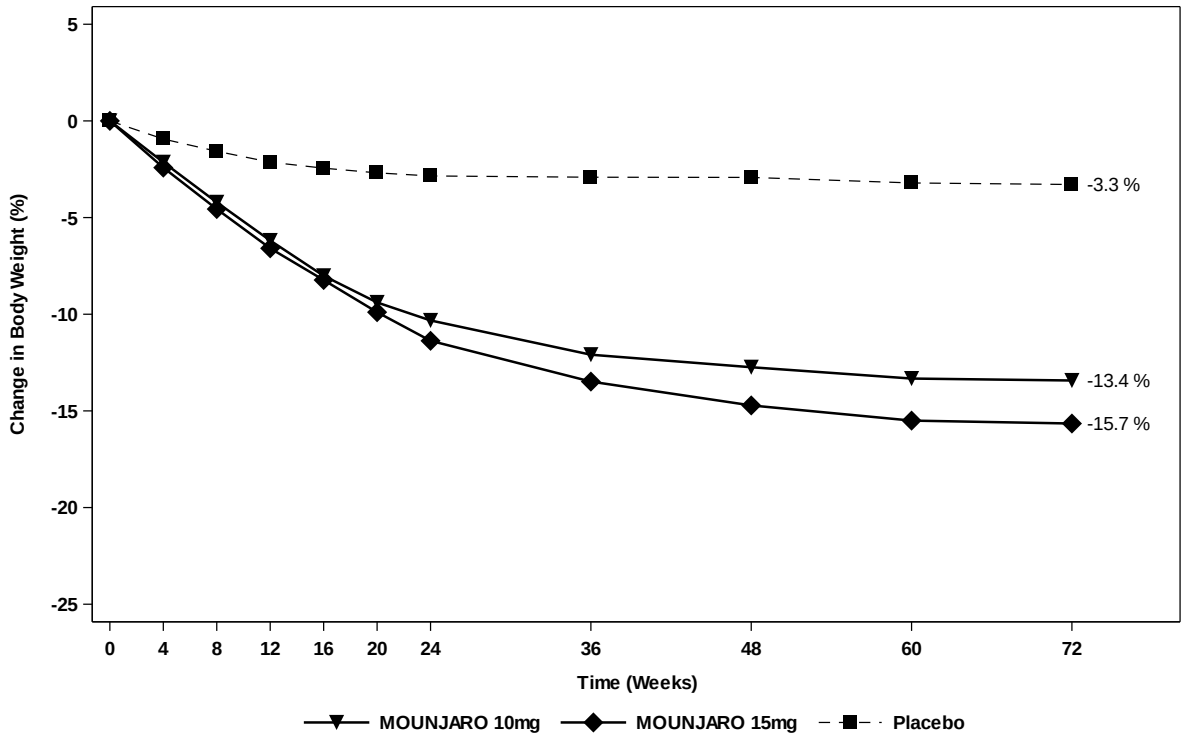


Figure 7. Mean change in body weight (%) from baseline to week 72

In SURMOUNT-2, pooled doses of tirzepatide 10 mg and 15 mg led to a significant improvement compared to placebo in systolic blood pressure (-7.2 mmHg vs. -1.0 mmHg), triglycerides (-28.6 % vs. -5.8 %), non-HDL-C (-6.6 % vs. 2.3 %), and HDL-C (8.2 % vs. 1.1 %).

SURMOUNT-3

In an 84 week study, 806 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight related comorbid condition, entered a 12 week intensive lifestyle intervention lead-in period consisting of a low calorie diet (1 200-1 500 kcal/day), increased physical activity and frequent behavioural counselling. At the end of the 12 week lead-in period, 579 patients who achieved ≥ 5.0 % weight reduction were randomised to tirzepatide maximum tolerated dose (MTD) of 10 mg or 15 mg once weekly or to placebo, for 72 weeks (double-blind phase). Patients were on a reduced-calorie diet and increased physical activity throughout the double-blind phase of the study. At randomisation patients had a mean age of 46 years and 63 % were women. Mean BMI at randomisation was 35.9 kg/m^2.

Table 9. SURMOUNT-3: Results at week 72

	Tirzepatide MTD	**Placebo**
mITT population (n)	287	292
Body weight		
Baseline[1] (kg)	102.3	101.3
Change (%) from baseline[1]	-21.1[††]	3.3[††]
Difference (%) from placebo [95 % CI]	-24.5[**] [-26.1, -22.8]	-
Change (kg) from baseline[1]	-21.5[††]	3.5[††]
Difference (kg) from placebo [95 % CI]	-25.0[##] [-26.9, -23.2]	-
Patients (%) achieving body weight reduction		
≥ 5 %	94.4[**]	10.7
≥ 10 %	88.0[**]	4.8
≥ 15 %	73.9[**]	2.1
≥ 20 %	54.9[**]	1.0
Patients (%) who maintain ≥80% of the body weight lost during the 12-week lead-in period	98.6[**]	37.8
Waist circumference (cm)		
Baseline[1]	109.2	109.6
Change from baseline[1]	-16.8[††]	1.1
Difference from placebo [95 % CI]	-17.9[**] [-19.5, -16.3]	-

[1]Randomisation (Week 0)
[††]$p < 0.001$ versus baseline[1].
[**]$p < 0.001$ versus placebo, adjusted for multiplicity.
[##]$p < 0.001$ versus placebo, not adjusted for multiplicity.

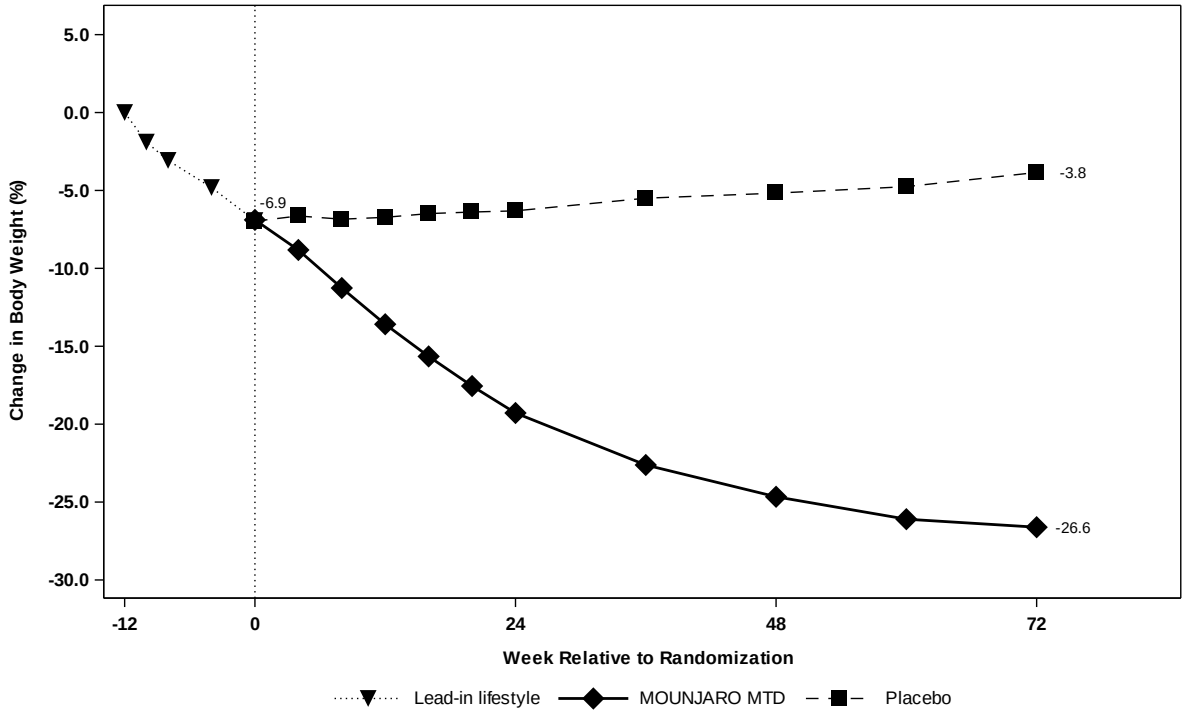


Figure 8. Mean change in body weight (%) from Week -12 to week 72

SURMOUNT-4

In an 88 week study, 783 adult patients with obesity (BMI ≥ 30 kg/m^2) or with overweight (BMI ≥ 27 kg/m^2 to < 30 kg/m^2) and at least one weight related comorbid condition, were enrolled in a 36 week open label tirzepatide lead-in phase. At the start of lead-in period, the enrolled patients had a mean body weight of 107.0 kg and a mean BMI of 38.3 kg/m^2. At the end of the lead-in period, 670 patients who achieved tirzepatide MTD of 10 mg or 15 mg dose were randomised to continue treatment with tirzepatide once weekly or to switch to placebo for 52 weeks (double-blind phase). Patients were counselled on a reduced calorie diet and increased physical activity throughout the trial. At randomisation (week 36), patients had a mean age of 49 years and 71 % were women. Mean body weight at randomisation was 85.2 kg and mean BMI was 30.5 kg/m^2.

Patients who continued treatment with tirzepatide for an additional 52 weeks (up to 88 weeks in total) maintained and experienced further weigh loss after the initial weight reduction achieved during the 36 week lead-in phase. The weight reduction was superior and clinically meaningful compared to the placebo group, in which a substantial regain of body weight lost during the lead-in phase was observed (see Table 10 and Figure 9). Nevertheless, the observed mean body weight for placebo-treated patients was lower at week 88 than at the start of the lead-in phase (see Figure 9).

Table 10. SURMOUNT-4: Results at week 88

	Tirzepatide MTD	**Placebo**
mITT population (n) only patients at Week 36	335	335
Body weight		
Weight (kg) at Week 0 (baseline)	106.7	107.8
Weight (kg) at Week 36 (randomisation)	84.5	85.9
Change (%) from Week 36 at Week 88	-6.7††	14.8††
Difference (%) from placebo at Week 88 [95 % CI]	-21.4** [-22.9, -20.0]	-
Change (kg) from Week 36 at Week 88	-5.7††	11.9††
Difference (kg) from placebo at Week 88 [95 % CI]	-17.6## [-18.8, -16.4]	-
Patients (%) achieving body weight reduction from Week 0 to Week 88		
≥ 5 %	98.5**	69.0
≥ 10 %	94.0**	44.4
≥ 15 %	87. 1**	24.0
≥ 20 %	72.6**	11.6
Patients (%) who maintain ≥80% of the body weight lost during the 36-week lead-in period at Week 88	93.4**	13.5
Waist circumference (cm)		
Baseline (Week 0)	114.9	115.6
Randomisation (Week 36)	96.7	98.2
Change from randomisation (Week 36)	-4.6††	8.3††
Difference from placebo [95 % CI]	-12.9** [-14.1, -11.7]	-

††p < 0.001 versus baseline.
**p < 0.001 versus placebo, adjusted for multiplicity.
##p < 0.001 versus placebo, not adjusted for multiplicity.

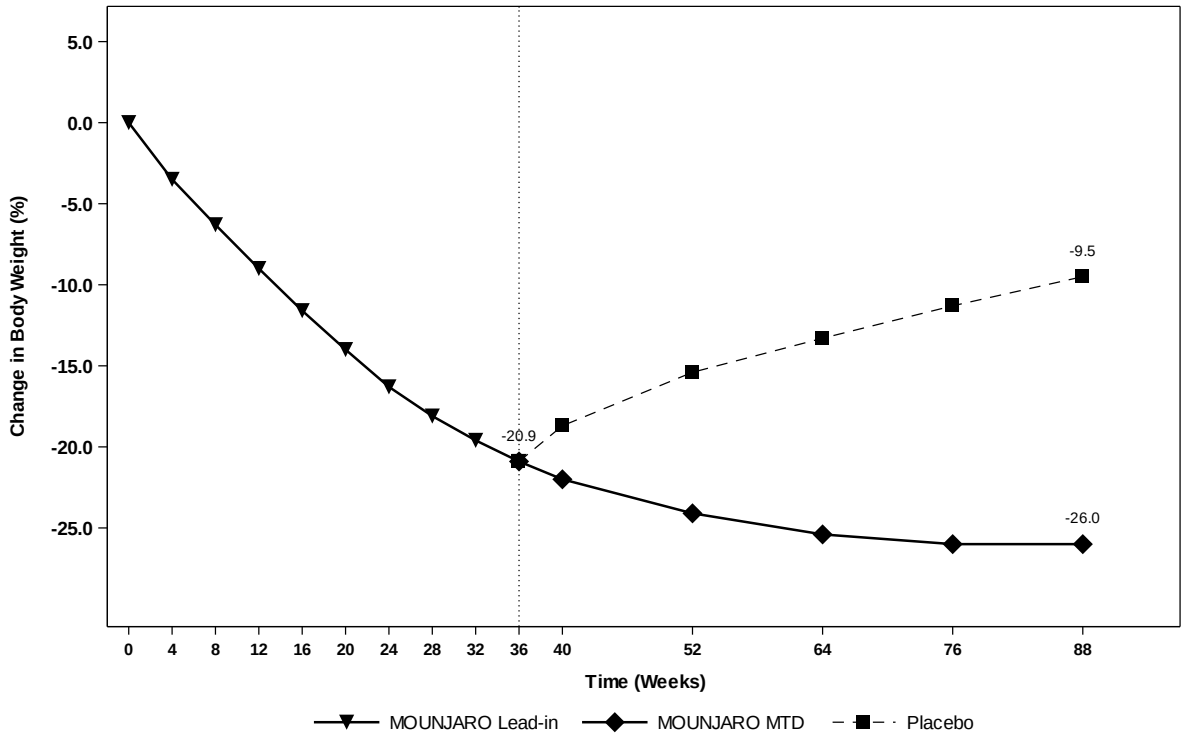


Figure 9. Mean change in body weight (%) from baseline (Week 0) to week 88

Risk of weight regain to > 95 % of study baseline (Week 0) weight at week 88
Time to event analysis showed that continued tirzepatide treatment during the double-blind period reduced the risk of returning to greater than 95 % body weight observed at Week 0, for those who had already lost at least 5 % since week 0 by approximately 99 % compared with placebo (hazard ratio, 0.013 [95 % CI, 0.004 to 0.046]; $p < 0.001$).

Effect on body composition

Changes in body composition were evaluated in a sub-study in SURMOUNT-1 using dual energy X-ray absorptiometry (DEXA). The results of the DEXA assessment showed that treatment with tirzepatide was accompanied by greater reduction in fat mass than in lean body mass leading to an improvement in body composition compared to placebo after 72 weeks. Furthermore, this reduction in total fat mass was accompanied by a reduction in visceral fat. These results suggest that most of the total weight loss was attributable to a reduction in fat tissue, including visceral fat.

Improvement in physical functioning

Patients with obesity or overweight without diabetes who received tirzepatide showed small improvements in health-related quality of life, including physical functioning. The improvements were greater in the tirzepatide-treated patients than in those who received placebo. Health-related quality of life was assessed using the generic questionnaire Short Form-36v2 Health Survey Acute, Version (SF-36v2).

Cardiovascular evaluation

Cardiovascular (CV) risk was assessed via a meta-analysis of patients with at least one adjudication confirmed major adverse cardiovascular event (MACE). The composite endpoint of MACE-4 included CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalisation for unstable angina.

In a primary meta-analysis of phase 2 and 3 registration studies in patients with type 2 diabetes, a total of 116 patients (tirzepatide: 60 [n = 4 410]; all comparators: 56 [n = 2 169]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with pooled comparators (HR: 0.81; CI: 0.52 to 1.26).

An additional analysis was conducted specifically for the SURPASS-4 study that enrolled patients with established CV disease. A total of 109 patients (tirzepatide: 47 [n = 995]; insulin glargine: 62 [n = 1 000]) experienced at least one adjudication confirmed MACE-4: The results showed that tirzepatide was not associated with excess risk for CV events compared with insulin glargine (HR: 0.74; CI: 0.51 to 1.08).

In 3 placebo-controlled weight management phase 3 studies (SURMOUNT 1-3), a total of 27 participants experienced at least one adjudication confirmed MACE (TZP: 17 (n = 2 806); placebo: 10 (n = 1 250)); the event rate was similar across placebo and tirzepatide.

Blood pressure
In the placebo-controlled phase 3 studies in patients with T2DM, treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 6 to 9 mmHg and 3 to 4 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of 2 mmHg each in placebo treated patients.

In 3 placebo-controlled weight management phase 3 studies (SURMOUNT 1-3), treatment with tirzepatide resulted in a mean decrease in systolic and diastolic blood pressure of 7 mmHg and 4 mmHg, respectively. There was a mean decrease in systolic and diastolic blood pressure of < 1 mmHg each in placebo treated patients.

Other information

Fasting serum glucose

Across SURPASS-1 to -5 trials, treatment with tirzepatide resulted in significant reductions from baseline in FSG (changes from baseline to primary end point were -2.4 mmol/L to -3.8 mmol/L). Significant reductions from baseline in FSG could be observed as early as 2 weeks. Further improvement in FSG was seen through to 42 weeks then was sustained through the longest study duration of 104 weeks.

Postprandial glucose

Across SURPASS-1 to -5 trials, treatment with tirzepatide resulted in significant reductions in mean 2 hour post prandial glucose (mean of 3 main meals of the day) from baseline (changes from baseline to primary end point were -3.35 mmol/L to -4.85 mmol/L).

Triglycerides

Across SURPASS-1 to -5 trials, tirzepatide 5 mg, 10 mg and 15 mg resulted in reduction in serum triglyceride of 15-19 %, 18-27 % and 21-25 % respectively.

In the 40 week trial versus semaglutide 1 mg, tirzepatide 5 mg, 10 mg and 15 mg resulted in 19 %, 24 % and 25 % reduction in serum triglycerides levels respectively compared to 12 % reduction with semaglutide 1 mg.

In the 72 week placebo-controlled phase 3 study in patients with obesity or overweight without T2DM (SURMOUNT-1), treatment with tirzepatide 5 mg, 10 mg, and 15 mg resulted in 24 %, 27 % and 31 % reduction in serum triglyceride levels respectively compared to 6 % reduction with placebo.

In the 72 week placebo-controlled phase 3 study in patients with obesity or overweight with T2DM (SURMOUNT-2), treatment with tirzepatide 10 mg and 15 mg resulted in 27 % and 31 % reduction in serum triglyceride levels respectively compared to 6 % reduction with placebo.

Proportion of patients reaching HbA1c < 5.7 % without clinically significant hypoglycaemia

In the 4 studies where tirzepatide was not combined with basal insulin (SURPASS-1 to -4), 93.6 % to 100 % of patients who achieved a normal glycaemia of HbA1c < 5.7 % (≤ 39 mmol/mol), at the primary endpoint visit with tirzepatide treatment did so without clinically significant hypoglycaemia. In Study SURPASS-5, 85.9 % of patients treated with tirzepatide who reached HbA1c < 5.7 % (≤ 39 mmol/mol) did so without clinically significant hypoglycaemia.

Special populations

The efficacy of tirzepatide for the treatment of T2DM was not impacted by age, gender, race, ethnicity, region, or by baseline BMI, HbA1c, diabetes duration and level of renal function impairment.

The efficacy of tirzepatide for weight management was not impacted by age, gender, race, ethnicity, region, baseline BMI, and presence or absence of prediabetes.

Paediatric population

The European Medicines Agency has deferred the obligation to submit the results of studies with Mounjaro in one or more subsets of the paediatric population for the treatment of type 2 diabetes mellitus and for weight management (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Tirzepatide consists of 39-amino acids and has a C20 fatty diacid moiety attached, which enables albumin binding and prolongs half-life.

Absorption

Maximum concentration of tirzepatide is reached 8 to 72 hours post dose. Steady state exposure is achieved following 4 weeks of once weekly administration. Tirzepatide exposure increases in a dose proportional manner.

Similar exposure was achieved with subcutaneous administration of tirzepatide in the abdomen, thigh, or upper arm.

Absolute bioavailability of subcutaneous tirzepatide was 80 %.

Distribution

The mean apparent steady-state volume of distribution of tirzepatide following subcutaneous administration in patients with type 2 diabetes is approximately 10.3 L, and 9.7 L in patients with obesity.

Tirzepatide is highly bound to plasma albumin (99 %).

Biotransformation

Tirzepatide is metabolised by proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety and amide hydrolysis.

Elimination

The apparent population mean clearance of tirzepatide is approximately 0.06 L/h with an elimination half-life of approximately 5 days, enabling once weekly administration.

Tirzepatide is eliminated by metabolism. The primary excretion routes of tirzepatide metabolites are via urine and faeces. Intact tirzepatide is not observed in urine or faeces.

Special populations

Age, gender, race, ethnicity, body weight

Age, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the pharmacokinetics (PK) of tirzepatide. Based on a population PK analysis, the exposure of tirzepatide increases with decreasing body weight; however, the effect of body weight on the PK of tirzepatide does not appear to be clinically relevant.

Renal impairment

Renal impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function and no clinically relevant differences were observed. This was also shown for patients with both type 2 diabetes mellitus and renal impairment based on data from clinical studies.

Hepatic impairment

Hepatic impairment does not impact the PK of tirzepatide. The PK of tirzepatide after a single 5 mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function and no clinically relevant differences were observed.

Paediatric population

Tirzepatide has not been studied in paediatric patients.

5.3 Preclinical safety data

Non-clinical data reveal no special hazards for humans based on conventional studies of safety pharmacology or repeat-dose toxicity or genotoxicity.

A 2-year carcinogenicity study was conducted with tirzepatide in male and female rats at doses of 0.15, 0.50, and 1.5 mg/kg (0.12, 0.36, and 1.02-fold the maximum recommended human dose (MRHD) based on AUC) administered by subcutaneous injection twice weekly. Tirzepatide caused an increase in thyroid C-cell tumours (adenomas and carcinomas) at all doses compared to controls. The human relevance of these findings is unknown.

In a 6-month carcinogenicity study in rasH2 transgenic mice, tirzepatide at doses of 1, 3, and 10 mg/kg administered by subcutaneous injection twice weekly did not produce increased incidences of thyroid C-cell hyperplasia or neoplasia at any dose.

Animal studies with tirzepatide did not indicate direct harmful effects with respect to fertility.

In animal reproduction studies, tirzepatide caused foetal growth reductions and foetal abnormalities at exposures below the MRHD based on AUC. An increased incidence of external, visceral, and skeletal malformations and visceral and skeletal developmental variations were observed in rats. Foetal growth

reductions were observed in rats and rabbits. All developmental effects occurred at maternally toxic doses.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pre-filled pen, single-dose; vial, single-dose

Disodium hydrogen phosphate heptahydrate (E339)
Sodium chloride
Concentrated hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

Pre-filled pen (KwikPen), multi-dose

Disodium hydrogen phosphate heptahydrate (E339)
Benzyl alcohol (E1519)
Glycerol
Phenol
Sodium chloride
Concentrated hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Pre-filled pen, single-dose; vial, single-dose

Before use
2 years

Mounjaro may be stored unrefrigerated for up to 21 cumulative days at a temperature below 30 ºC and then the pre-filled pen or vial must be discarded.

Pre-filled pen (KwikPen), multi-dose

Before use
2 years

After first use
30 days. Store unrefrigerated at room temperature below 30 ºC. The pre-filled KwikPen must be discarded 30 days after first use.

6.4 Special precautions for storage

Store in a refrigerator (2 ºC – 8 ºC).
Do not freeze.

Pre-filled pen, single-dose; vial, single-dose

Store in original package in order to protect from light.

Pre-filled pen (KwikPen), multi-dose

For storage conditions after first use of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Pre-filled pen, single-dose

Glass syringe encased in a disposable pre-filled pen.

The pre-filled pen has a hidden needle, which will automatically insert into the skin when the injection button is pressed.
Each pre-filled pen contains 0.5 ml of solution.

Pack sizes of 2 pre-filled pens, 4 pre-filled pens and multipack containing 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be marketed.

Vial, single-dose

Clear glass vial with a sealed stopper.
Each vial contains 0.5 ml of solution.
Pack sizes of 1 vial, 4 vials, 12 vials, multipack containing 4 (4 packs of 1) vials or multipack containing 12 (12 packs of 1) vials. Not all pack sizes may be marketed.

Pre-filled pen (KwikPen), multi-dose

Clear glass cartridge encased in a multi-dose pre-filled pen.

Each pre-filled KwikPen contains 2.4 ml of solution for injection (4 doses of 0.6 ml). Each pen has excess volume for priming. However, attempting to inject any leftover medicinal product will result in an incomplete dose even though the pen still has medicinal product left in it. Needles are not included.

Pack sizes of 1 and 3 pre-filled KwikPens. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Instructions for use

Inspect Mounjaro visually before use and discard for particulate matter or discolouration.
Mounjaro that has been frozen must not be used.

Pre-filled pen, single-dose
The pre-filled pen is for single-use only.

The instructions for using the pen, included with the package leaflet, must be followed carefully.

Vial, single-dose
The vial is for single-use only.

The instructions in the package leaflet for how to inject Mounjaro from a vial must be followed carefully.

Pre-filled pen (KwikPen), multi-dose
The pre-filled KwikPen is for multiple doses. Each KwikPen contains 4 doses. Dispose of the pen after 4 weekly doses.

The instructions for using the KwikPen, included with the package leaflet, must be followed carefully.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

8. MARKETING AUTHORISATION NUMBER

EU/1/22/1685/001
EU/1/22/1685/002
EU/1/22/1685/003
EU/1/22/1685/004
EU/1/22/1685/005
EU/1/22/1685/006
EU/1/22/1685/007
EU/1/22/1685/008
EU/1/22/1685/009
EU/1/22/1685/010
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EU/1/22/1685/056
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EU/1/22/1685/059
EU/1/22/1685/060

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Pre-filled pen, single-dose; Vial, single-dose; Pre-filled pen (KwikPen), multi-dose

Eli Lilly Italia S.p.A.
Via Gramsci 731/733
50019, Sesto Fiorentino
Firenze (FI)
Italy

Pre-filled pen, single-dose; Pre-filled pen (KwikPen), multi-dose

Lilly France
2, rue du Colonel Lilly
67640 Fegersheim
France

Vial, single-dose; Pre-filled pen (KwikPen), multi-dose

Lilly S.A.
Avda. de la Industria, 30
28108 Alcobendas, Madrid
Spain

Pre-filled pen (KwikPen), multi-dose

Millmount Healthcare Limited
Block 7 City North Business Campus
Stamullen, K32 YD60
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/001 2 pre-filled pens
EU/1/22/1685/002 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 2.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 2.5 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/004 2 pre-filled pens
EU/1/22/1685/005 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/006

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 5 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/007 2 pre-filled pens
EU/1/22/1685/008 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/009

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 7.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 7.5 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/010 2 pre-filled pens
EU/1/22/1685/011 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/012

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 10 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 10 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/013 2 pre-filled pens
EU/1/22/1685/014 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/015

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 12.5 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
2 pre-filled pens
4 pre-filled pens

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/016 2 pre-filled pens
EU/1/22/1685/017 4 pre-filled pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 12 (3 packs of 4) pre-filled pens.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – PRE-FILLED PEN SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in pre-filled pen

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

4 pre-filled pens. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly

Mark the day of the week you want to use your medicine to help you remember.

	Mon.	Tue.	Wed.	Thu.	Fri.	Sat.	Sun.
Week 1							
Week 2							
Week 3							
Week 4							

Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MOUNJARO 15 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 15 mg solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/019
EU/1/22/1685/025
EU/1/22/1685/026

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/027
EU/1/22/1685/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/027
EU/1/22/1685/028

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 2.5 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/020
EU/1/22/1685/029
EU/1/22/1685/030

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/031
EU/1/22/1685/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/031
EU/1/22/1685/032

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 5 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/021
EU/1/22/1685/033
EU/1/22/1685/034

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/035
EU/1/22/1685/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/035
EU/1/22/1685/036

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 7.5 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/022
EU/1/22/1685/037
EU/1/22/1685/038

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/039
EU/1/22/1685/040

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/039
EU/1/22/1685/040

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 10 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/023
EU/1/22/1685/041
EU/1/22/1685/042

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/043
EU/1/22/1685/044

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/043
EU/1/22/1685/044

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 12.5 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection
1 vial
4 vials
12 vials

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/024
EU/1/22/1685/045
EU/1/22/1685/046

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (with Blue Box) – multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

Multi-pack: 4 (4 packs of 1) vials of 0.5 ml solution.
Multi-pack: 12 (12 packs of 1) vials of 0.5 ml solution.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/047
EU/1/22/1685/048

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON OUTER PACKAGING

INNER CARTON (without Blue Box) component of a multipack – VIAL SINGLE-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg solution for injection in vial

tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml)

3. LIST OF EXCIPIENTS

Excipients: Disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide, concentrated hydrochloric acid; water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 vial. Component of a multipack, can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only
Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Can be stored unrefrigerated below 30 ºC for up to 21 days.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/047
EU/1/22/1685/048

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL SINGLE-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Mounjaro 15 mg injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN (KWIKPEN) MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 2.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 10 mg of tirzepatide in 2.4 ml (4.17 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/049 – 1 pen
EU/1/22/1685/050 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 2.5 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 2.5 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN (KWIKPEN) MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 20 mg of tirzepatide in 2.4 ml (8.33 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/051 – 1 pen
EU/1/22/1685/052 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 5 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 5 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN (KWIKPEN) MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 7.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 30 mg of tirzepatide in 2.4 ml (12.5 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/053 – 1 pen
EU/1/22/1685/054 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 7.5 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 7.5 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

METHOD OF ADMINISTRATION

Once weekly

EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN (KWIKPEN) MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 10 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 40 mg of tirzepatide in 2.4 ml (16.7 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/055 – 1 pen
EU/1/22/1685/056 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 10 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 10 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED PEN (KWIKPEN) MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 12.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 50 mg of tirzepatide in 2.4 ml (20.8 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/057 – 1 pen
EU/1/22/1685/058 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 12.5 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 12.5 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON – PRE-FILLED (KWIKPEN) PEN MULTI-DOSE

1. NAME OF THE MEDICINAL PRODUCT

Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

2. STATEMENT OF ACTIVE SUBSTANCE

Each dose contains 15 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 60 mg of tirzepatide in 2.4 ml (25 mg/ml).

3. LIST OF EXCIPIENTS

Excipients: E339, E1519, glycerol, phenol, sodium chloride, sodium hydroxide, concentrated hydrochloric acid, water for injections. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection

1 pen (4 doses)
3 pens (each pen delivers 4 doses)

5. METHOD AND ROUTES OF ADMINISTRATION

Once weekly
Read the package leaflet before use.
Subcutaneous use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING, IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

After first use store unrefrigerated below 30 ºC for up to 30 days. Discard pen 30 days after first use.
Do not freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eli Lilly Nederland B.V.
Papendorpseweg 83, 3528 BJ Utrecht
The Netherlands

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1685/059 – 1 pen
EU/1/22/1685/060 – 3 pens

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Mounjaro 15 mg/dose KwikPen

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED PEN (KWIKPEN) MULTI-DOSE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTES OF ADMINISTRATION

Mounjaro 15 mg/dose KwikPen solution for injection

tirzepatide
Subcutaneous use

2. METHOD OF ADMINISTRATION

Once weekly

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.4 ml
4 doses

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Mounjaro 2.5 mg solution for injection in pre-filled pen
Mounjaro 5 mg solution for injection in pre-filled pen
Mounjaro 7.5 mg solution for injection in pre-filled pen
Mounjaro 10 mg solution for injection in pre-filled pen
Mounjaro 12.5 mg solution for injection in pre-filled pen
Mounjaro 15 mg solution for injection in pre-filled pen
tirzepatide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mounjaro is and what it is used for

Mounjaro contains an active substance called tirzepatide and is used to treat adults with type 2 diabetes mellitus. Mounjaro reduces the level of sugar in the body only when the levels of sugar are high.

Mounjaro is also used to treat adults with obesity or overweight (with BMI of at least 27 kg/m^2). Mounjaro influences appetite regulation, which may help you eat less food and reduce your body weight.

In type 2 diabetes, Mounjaro is used:
- on its own when you can't take metformin (another diabetes medicine).
- with other medicines for diabetes when they are not enough to control your blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

Mounjaro is also used together with diet and exercise for weight loss and to help keep the weight under control in adults, who have:
- a BMI of 30 kg/m² or greater (obesity) or
- a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) and weight-related health problems (such as prediabetes, type 2 diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems)

BMI (Body Mass Index) is a measure of your weight in relation to your height.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, nurse or pharmacist.

2. What you need to know before you use Mounjaro

Do not use Mounjaro
- if you are allergic to tirzepatide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, nurse or pharmacist before using Mounjaro if:
- you have severe problems with food digestion or food remaining in your stomach for longer than normal (including severe gastroparesis).
- you have ever had pancreatitis (inflammation of the pancreas which may cause severe pain in the stomach and back which does not go away).
- you have a problem with your eyes (diabetic retinopathy or macular oedema).
- you are using a sulphonylurea (another diabetes medicine) or insulin for your diabetes, as low blood sugar (hypoglycaemia) can occur. Your doctor may need to change your dose of these other medicines to reduce this risk.

When starting treatment with Mounjaro, in some cases you may experience loss of fluids/dehydration, e.g. due to vomiting, nausea and/or diarrhoea, which may lead to a decrease in kidney function. It is important to avoid dehydration by drinking plenty of fluids. Contact your doctor if you have any questions or concerns.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Mounjaro.

Children and adolescents
This medicine should not be given to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Mounjaro
Tell your doctor, nurse or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. This medicine should not be used during pregnancy as the effects of this medicine on an unborn child are not known. Therefore, it is recommended to use contraception while using this medicine.

Breast-feeding
It is unknown whether tirzepatide passes into breast milk. A risk to newborns/infants cannot be ruled out. If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you should stop breast-feeding or delay using Mounjaro.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines. However, if you use Mounjaro in combination with a sulphonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar, e.g. headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating (see section 4). See section 2, ‘Warnings and precautions’ for information on increased risk of low blood sugar. Talk to your doctor for further information.

Mounjaro contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Mounjaro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure how to use this medicine.

How much to use
- The starting dose is 2.5 mg once a week for four weeks. After four weeks your doctor will increase your dose to 5 mg once a week.
- Your doctor may increase your dose by 2.5 mg increments to 7.5 mg, 10 mg, 12.5 mg or 15 mg once a week if you need it. In each case your doctor will tell you to stay on a particular dose for at least 4 weeks before going to a higher dose.

Do not change your dose unless your doctor has told you to.

Each pen contains one dose of Mounjaro either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg.

Choosing when to use Mounjaro
You can use your pen at any time of the day, with or without meals. You should use it on the same day each week if you can. To help you remember, when to use Mounjaro, you may wish to tick the day of the week when you inject your first dose on the box that your pen comes in, or mark it on a calendar.

If necessary, you can change the day of your weekly Mounjaro injection, as long as it has been at least 3 days since your last injection. After selecting a new dosing day, continue with once-a-week dosing on that new day.

How to inject Mounjaro
Mounjaro is injected under the skin (subcutaneous injection) of your stomach area (abdomen) at least 5 cm from the belly button or upper leg (thigh) or upper arm. You may need help from someone else if you want to inject in your upper arm.

If you want to do so, you can use the same area of your body each week. But be sure to choose a different injection site within that area. If you also inject insulin choose a different injection site for that injection.

Read the "Instructions for Use" for the pen carefully before using Mounjaro.

Testing blood glucose levels
If you are using Mounjaro with a sulphonylurea or insulin, it is important that you test your blood glucose levels as instructed by your doctor, nurse or pharmacist (see section 2, 'Warnings and precautions').

If you use more Mounjaro than you should
If you use more Mounjaro than you should talk to your doctor immediately. Too much of this medicine may cause low blood sugar (hypoglycaemia) and can make you feel sick or be sick.

If you forget to use Mounjaro
If you forget to inject a dose and,
- it has been **4 days or less** since you should have used Mounjaro, use it as soon as you remember. Then inject your next dose as usual on your scheduled day.
- If it has been **more than 4 days** since you should have used Mounjaro, skip the missed dose. Then inject your next dose as usual on your scheduled day.

Do not use a double dose to make up for a forgotten dose. The minimum time between two doses must be at least 3 days.

If you stop using Mounjaro
Do not stop using Mounjaro without talking with your doctor. If you stop using Mounjaro, and you have type 2 diabetes, your blood sugar levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Uncommon (may affect up to 1 in 100 people)
- Inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.

Rare (may affect up to 1 in 1 000 people)
- Severe allergic reactions (e.g. anaphylactic reaction, angioedema). You should get immediate medical help and inform your doctor if you experience symptoms such as breathing problems, rapid swelling of the lips, tongue and/or throat with difficulty swallowing and a fast heartbeat.

Other side effects

Very common **(**may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Diarrhoea
- Stomach (abdominal) pain reported in patients treated for weight management
- Being sick (vomiting) reported in patients treated for weight management
- Constipation reported in patients treated for weight management

These side effects are usually not severe. Nausea, diarrhoea, and vomiting are most common when first starting tirzepatide but decrease over time in most patients.

- Low blood sugar (hypoglycaemia) is very common when tirzepatide is used with medicines that contain a sulphonylurea and/or insulin. If you are using a sulphonylurea or insulin for type 2 diabetes, the dose may need to be lowered while you use tirzepatide (see section 2, 'Warnings and precautions'). Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating. Your doctor should tell you how to treat low blood sugar.

Common **(**may affect up to 1 in 10 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used for type 2 diabetes with both metformin and a sodium-glucose co-transporter 2 inhibitor (another diabetes medicine)
- Allergic reaction (hypersensitivity) (e.g., rash, itching, and eczema)
- Dizziness reported in patients treated for weight management
- Low blood pressure reported in patients treated for weight management
- Feeling less hungry (decreased appetite) reported in patients treated for type 2 diabetes
- Stomach (abdominal) pain reported in patients treated for type 2 diabetes
- Being sick (vomiting) reported in patients treated for type 2 diabetes - this usually decreases over time
- Indigestion (dyspepsia)

- Constipation reported in patients treated for type 2 diabetes
- Bloating of the stomach
- Burping (eructation)
- Gas (flatulence)
- Reflux or heartburn (also called gastroesophageal reflux disease – GERD) -–a disease caused by stomach acid coming up into the tube from your stomach to your mouth
- Hair loss reported in patients treated for weight management
- Feeling tired (fatigue)
- Injection site reactions (e.g. itching or redness)
- Fast pulse
- Increased levels of pancreatic enzymes (such as lipase and amylase) in blood
- Increased calcitonin levels in blood in patients treated for weight management.

Uncommon **(**may affect up to 1 in 100 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used with metformin for type 2 diabetes.
- Gallstones
- Inflammation of the gallbladder
- Weight loss reported in patients treated for type 2 diabetes
- Injection site pain
- Increased calcitonin levels in blood in patients treated for type 2 diabetes
- Changed sense of taste

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Mounjaro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. If the pen has been frozen, DO NOT USE.

Store in the original packaging in order to protect from light.

Mounjaro can be stored unrefrigerated below 30 ºC for up to 21 cumulative days and then the pen must be discarded.

Do not use this medicine if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mounjaro contains
The active substance is tirzepatide.
- *Mounjaro 2.5 mg:* Each pre-filled pen contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).
- *Mounjaro 5 mg:* Each pre-filled pen contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).

- *Mounjaro 7.5 mg:* Each pre-filled pen contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).
- *Mounjaro 10 mg:* Each pre-filled pen contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).
- *Mounjaro 12.5 mg:* Each pre-filled pen contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).
- *Mounjaro 15 mg:* Each pre-filled pen contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

The other ingredients are disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide (see section 2 under 'Mounjaro contains sodium' for further information); concentrated hydrochloric acid and water for injections.

What Mounjaro looks like and contents of the pack
Mounjaro is a clear, colourless to slightly yellow, solution for injection in a pre-filled pen.
The pre-filled pen has a hidden needle which will automatically insert into the skin when the injection button is pressed. The pre-filled pen will retract the needle when the injection is completed.
Each pre-filled pen contains 0.5 ml solution.
The pre-filled pen is for single use only.
Pack sizes of 2 pre-filled pens, 4 pre-filled pens or multipack of 12 (3 packs of 4) pre-filled pens. Not all pack sizes may be available in your country.

Marketing Authorisation Holder
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Manufacturer
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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instructions for use

Mounjaro 2.5 mg solution for injection in pre-filled pen
Mounjaro 5 mg solution for injection in pre-filled pen
Mounjaro 7.5 mg solution for injection in pre-filled pen
Mounjaro 10 mg solution for injection in pre-filled pen
Mounjaro 12.5 mg solution for injection in pre-filled pen
Mounjaro 15 mg solution for injection in pre-filled pen

tirzepatide

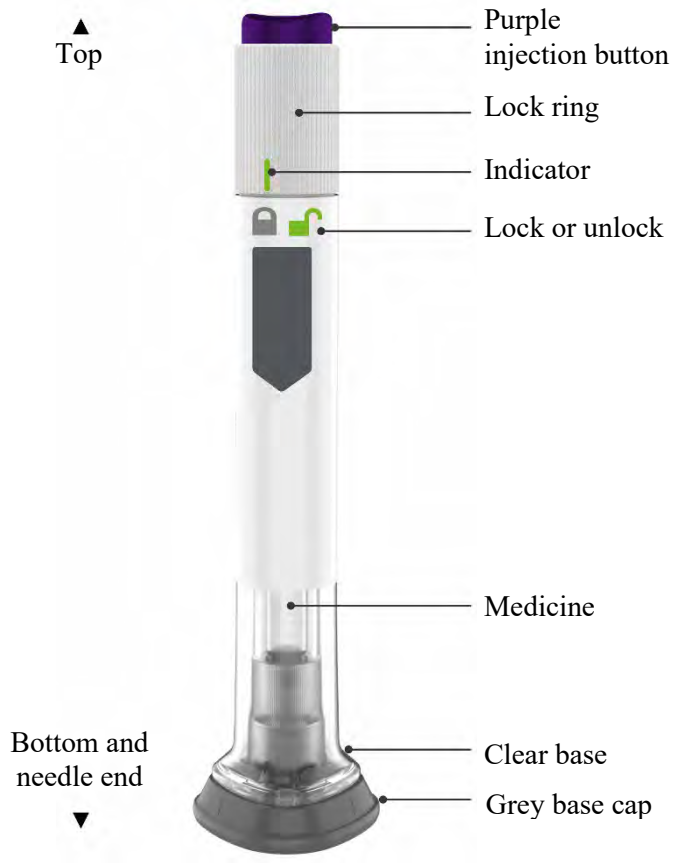
Important information you need to know before injecting Mounjaro.

Read this instructions for use and the package leaflet before using your Mounjaro pre-filled pen (pen) and each time you get a new pen. There may be new information. This information does not take the place of talking to your doctor, nurse or pharmacist about your medical condition or treatment.

Talk to your doctor, nurse or pharmacist about how to inject Mounjaro the right way.

- Mounjaro is a single-dose pre-filled pen.
- The pen has a hidden needle which will automatically insert into your skin when the injection button is pressed. The pen will retract the needle when the injection is completed.
- Mounjaro is used 1 time each week.
- Inject under the skin (subcutaneously) only.
- You or another person can inject into your stomach (abdomen), upper leg (thigh) or upper arm.
- You may need help from someone else if you want to inject in your upper arm.

Guide to parts

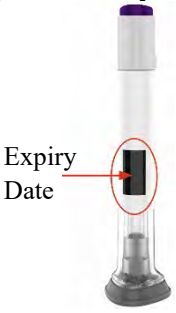


Preparing to inject Mounjaro

Remove the pen from the refrigerator.

Leave the grey base cap on until you are ready to inject.

Check the pen label to make sure you have the right medicine and dose, and that it has not expired.



Inspect the pen to make sure that it is not damaged.

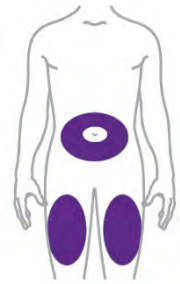
Make sure the medicine is:

- not frozen
- colourless to slightly yellow
- not cloudy
- does not have particles

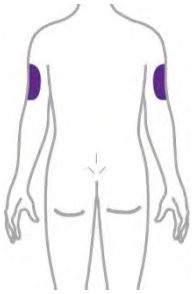
Wash your hands.

Choose your injection site

Your doctor, nurse or pharmacist can help you choose the injection site that is best for you.



You or another person can inject the medicine in your stomach (abdomen) at least 5 cm from the belly button or thigh.

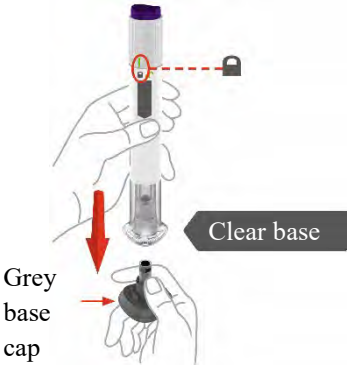


Another person should give you the injection in the back of your upper arm.

Change (rotate) your injection site each week.

You may use the same area of your body, but be sure to choose a different injection site in that area.

Step **1** **Pull off the grey base cap**



Make sure the pen is **locked**.

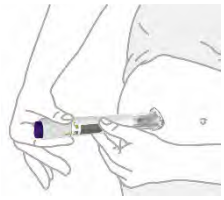
Do not unlock the pen until you place the clear base on your skin and are ready to inject.

Pull the grey base cap straight off and throw it away.

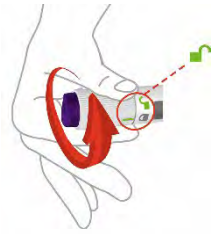
Do not put the grey base cap back on – this could damage the needle.

Do not touch the needle.

Step **2** **Place clear base on skin, then unlock**

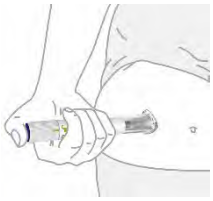


Place the clear base flat against your skin at the injection site.



Unlock by turning the lock ring.

Step **3** **Press and hold up to 10 seconds**



Press and hold the purple injection button.

Listen for:
- First click = injection started
- Second click = injection completed

You will know your injection is complete when the grey plunger is visible.

After your injection, place the used pen in a sharps disposal container.

Disposal of your used pen

- Throw away (dispose of) the pen in a sharps disposal container or as directed by your doctor, nurse or pharmacist. **Do not** throw away (dispose of) pens in your household waste.
- Do not recycle your used sharps disposal container.
- Ask your doctor, nurse or pharmacist about how to dispose of medicines you no longer use.

Storage and handling
- For storage instructions refer to section 5 of the patient information leaflet.
- The pen has glass parts. Handle it carefully. If you drop the pen on a hard surface, **do not** use it. Use a new pen for your injection.

Commonly asked questions

What if I see air bubbles in my pen?
Air bubbles are normal.

What if my pen is not at room temperature?
It is not necessary to warm the pen to room temperature.

What if I unlock the pen and press the purple injection button before pulling off the grey base cap?
Do not remove the grey base cap. Throw away the pen and get a new pen.

What if there is a drop of liquid on the tip of the needle when I remove the grey base cap?
A drop of liquid on the tip of the needle is normal. **Do not** touch the needle.

Do I need to hold the injection button down until the injection is complete?
This is not necessary, but it may help you keep the pen steady against your skin.

I heard more than 2 clicks during my injection — 2 loud clicks and 1 soft one. Did I get my complete injection?

Some people may hear a soft click right before the second loud click. That is the normal operation of the pen. **Do not** remove the pen from your skin until you hear the second loud click.

I am not sure if my pen worked the right way.

Check to see if you have received your dose. Your dose was delivered the right way if the grey plunger is visible. Also, see **Step 3** of the instructions.

If you do not see the grey plunger, contact Lilly for further instructions. Until then, store your pen safely to avoid an accidental needle injury.

What if there is a drop of liquid or blood on my skin after my injection?

This is normal. Press a cotton ball or gauze over the injection site. **Do not** rub the injection site.

Other information

- If you have vision problems, **do not** use your pen without help from a person trained to use the Mounjaro pen.

Where to learn more

- If you have questions or problems with your Mounjaro pen, contact Lilly or your doctor, nurse or pharmacist.

Last revised in

Package leaflet: Information for the patient

Mounjaro 2.5 mg solution for injection in vial
Mounjaro 5 mg solution for injection in vial
Mounjaro 7.5 mg solution for injection in vial
Mounjaro 10 mg solution for injection in vial
Mounjaro 12.5 mg solution for injection in vial
Mounjaro 15 mg solution for injection in vial
tirzepatide

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mounjaro is and what it is used for

Mounjaro contains an active substance called tirzepatide and is used to treat adults with type 2 diabetes mellitus. Mounjaro reduces the level of sugar in the body only when the levels of sugar are high.

Mounjaro is also used to treat adults with obesity or overweight (with BMI of at least 27 kg/m2). Mounjaro influences appetite regulation, which may help you eat less food and reduce your body weight.

In type 2 diabetes, Mounjaro is used:
- on its own when you can't take metformin (another diabetes medicine).
- with other medicines for diabetes when they are not enough to control your blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

Mounjaro is also used together with diet and exercise for weight loss and to help keep the weight under control in adults, who have:
- a BMI of 30 kg/m² or greater (obesity) or
- a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) and weight-related health problems (such as prediabetes, type 2 diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems)

BMI (Body Mass Index) is a measure of your weight in relation to your height.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, nurse or pharmacist.

2. What you need to know before you use Mounjaro

Do not use Mounjaro
- if you are allergic to tirzepatide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, nurse or pharmacist before using Mounjaro if:
- you have severe problems with food digestion or food remaining in your stomach for longer than normal (including severe gastroparesis).
- you have ever had pancreatitis (inflammation of the pancreas which may cause severe pain in the stomach and back which does not go away).
- you have a problem with your eyes (diabetic retinopathy or macular oedema).
- you are using a sulphonylurea (another diabetes medicine) or insulin for your diabetes, as low blood sugar (hypoglycaemia) can occur. Your doctor may need to change your dose of these other medicines to reduce this risk.

When starting treatment with Mounjaro, in some cases you may experience loss of fluids/dehydration, e.g. due to vomiting, nausea and/or diarrhoea, which may lead to a decrease in kidney function. It is important to avoid dehydration by drinking plenty of fluids. Contact your doctor if you have any questions or concerns.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Mounjaro.

Children and adolescents
This medicine should not be given to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Mounjaro
Tell your doctor, nurse or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. This medicine should not be used during pregnancy as the effects of this medicine on an unborn child are not known. Therefore, it is recommended to use contraception while using this medicine.

Breast-feeding
It is unknown whether tirzepatide passes into breast milk. A risk to newborns/infants cannot be ruled out. If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you should stop breast-feeding or delay using Mounjaro.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines. However, if you use Mounjaro in combination with a sulphonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar, e.g. headache, drowsiness, weakness, dizziness, feeling hungry, confusion,

irritability, fast heartbeat and sweating (see section 4). See section 2, 'Warnings and precautions' for information on increased risk of low blood sugar. Talk to your doctor for further information.

Mounjaro contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

3. How to use Mounjaro

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure how to use this medicine.

How much to use
- The starting dose is 2.5 mg once a week for four weeks. After four weeks your doctor will increase your dose to 5 mg once a week.
- Your doctor may increase your dose by 2.5 mg increments to 7.5 mg, 10 mg, 12.5 mg or 15 mg once a week if you need it. In each case your doctor will tell you to stay on a particular dose for at least 4 weeks before going to a higher dose.

Do not change your dose unless your doctor has told you to.

Each vial contains one dose of Mounjaro either 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, or 15 mg.

Choosing when to use Mounjaro
You can use Mounjaro at any time of the day, with or without meals. You should use it on the same day each week if you can. To help you remember when to use Mounjaro, you may wish to mark on a calendar the day of the week when you inject your first dose.

If necessary, you can change the day of your weekly Mounjaro injection, as long as it has been at least 3 days since your last injection. After selecting a new dosing day, continue with once-a-week dosing on that new day.

How to inject Mounjaro
Always use Mounjaro exactly as your doctor has told you. Before you begin using Mounjaro, always read the "Instructions for Use" below carefully, and talk to your doctor, nurse or pharmacist if you are not sure about how to inject Mounjaro correctly.

Mounjaro is injected under the skin (subcutaneous injection) of your stomach area (abdomen) or upper leg (thigh) or upper arm. You may need help from someone else if you want to inject in your upper arm. **Do not** inject Mounjaro directly into a vein, as this will change its action.

If you want to do so, you can use the same area of your body each week. But be sure to choose a different injection site within that area. If you also inject insulin choose a different injection site for that injection. If you are blind or visually impaired, you will need help from someone to make your injection.

Instructions for Use
1. First wash your hands with soap and water.
2. Check that the Mounjaro in the vial looks clear and colourless to slightly yellow. **Do not** use if it is frozen, cloudy, or has particles in it.
3. Pull off the vial plastic protective cap, but do not remove the stopper. Clean the stopper on the vial with a swab and prepare a new syringe. **Do not share or reuse your needle or syringe.**
4. Draw a small amount of air into the syringe. Put the needle through the rubber stopper on top of the Mounjaro vial and inject the air into the vial.

5. Turn the Mounjaro vial and the syringe upside down and slowly pull the syringe plunger down to withdraw all the Mounjaro solution from the vial. The vial is filled to enable delivery of a single 0.5 ml dose of Mounjaro.
6. If there are air bubbles in the syringe, tap the syringe gently a few times to let any air bubbles rise to the top. Slowly push the plunger up until there is no more air in the syringe.
7. Pull the syringe out of the vial stopper.
8. Before you make an injection, clean your skin.
9. Gently pinch and hold a fold of skin where you will inject.
10. Inject under the skin, as you have been instructed. Inject all the solution from the syringe to receive a full dose. After your injection, the needle should stay under your skin for 5 seconds to make sure you receive the full dose.
11. Pull the needle out of your skin.
12. Throw away the vial, used needle and syringe immediately after each injection in a puncture resistant container, or as instructed by your doctor, nurse or pharmacist.

Testing blood glucose levels
If you are using Mounjaro with a sulphonylurea or insulin, it is important that you test your blood glucose levels as instructed by your doctor, nurse or pharmacist (see section 2, 'Warnings and precautions').

If you use more Mounjaro than you should
If you use more Mounjaro than you should talk to your doctor immediately. Too much of this medicine may cause low blood sugar (hypoglycaemia) and can make you feel sick or be sick.

If you forget to use Mounjaro
If you forget to inject a dose and,
- it has been **4 days or less** since you should have used Mounjaro, use it as soon as you remember. Then inject your next dose as usual on your scheduled day.
- If it has been **more than 4 days** since you should have used Mounjaro, skip the missed dose. Then inject your next dose as usual on your scheduled day.

Do not use a double dose to make up for a forgotten dose. The minimum time between two doses must be at least 3 days.

If you stop using Mounjaro
Do not stop using Mounjaro without talking with your doctor. If you stop using Mounjaro, and you have type 2 diabetes, your blood sugar levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Uncommon (may affect up to 1 in 100 people)
- Inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.

Rare (may affect up to 1 in 1 000 people)
- Severe allergic reactions (e.g. anaphylactic reaction, angioedema). You should get immediate medical help and inform your doctor if you experience symptoms such as breathing problems, rapid swelling of the lips, tongue and/or throat with difficulty swallowing and a fast heartbeat.

Other side effects

Very common **(**may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Diarrhoea
- Stomach (abdominal) pain reported in patients treated for weight management
- Being sick (vomiting) reported in patients treated for weight management
- Constipation reported in patients treated for weight management

These side effects are usually not severe. Nausea, diarrhoea, and vomiting are most common when first starting tirzepatide but decrease over time in most patients.

- Low blood sugar (hypoglycaemia) is very common when tirzepatide is used with medicines that contain a sulphonylurea and/or insulin. If you are using a sulphonylurea or insulin for type 2 diabetes, the dose may need to be lowered while you use tirzepatide (see section 2, 'Warnings and precautions'). Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating. Your doctor should tell you how to treat low blood sugar.

Common **(**may affect up to 1 in 10 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used for type 2 diabetes with both metformin and a sodium-glucose co-transporter 2 inhibitor (another diabetes medicine)
- Allergic reaction (hypersensitivity) (e.g., rash, itching, and eczema)
- Dizziness reported in patients treated for weight management
- Low blood pressure reported in patients treated for weight management
- Feeling less hungry (decreased appetite) reported in patients treated for type 2 diabetes
- Stomach (abdominal) pain reported in patients treated for type 2 diabetes
- Being sick (vomiting) reported in patients treated for type 2 diabetes - this usually decreases over time
- Indigestion (dyspepsia)
- Constipation reported in patients treated for type 2 diabetes
- Bloating of the stomach
- Burping (eructation)
- Gas (flatulence)
- Reflux or heartburn (also called gastroesophageal reflux disease – GERD) - a disease caused by stomach acid coming up into the tube from your stomach to your mouth
- Hair loss reported in patients treated for weight management
- Feeling tired (fatigue)
- Injection site reactions (e.g. itching or redness)
- Fast pulse
- Increased levels of pancreatic enzymes (such as lipase and amylase) in blood
- Increased calcitonin levels in blood in patients treated for weight management.

Uncommon **(**may affect up to 1 in 100 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used with metformin for type 2 diabetes.
- Gallstones
- Inflammation of the gallbladder
- Weight loss reported in patients treated for type 2 diabetes
- Injection site pain
- Increased calcitonin levels in blood in patients treated for type 2 diabetes
- Changed sense of taste

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Mounjaro

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. If the vial has been frozen, DO NOT USE.

Store in the original packaging in order to protect from light.

Mounjaro can be stored unrefrigerated below 30 ºC for up to 21 cumulative days and then the vial must be discarded.

Do not use this medicine if you notice that the vial, seal or stopper is damaged, or the medicine is cloudy, discoloured or has particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mounjaro contains
The active substance is tirzepatide.
- *Mounjaro 2.5 mg:* Each vial contains 2.5 mg of tirzepatide in 0.5 ml solution (5 mg/ml).
- *Mounjaro 5 mg:* Each vial contains 5 mg of tirzepatide in 0.5 ml solution (10 mg/ml).
- *Mounjaro 7.5 mg:* Each vial contains 7.5 mg of tirzepatide in 0.5 ml solution (15 mg/ml).
- *Mounjaro 10 mg:* Each vial contains 10 mg of tirzepatide in 0.5 ml solution (20 mg/ml).
- *Mounjaro 12.5 mg:* Each vial contains 12.5 mg of tirzepatide in 0.5 ml solution (25 mg/ml).
- *Mounjaro 15 mg:* Each vial contains 15 mg of tirzepatide in 0.5 ml solution (30 mg/ml).

The other ingredients are disodium hydrogen phosphate heptahydrate (E339), sodium chloride, sodium hydroxide (see section 2 under ‘Mounjaro contains sodium’ for further information); concentrated hydrochloric acid and water for injections.

What Mounjaro looks like and contents of the pack
Mounjaro is a clear, colourless to slightly yellow, solution for injection in a vial.
Each vial contains 0.5 ml solution.
The vial is for single use only.
Pack sizes of 1 vial, 4 vials, 12 vials, multipack containing 4 (4 packs of 1) vials or multipack containing 12 (12 packs of 1) vials. Not all pack sizes may be available in your country.
Needles and syringe are not provided in this pack.

Marketing Authorisation Holder
Eli Lilly Nederland B.V., Papendorpseweg 83, 3528 BJ Utrecht, The Netherlands.

Manufacturer
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Package leaflet: Information for the patient

Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 7.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, nurse or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Mounjaro KwikPen is and what it is used for

Mounjaro contains an active substance called tirzepatide and is used to treat adults with type 2 diabetes mellitus. Mounjaro reduces the level of sugar in the body only when the levels of sugar are high.

Mounjaro is also used to treat adults with obesity or overweight (with BMI of at least 27 kg/m2). Mounjaro influences appetite regulation, which may help you eat less food and reduce your body weight.

In type 2 diabetes, Mounjaro is used:
- on its own when you can't take metformin (another diabetes medicine).
- with other medicines for diabetes when they are not enough to control your blood sugar levels. These other medicines may be medicines taken by mouth and/or insulin given by injection.

Mounjaro is also used together with diet and exercise for weight loss and to help keep the weight under control in adults, who have:
- a BMI of 30 kg/m² or greater (obesity) or
- a BMI of at least 27 kg/m² but less than 30 kg/m² (overweight) and weight-related health problems (such as prediabetes, type 2 diabetes, high blood pressure, abnormal levels of fats in the blood, breathing problems during sleep called 'obstructive sleep apnoea' or a history of heart attack, stroke or blood vessel problems)

BMI (Body Mass Index) is a measure of your weight in relation to your height.

It is important to continue to follow the advice on diet and exercise given to you by your doctor, nurse or pharmacist.

2. What you need to know before you use Mounjaro KwikPen

Do not use Mounjaro KwikPen
- if you are allergic to tirzepatide or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, nurse or pharmacist before using Mounjaro if:
- you have severe problems with food digestion or food remaining in your stomach for longer than normal (including severe gastroparesis).
- you have ever had pancreatitis (inflammation of the pancreas which may cause severe pain in the stomach and back which does not go away).
- you have a problem with your eyes (diabetic retinopathy or macular oedema).
- you are using a sulphonylurea (another diabetes medicine) or insulin for your diabetes, as low blood sugar (hypoglycaemia) can occur. Your doctor may need to change your dose of these other medicines to reduce this risk.

When starting treatment with Mounjaro, in some cases you may experience loss of fluids/dehydration, e.g. due to vomiting, nausea and/or diarrhoea, which may lead to a decrease in kidney function. It is important to avoid dehydration by drinking plenty of fluids. Contact your doctor if you have any questions or concerns.

If you know that you are due to have surgery where you will be under anaesthesia (sleeping), please tell your doctor that you are taking Mounjaro.

Children and adolescents
This medicine should not be given to children and adolescents under 18 years of age because it has not been studied in this age group.

Other medicines and Mounjaro
Tell your doctor, nurse or pharmacist if you are using, have recently used or might use any other medicines.

Pregnancy
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine. This medicine should not be used during pregnancy as the effects of this medicine on an unborn child are not known. Therefore, it is recommended to use contraception while using this medicine.

Breast-feeding
It is unknown whether tirzepatide passes into breast milk. A risk to newborns/infants cannot be ruled out. If you are breast-feeding or are planning to breast-feed, talk to your doctor before using this medicine. You and your doctor should decide if you should stop breast-feeding or delay using Mounjaro.

Driving and using machines
It is unlikely that this medicine will affect your ability to drive and use machines. However, if you use Mounjaro in combination with a sulphonylurea or insulin, low blood sugar (hypoglycaemia) may occur which may reduce your ability to concentrate. Avoid driving or using machines if you get any signs of low blood sugar, e.g. headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating (see section 4). See section 2, ‘Warnings and precautions’ for information on increased risk of low blood sugar. Talk to your doctor for further information.

Mounjaro KwikPen contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'.

Mounjaro KwikPen contains benzyl alcohol
This medicine contains 5.4 mg benzyl alcohol in each 0.6 ml dose. Benzyl alcohol may cause allergic reactions.

Ask your doctor, nurse or pharmacist for advice if you are pregnant or breast-feeding or if you have a liver or kidney disease. This is because large amounts of benzyl alcohol can build-up in your body and may cause side effects (called "metabolic acidosis").

3. How to use Mounjaro KwikPen

Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure how to use this medicine.

How much to use
- The starting dose is 2.5 mg once a week for four weeks. After four weeks your doctor will increase your dose to 5 mg once a week.
- Your doctor may increase your dose by 2.5 mg increments to 7.5 mg, 10 mg, 12.5 mg or 15 mg once a week if you need it. In each case your doctor will tell you to stay on a particular dose for at least 4 weeks before going to a higher dose.

Do not change your dose unless your doctor has told you to.

Choosing when to use Mounjaro
You can use your pen at any time of the day, with or without meals. You should use it on the same day each week if you can. To help you remember, when to use Mounjaro, you may wish to mark it on a calendar.

If necessary, you can change the day of your weekly Mounjaro injection, as long as it has been at least 3 days since your last injection. After selecting a new dosing day, continue with once-a-week dosing on that new day.

How to inject Mounjaro KwikPen
Mounjaro is injected under the skin (subcutaneous injection) of your stomach area (abdomen) at least 5 cm from the belly button or upper leg (thigh) or upper arm. You may need help from someone else if you want to inject in your upper arm.

If you want to do so, you can use the same area of your body each week. But be sure to choose a different injection site within that area. If you also inject insulin choose a different injection site for that injection.

Read the "Instructions for Use" for the pen carefully before using Mounjaro KwikPen.

Testing blood glucose levels
If you are using Mounjaro with a sulphonylurea or insulin, it is important that you test your blood glucose levels as instructed by your doctor, nurse or pharmacist (see section 2, 'Warnings and precautions').

If you use more Mounjaro than you should
If you use more Mounjaro than you should talk to your doctor immediately. Too much of this medicine may cause low blood sugar (hypoglycaemia) and can make you feel sick or be sick.

If you forget to use Mounjaro
If you forget to inject a dose and,
- it has been **4 days or less** since you should have used Mounjaro, use it as soon as you remember. Then inject your next dose as usual on your scheduled day.
- If it has been **more than 4 days** since you should have used Mounjaro, skip the missed dose. Then inject your next dose as usual on your scheduled day.

Do not use a double dose to make up for a forgotten dose. The minimum time between two doses must be at least 3 days.

If you stop using Mounjaro
Do not stop using Mounjaro without talking with your doctor. If you stop using Mounjaro, and you have type 2 diabetes, your blood sugar levels can increase.

If you have any further questions on the use of this medicine, ask your doctor, nurse or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Uncommon (may affect up to 1 in 100 people)
- Inflamed pancreas (acute pancreatitis) which could cause severe pain in the stomach and back which does not go away. You should see a doctor immediately if you experience such symptoms.

Rare (may affect up to 1 in 1 000 people)
- Severe allergic reactions (e.g. anaphylactic reaction, angioedema). You should get immediate medical help and inform your doctor if you experience symptoms such as breathing problems, rapid swelling of the lips, tongue and/or throat with difficulty swallowing and a fast heartbeat.

Other side effects

Very common **(**may affect more than 1 in 10 people)
- Feeling sick (nausea)
- Diarrhoea
- Stomach (abdominal) pain reported in patients treated for weight management
- Being sick (vomiting) reported in patients treated for weight management
- Constipation reported in patients treated for weight management

These side effects are usually not severe. Nausea, diarrhoea, and vomiting are most common when first starting tirzepatide but decrease over time in most patients.

- Low blood sugar (hypoglycaemia) is very common when tirzepatide is used with medicines that contain a sulphonylurea and/or insulin. If you are using a sulphonylurea or insulin for type 2 diabetes, the dose may need to be lowered while you use tirzepatide (see section 2, 'Warnings and precautions'). Symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, feeling hungry, confusion, irritability, fast heartbeat and sweating. Your doctor should tell you how to treat low blood sugar.

Common **(**may affect up to 1 in 10 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used for type 2 diabetes with both metformin and a sodium-glucose co-transporter 2 inhibitor (another diabetes medicine)
- Allergic reaction (hypersensitivity) (e.g., rash, itching, and eczema)
- Dizziness reported in patients treated for weight management
- Low blood pressure reported in patients treated for weight management

- Feeling less hungry (decreased appetite) reported in patients treated for type 2 diabetes
- Stomach (abdominal) pain reported in patients treated for type 2 diabetes
- Being sick (vomiting) reported in patients treated for type 2 diabetes – this usually decreases over time
- Indigestion (dyspepsia)
- Constipation reported in patients treated for type 2 diabetes
- Bloating of the stomach
- Burping (eructation)
- Gas (flatulence)
- Reflux or heartburn (also called gastroesophageal reflux disease – GERD) - a disease caused by stomach acid coming up into the tube from your stomach to your mouth
- Hair loss reported in patients treated for weight management
- Feeling tired (fatigue)
- Injection site reactions (e.g. itching or redness)
- Fast pulse
- Increased levels of pancreatic enzymes (such as lipase and amylase) in blood
- Increased calcitonin levels in blood in patients treated for weight management.

Uncommon **(**may affect up to 1 in 100 people)
- Low blood sugar (hypoglycaemia) when tirzepatide is used with metformin for type 2 diabetes.
- Gallstones
- Inflammation of the gallbladder
- Weight loss reported in patients treated for type 2 diabetes
- Injection site pain
- Increased calcitonin levels in blood in patients treated for type 2 diabetes
- Changed sense of taste

Reporting of side effects
If you get any side effects, talk to your doctor, nurse or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Mounjaro KwikPen

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pen label and on the carton after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C – 8 °C). Do not freeze. If the pen has been frozen, DO NOT USE.

Mounjaro KwikPen can be stored unrefrigerated below 30 ºC for up to 30 days after first use and then the pen must be discarded.

Do not use this medicine if you notice that the pen is damaged, or the medicine is cloudy, discoloured or has particles in it.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Mounjaro KwikPen contains
The active substance is tirzepatide.

Mounjaro 2.5 mg/dose KwikPen: Each dose contains 2.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 10 mg of tirzepatide in 2.4 ml (4.17 mg/ml). Each pen delivers 4 doses of 2.5 mg.
Mounjaro 5 mg/dose KwikPen: Each dose contains 5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 20 mg of tirzepatide in 2.4 ml (8.33 mg/ml). Each pen delivers 4 doses of 5 mg.
Mounjaro 7.5 mg/dose KwikPen: Each dose contains 7.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 30 mg of tirzepatide in 2.4 ml (12.5 mg/ml). Each pen delivers 4 doses of 7.5 mg.
Mounjaro 10 mg/dose KwikPen: Each dose contains 10 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 40 mg of tirzepatide in 2.4 ml (16.7 mg/ml). Each pen delivers 4 doses of 10 mg.
Mounjaro 12.5 mg/dose KwikPen: Each dose contains 12.5 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 50 mg of tirzepatide in 2.4 ml (20.8 mg/ml). Each pen delivers 4 doses of 12.5 mg.
Mounjaro 15 mg/dose KwikPen: Each dose contains 15 mg of tirzepatide in 0.6 ml solution. Each multi-dose pre-filled pen contains 60 mg of tirzepatide in 2.4 ml (25 mg/ml). Each pen delivers 4 doses of 15 mg.

The other ingredients are disodium hydrogen phosphate heptahydrate (E339), benzyl alcohol (E1519) (see section 2 under ‘Mounjaro KwikPen contains benzyl alcohol’ for further information), glycerol, phenol, sodium chloride, sodium hydroxide (see section 2 under ‘Mounjaro contains sodium’ for further information); concentrated hydrochloric acid and water for injections.

What Mounjaro looks like and contents of the pack
Mounjaro is a clear, colourless to slightly yellow, solution for injection in a pre-filled pen (KwikPen). Each KwikPen contains 2.4 ml solution for injection (4 doses of 0.6 ml), and excess for priming. Needles are not included.
Pack sizes of 1 and 3 KwikPens
Not all pack sizes may be available in your country.

Marketing Authorisation Holder
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Lilly France, 2, rue du Colonel Lilly, 67640 Fegersheim, France
Millmount Healthcare Limited, Block 7 City North Business Campus, Stamullen, K32 YD60, Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Instruction for use

Multi-dose pre-filled pen
Each pen contains 4 fixed doses, one dose taken weekly.

Mounjaro 2.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 7.5 mg/dose KwikPen mg solution for injection in pre-filled pen
Mounjaro 10 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 12.5 mg/dose KwikPen solution for injection in pre-filled pen
Mounjaro 15 mg/dose KwikPen solution for injection in pre-filled pen
tirzepatide

This instructions for use contains information on how to inject Mounjaro KwikPen

Important information you need to know before injecting Mounjaro KwikPen.

Read this instructions for use and the package leaflet before you start injecting Mounjaro KwikPen and each time you get another new pen**.** There may be new information. This information does not take the place of talking to your doctor, pharmacist or nurse about your medical condition or treatment.

Mounjaro KwikPen is a disposable multi-dose pre-filled pen. **The pen contains 4 fixed doses, one dose taken weekly.** Inject a single weekly injection, under the skin (subcutaneously).

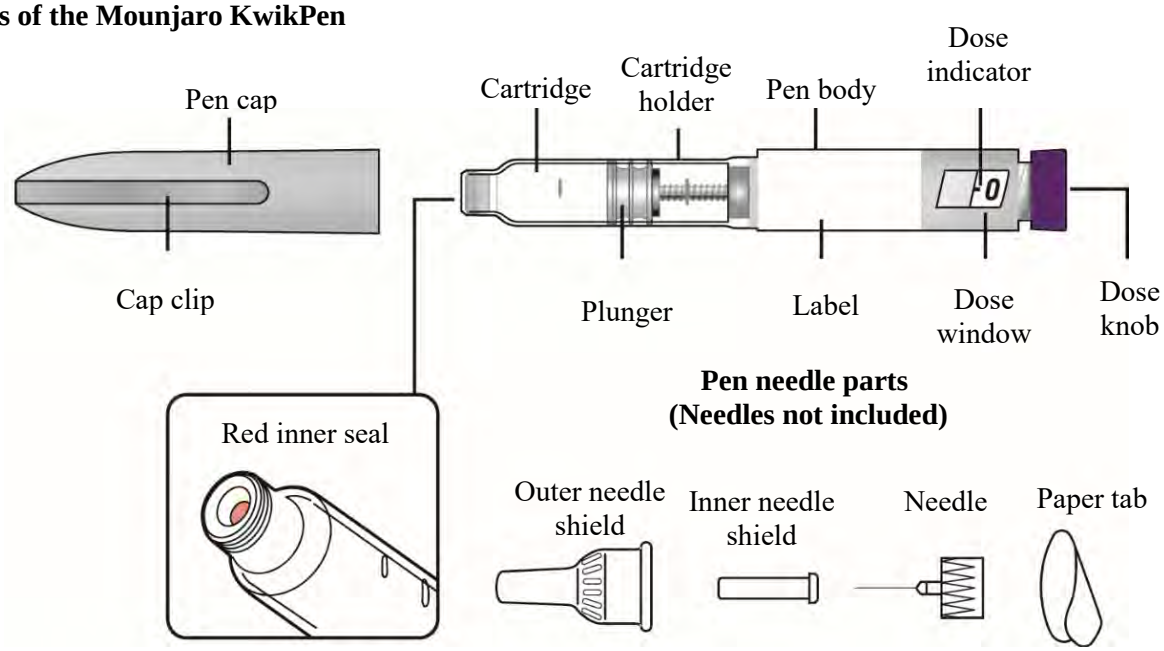
After 4 doses, throw away (discard) the pen, including the unused medicine. The pen will prevent you from dialling a full dose after you have given yourself 4 weekly doses. **Do not** inject the leftover medicine. Do not transfer the medicine from your pen into a syringe.

Do not share your Mounjaro KwikPen with other people, even if the pen needle has been changed. You may give other people a serious infection or get a serious infection from them.

People who are blind or have vision problems should not use the pen without help from a person trained to use the pen.

Guide to parts

Parts of the Mounjaro KwikPen

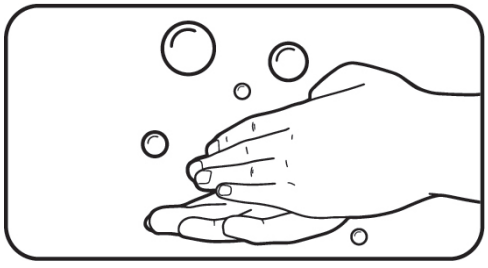


KwikPen compatible needle (If you do not know what pen needle to use, talk to your healthcare professional)

Supplies needed to give your injection

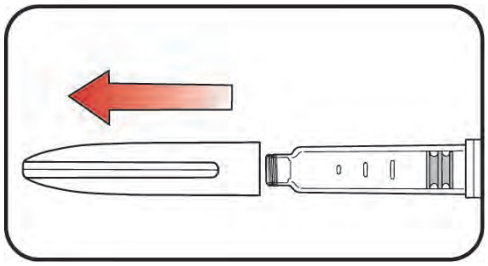
- Mounjaro KwikPen
- KwikPen compatible needle (If you do not know what pen needle to use, talk to your healthcare professional)
- Swab, gauze or cotton ball
- Sharps disposal container or household container

Preparing to inject Mounjaro KwikPen



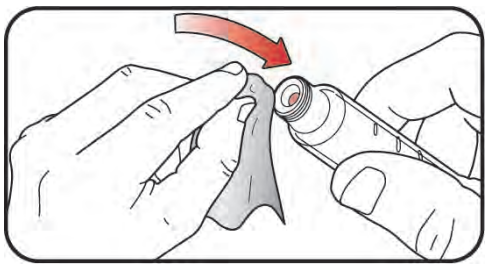
Step 1:

- Wash your hands with soap and water.



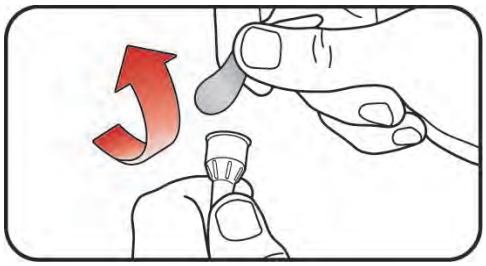
Step 2:

- Pull the pen cap straight off.
- Inspect the pen and label. **Do not** use if:
  - the medicine name or dose strength does not match your prescription.
  - the pen is expired (EXP) or looks damaged.
  - the medicine has been frozen, has particles, is cloudy, or is discoloured. Mounjaro should be colourless to slightly yellow.



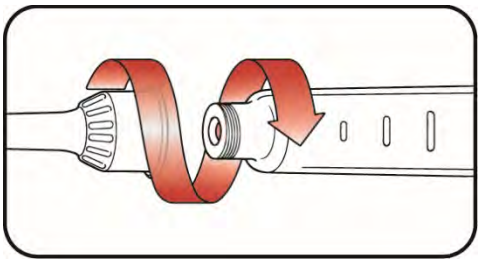
Step 3:

- Wipe the red inner seal with a swab.



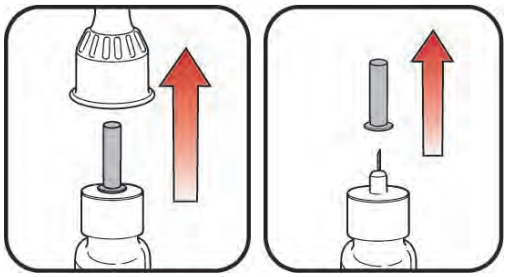
Step 4:

- **Select a new pen needle.** Always use a new pen needle for each injection to help prevent infections and blocked needles.
- Pull off the paper tab from the outer needle shield.



Step 5:

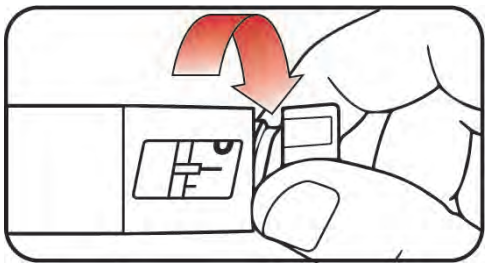
- Push the capped needle straight onto the pen and twist the needle on until it is tight.



a. Outer needle shield **b. Inner needle shield**

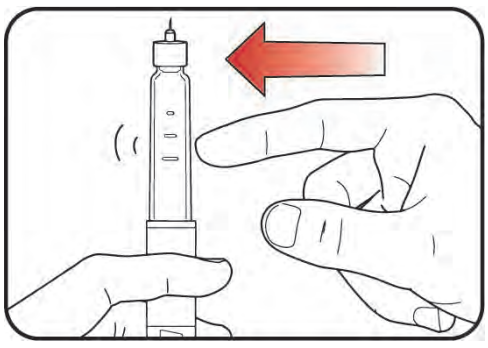
Step 6:

a. Pull off the outer needle shield and keep it. This will be reused.
b. Pull off the inner needle shield and throw it away.



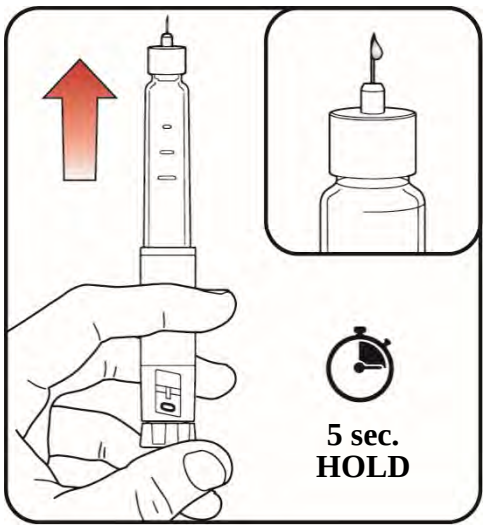
Step 7:

- Slowly turn the dose knob until you hear **2 clicks** and the  extended line is shown in the dose window. This is the prime position. It can be corrected by turning the dose knob in either direction until the prime position lines up to the dose indicator.



Step 8:

- Hold your pen with the needle pointing up.
- Tap the cartridge holder gently to collect air bubbles at the top.

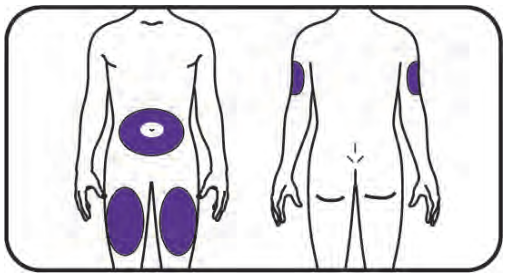


Step 9:

- Release some medicine into the air by **pushing the dose knob in** until it stops, then **slowly count to 5 while holding the dose knob**. The 0 icon must be shown in the dose window. **Do not** inject into your body.

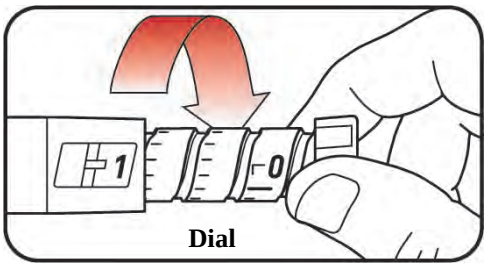
  Priming removes air from the cartridge and makes sure that your pen is working correctly. Your pen has been primed if a small amount of medicine comes out of the tip of the pen needle.
  - If you do not see medicine, repeat **steps 7-9**, no more than 2 additional times.
  - If you still do not see medicine, then change the pen needle and repeat **steps 7-9**, no more than 1 additional time.
  - If you still do not see medicine, contact your local Lilly office listed in the patient information leaflet.

Injecting Mounjaro KwikPen



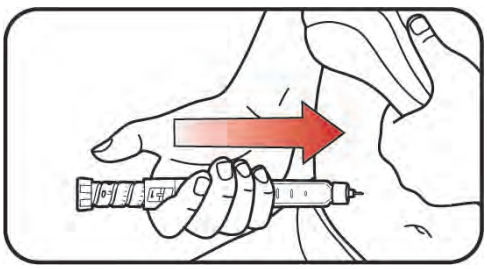
Step 10:

- Choose an injection site.
  - **a.** You or another person can inject the medicine in your thigh or stomach (abdomen) at least 5 cm from the belly button.
  - **b.** Another person should give you the injection in the back of your upper arm.
- **Change** your injection site each week. You may use the same area of your body but be sure to choose a different injection site in that area.



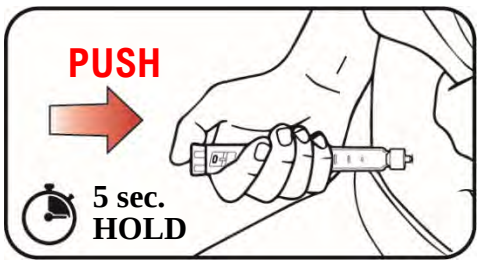
Step 11:

- Turn the dose knob until it stops and the 1 icon is shown in the dose window. **The 1 icon is equal to a full dose.**

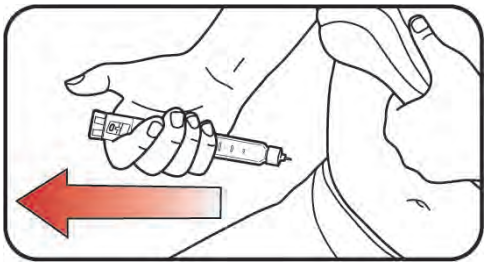


Step 12:

- **a.** Insert the needle into your skin.



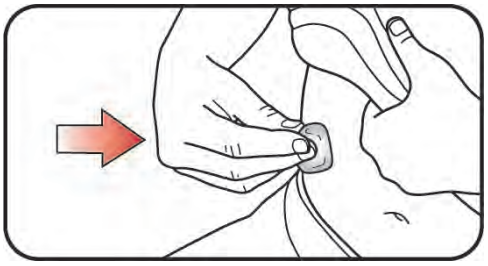
b. Inject the medicine by **pushing the dose knob in** until it stops then **slowly count to 5 while holding the dose knob**. The 0 icon must be shown in the dose window before removing the needle.



Step 13:

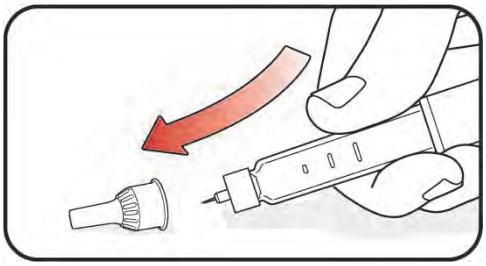
- Pull the needle out of your skin. A drop of medicine on the needle tip is normal. It will not affect your dose.
- Confirm the 0 icon is in the dose window. If you see the 0 icon in the window, you have received the full dose.
  If you do not see the 0 icon in the dose window, insert the needle back into your skin and finish your injection. **Do not** redial the dose.
  If you still do not think you received the full dose, **do not** start over or repeat the injection. Contact your local Lilly office listed in the patient information leaflet.

After your Mounjaro KwikPen injection



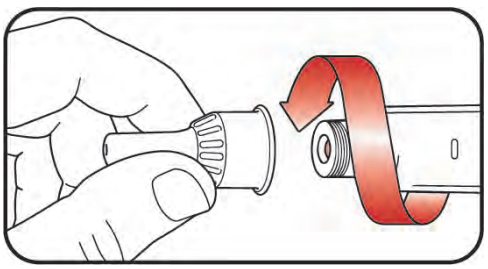
Step 14:

- If you see blood after you pull the needle out of your skin, lightly press the injection site with gauze or a cotton ball. **Do not** rub the injection site.



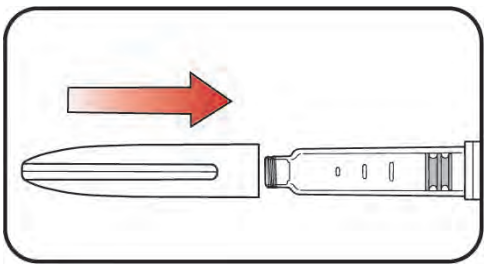
Step 15:

- Carefully replace the outer needle shield.



Step 16:

- Unscrew the capped needle and put the needle in a sharps disposal container (see “Disposing of Mounjaro KwikPen and pen needles”).
  Do not store the pen with the needle attached to prevent leaking, blocking the needle, and air from entering the pen.



Step 17:

- Replace the pen cap.
  Do not store the pen without the pen cap attached.

Storing your Mounjaro KwikPen

Unused pens:

- Store **unused pens** in the **refrigerator** between 2°C to 8°C.
- Unused pens may be used until the expiration date printed on the label if the pen has been kept in the refrigerator.
- **Do not** freeze your pen. Throw away (dispose) the pen if it has been frozen.

Used pens:

- You may store your **used pen** at **room temperature** below 30°C after your injection.
- Keep your pen and needles out of the sight and reach of children.
- Dispose of the pen 30 days after first use even though the pen has medicine left in it.
- Dispose of the pen after receiving 4 weekly doses. Attempting to inject any leftover medicine could result in an incomplete dose even though the pen still has medicine left in it.

Disposing of Mounjaro KwikPen and pen needles

- Put your used pen needles in a sharps disposal container or a hard plastic container with a secure lid.
- **Do not** throw away (dispose) loose pen needles in your household waste.
- Dispose of the used pen as instructed by your healthcare professional.
- Ask your healthcare professional about options to dispose of the sharps disposal container properly.
- Do not recycle your used sharps disposal container.

Commonly asked questions

- If you cannot remove the pen cap, gently twist the pen cap back and forth, and then pull the pen cap straight off.
- If the dose knob is hard to push:
  – pushing the dose knob more slowly will make it easier to inject.
  – your needle may be blocked. Put on a new needle and prime the pen.
  – you may have dust, food, or liquid inside the pen. Throw the pen away and get a new pen.

Additional information

If you have any questions or problems with Mounjaro KwikPen:

- Contact Lilly or your doctor, nurse or pharmacist.

Medicine calendar

Use Mounjaro KwikPen 1 time a week. Write the day of the week you choose to inject. Inject on this day each week (Example: Monday).	I inject my weekly dose on the dates below. (Day/Month)	(Day/Month)	(Day/Month)	(Day/Month)

Last revised in

Tirzepatide: Core Data Sheet

ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

1.7　同種同効品一覧表

日本イーライリリー株式会社

目次

1.7　同種同効品一覧表

本剤は、グルコース依存性インスリン分泌刺激ポリペプチド（glucose-dependent insulinotropic polypeptide：GIP）受容体及びグルカゴン様ペプチド-1（glucagon-likepeptide-1：GLP-1）受容体の両方に結合するアゴニストである。現時点で、肥満症を適応とするGIP/GLP-1 受容体作動薬として承認されている他の薬剤はないため、本剤の同種同効品として、現在承認されている GLP-1 受容体作動薬である「ウゴービ皮下注 0.25mg SD、同皮下注 0.5mg SD、同皮下注 1.0mg SD、同皮下注 1.7mg SD、及び同皮下注 2.4mg SD」、また、薬理作用は異なるが、高度肥満症に対する治療薬である「サノレックス錠 0.5mg」を表 1.7-1 に示す。

表 1.7-1　同種同効品一覧表

販売名	ゼップバウンド皮下注 2.5mg アテオス ゼップバウンド皮下注 5mg アテオス ゼップバウンド皮下注 7.5mg アテオス ゼップバウンド皮下注 10mg アテオス ゼップバウンド皮下注 12.5mg アテオス ゼップバウンド皮下注 15mg アテオス	ウゴービ皮下注 0.25mg SD ウゴービ皮下注 0.5mg SD ウゴービ皮下注 1.0mg SD ウゴービ皮下注 1.7mg SD ウゴービ皮下注 2.4mg SD	サノレックス錠 0.5mg
一般名	チルゼパチド	セマグルチド（遺伝子組換え）	マジンドール
会社名	日本イーライリリー株式会社	ノボ ノルディスク ファーマ株式会社	富士フイルム富山化学株式会社
効能又は効果	肥満症 ただし、高血圧、脂質異常症又は 2 型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。 ・BMI が 27kg/m^2 以上であり、2 つ以上の肥満に関連する健康障害を有する ・BMI が 35kg/m^2 以上	肥満症 ただし、高血圧、脂質異常症又は 2 型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。 ・BMI が 27kg/m^2 以上であり、2 つ以上の肥満に関連する健康障害を有する ・BMI が 35kg/m^2 以上	あらかじめ適用した食事療法及び運動療法の効果が不十分な高度肥満症（肥満度が+70%以上又は BMI が 35 以上）における食事療法及び運動療法の補助
添付文書改訂日	-	2023 年 11 月改訂	2024 年 8 月改訂

*2023 年 11 月改訂（第 2 版）
2023 年 3 月作成（第 1 版）

貯　　法：凍結を避け、2～8℃に保存
有効期間：24 ヵ月

日本標準商品分類番号	872499

	承認番号	販売開始
0.25mg	30500AMX00105000	2024 年 2 月
0.5mg	30500AMX00106000	
1.0mg	30500AMX00107000	
1.7mg	30500AMX00108000	
2.4mg	30500AMX00109000	

肥満症治療剤 持続性 GLP-1 受容体作動薬
セマグルチド（遺伝子組換え）

ウゴービ® 皮下注 0.25mg SD
ウゴービ® 皮下注 0.5mg SD
ウゴービ® 皮下注 1.0mg SD
ウゴービ® 皮下注 1.7mg SD
ウゴービ® 皮下注 2.4mg SD

劇薬
処方箋医薬品注）

最適使用推進ガイドライン対象品目

Wegovy® Subcutaneous Injection SD

注）注意-医師等の処方箋により使用すること

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 糖尿病性ケトアシドーシス、糖尿病性昏睡又は前昏睡、1 型糖尿病の患者［インスリン製剤による速やかな治療が必須となるので、本剤を投与すべきでない。］
2.3 2 型糖尿病を有する患者における重症感染症、手術等の緊急の場合［インスリン製剤による血糖管理が望まれるので、本剤の投与は適さない。］

3. 組成・性状

3.1 組成

1 筒

製剤		ウゴービ皮下注 SD				
		0.25mg	0.5mg	1.0mg	1.7mg	2.4mg
容量	1 筒	0.5mL	0.5mL	0.5mL	0.75mL	0.75mL
有効成分	セマグルチド（遺伝子組換え）	0.25mg	0.5mg	1.0mg	1.7mg	2.4mg
添加剤	リン酸水素二ナトリウム二水和物	0.71mg	0.71mg	0.71mg	1.07mg	1.07mg
	塩化ナトリウム	4.13mg	4.13mg	4.13mg	6.19mg	6.19mg
	水酸化ナトリウム	適量				
	塩酸	適量				

本剤は出芽酵母を用いて製造される。

3.2 製剤の性状

製剤	ウゴービ皮下注 SD				
	0.25mg	0.5mg	1.0mg	1.7mg	2.4mg
形態	固定注射針付きシリンジを注入器にセットした単回使用のコンビネーション製品				
識別（カラー帯の色）	ライトグリーン	ディープピンク	ブラウン	クールブルー	チャコールグレー
剤形・性状	注射剤 無色～ほぼ無色の液である。				
pH	7.10～7.70				
浸透圧比（生理食塩液に対する比）	約 1				

4. 効能又は効果

肥満症
ただし、高血圧、脂質異常症又は 2 型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。
- **BMI が 27kg/m² 以上であり、2 つ以上の肥満に関連する健康障害を有する**
- **BMI が 35kg/m² 以上**

5. 効能又は効果に関連する注意

本剤の適用にあたっては、あらかじめ肥満症治療の基本である食事療法・運動療法を行っても、十分な効果が得られない場合で、薬物治療の対象として適切と判断された患者のみを対象とすること。肥満に関連する健康障害は、臨床試験に組み入れられた患者背景を参考に判断すること。［17.1.1 参照］

6. 用法及び用量

通常、成人には、セマグルチド（遺伝子組換え）として 0.25mg から投与を開始し、週 1 回皮下注射する。その後は 4 週間の間隔で、週 1 回 0.5mg、1.0mg、1.7mg 及び 2.4mg の順に増量し、以降は 2.4mg を週 1 回皮下注射する。なお、患者の状態に応じて適宜減量する。

7. 用法及び用量に関連する注意

7.1 本剤は週 1 回投与する薬剤であり、同一曜日に投与させること。
7.2 胃腸障害等の発現により忍容性が得られない場合は減量又は漸増の延期を検討すること。
7.3 投与を忘れた場合は、次回投与までの期間が 2 日間（48 時間）以上であれば、気づいた時点で直ちに投与し、その後はあらかじめ定めた曜日に投与すること。次回投与までの期間が 2 日間（48 時間）未満であれば投与せず、次のあらかじめ定めた曜日に投与すること。なお、週 1 回投与の定めた曜日を変更する必要がある場合は、前回投与から少なくとも 3 日間（72 時間）以上間隔を空けること。

8. 重要な基本的注意

8.1 本剤投与中は食事療法・運動療法を継続すること。定期的に体重、血糖、血圧、脂質等を確認し、3～4ヵ月間投与しても改善傾向が認められない場合には、本剤の投与を中止すること。その後も定期的に体重、血糖、血圧、脂質等を確認して患者の状態を十分に観察し、効果が不十分な場合には本剤の投与中止を検討すること。

8.2 本剤は持続性製剤であり、本剤中止後も効果が持続する可能性があるため、副作用予防、副作用発現時の処置について十分留意すること。［16.1 参照］

8.3 急性膵炎の初期症状（嘔吐を伴う持続的な激しい腹痛等）があらわれた場合は、使用を中止し、速やかに医師の診断を受けるよう指導すること。［9.1.1、11.1.2 参照］

8.4 胃腸障害が発現した場合、急性膵炎の可能性を考慮し、必要に応じて画像検査等による原因精査を考慮する等、慎重に対応すること。［9.1.1、11.1.2 参照］

8.5 下痢、嘔吐から脱水を続発し、急性腎障害に至るおそれがあるので、患者の状態に注意すること。

8.6 本剤投与中は、甲状腺関連の症候の有無を確認し、異常が認められた場合には、専門医を受診するよう指導すること。［15.2 参照］

8.7 胆石症、胆嚢炎、胆管炎又は胆汁うっ滞性黄疸が発現するおそれがあるので、腹痛等の腹部症状がみられた場合には、必要に応じて画像検査等による原因精査を考慮するなど、適切に対応すること。［11.1.3 参照］

8.8 本剤の自己注射にあたっては、以下の点に留意すること。

・投与法について十分な教育訓練を実施したのち、患者自ら確実に投与できることを確認した上で、医師の管理指導の下で実施すること。
・全ての器具の安全な廃棄方法について指導を徹底すること。
・添付されている取扱説明書を必ず読むよう指導すること。

8.9 本剤は血糖降下作用を有するが、インスリンの代替薬ではない。2型糖尿病を有する患者に対する本剤の投与に際しては、患者のインスリン依存状態を確認し、投与の可否を判断すること。インスリン依存状態の患者で、インスリンから GLP-1 受容体作動薬に切り替え、急激な高血糖及び糖尿病性ケトアシドーシスが発現した症例が報告されている。

8.10 本剤の使用にあたっては、患者に対し、低血糖症状及びその対処方法について十分説明すること。［9.1.3、11.1.1 参照］

8.11 低血糖症状を起こすことがあるので、高所作業、自動車の運転等に従事している患者に投与するときには注意すること。［11.1.1 参照］

8.12 急激な血糖コントロールの改善に伴い、糖尿病網膜症の顕在化又は増悪があらわれることがあるので、注意すること。

8.13 本剤はセマグルチド（遺伝子組換え）を含有しているため、オゼンピック等他のセマグルチド（遺伝子組換え）含有製剤あるいはその他の GLP-1 受容体作動薬等の GLP-1 受容体に対するアゴニスト作用を有する薬剤と併用しないこと。

8.14 本剤と DPP-4 阻害剤はいずれも GLP-1 受容体を介した血糖降下作用を有している。2 型糖尿病を有する患者において両剤を併用した際の臨床試験成績はなく、有効性及び安全性は確認されていない。

8.15 2 型糖尿病を有する患者において 1.0mg を超えるセマグルチド（遺伝子組換え）皮下投与製剤とインスリン製剤との併用における有効性及び安全性は検討されていない。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 膵炎の既往歴のある患者

［8.3、8.4、11.1.2 参照］

9.1.2 重度胃不全麻痺等、重度の胃腸障害のある患者

十分な使用経験がなく、胃腸障害の症状が悪化するおそれがある。

9.1.3 低血糖を起こすおそれがある以下の患者又は状態

・脳下垂体機能不全又は副腎機能不全
・栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態
・激しい筋肉運動
・過度のアルコール摂取者

［8.10、11.1.1 参照］

9.4 生殖能を有する者

2ヵ月以内に妊娠を予定する女性では本剤の投与を中止すること。［9.5 参照］

9.5 妊婦

妊婦、妊娠している可能性のある女性には本剤を投与しないこと。動物試験において、臨床用量に相当する又は下回る用量（最大臨床用量での AUC 比較においてラットで約 0.1 倍、ウサギで約 0.1 倍、サルで約 1.1～1.7 倍）で、胎児毒性（ラット：胚生存率の減少、胚発育の抑制、骨格及び血管異常の発生頻度増加[1]、ウサギ：早期妊娠損失、骨格異常及び内臓異常の発生頻度増加[2]、サル：早期妊娠損失、外表異常及び骨格異常の発生頻度増加[3][4]）が認められている。これらの所見は母動物の体重減少を伴うものであった。［9.4 参照］

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。

ラットで乳汁中への移行が報告されている。ヒトでの乳汁移行に関するデータ及びヒトの哺乳中の児への影響に関するデータはない。

9.7 小児等

小児等を対象とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。［16.6.3 参照］

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
糖尿病用薬 ビグアナイド系薬剤 スルホニルウレア剤 速効型インスリン分泌促進剤 α-グルコシダーゼ阻害剤 チアゾリジン系薬剤 DPP-4 阻害剤 SGLT2 阻害剤 インスリン製剤 等 ［11.1.1 参照］	低血糖症の発現に注意すること。特に、インスリン製剤又はスルホニルウレア剤と併用する場合、低血糖のリスクが増加するおそれがあるため、定期的な血糖測定を行い、必要に応じ、これらの薬剤の減量を検討すること。	血糖降下作用が増強される。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 低血糖（頻度不明）

脱力感、倦怠感、高度の空腹感、冷汗、顔面蒼白、動悸、振戦、頭痛、めまい、嘔気、視覚異常等の低血糖症状があらわれることがある。また、2 型糖尿病患者においてインスリン製剤又はスルホニルウレア剤との併用時に重篤な低血糖症状があらわれ意識消失を来す例も報告されている。

低血糖症状が認められた場合には、糖質を含む食品を摂取するなど適切な処置を行うこと。ただし、α-グルコシダーゼ阻害剤との併用時はブドウ糖を投与すること。また、患者の状態に応じて、本剤あるいは併用している糖尿病用薬を減量するなど適切な処置を行うこと。［8.10、8.11、9.1.3、10.2、17.1.1、17.1.3 参照］

11.1.2 急性膵炎（0.1%）

嘔吐を伴う持続的な激しい腹痛等、異常が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。また、膵炎と診断された場合は、再投与は行わないこと。［8.3、8.4、9.1.1 参照］

11.1.3 胆嚢炎、胆管炎、胆汁うっ滞性黄疸（いずれも頻度不明）

［8.7 参照］

11.2 その他の副作用

	5%以上	1～5%未満	0.5～1%未満	頻度不明
感染症		胃腸炎		
代謝及び栄養障害	食欲減退			
神経系障害	頭痛	浮動性めまい、味覚不全		
眼障害				糖尿病網膜症
心臓障害				心拍数増加[注1]
胃腸障害	悪心、下痢、嘔吐、便秘、消化不良、おくび、腹痛、腹部膨満	腹部不快感、胃食道逆流性疾患、鼓腸、胃炎、胃酸過多、口内乾燥	胃腸障害	胃排出遅延
肝胆道系障害				胆石症
全身障害及び投与部位状態		注射部位反応、疲労、無力症、早期満腹	倦怠感	
皮膚及び皮下組織障害		脱毛症		
精神障害			不眠症	
臨床検査[注2]			リパーゼ増加	アミラーゼ増加

注 1：心拍数の増加が持続的にみられた場合には患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

注 2：これらの臨床検査値の変動に関連した症状は認められなかった。

14. 適用上の注意

14.1 薬剤投与前の注意

注入器の破損又は異常がないこと、薬液が無色澄明で浮遊物がないことを確認した上で使用すること。

14.2 薬剤投与時の注意

14.2.1 投与部位

皮下注射は、腹部、大腿、上腕に行う。注射箇所は毎回変更し、少なくとも前回の注射箇所より 2～3cm 離すこと。

14.2.2 投与経路

静脈内及び筋肉内に投与しないこと。

14.2.3 その他

(1) 本剤は単回使用の製剤である。

(2) 本剤は他の製剤との混合により、成分が分解するおそれがあるため、本剤と他の製剤を混合しないこと。

15. その他の注意

15.2 非臨床試験に基づく情報

ラット[5]及びマウス[6]における 2 年間がん原性試験において、臨床用量を下回る用量（最大臨床用量での AUC 比較においてラットでは定量下限未満のため算出できず、マウスで約 0.5 倍）で、甲状腺 C 細胞腫瘍の発生頻度の増加が認められたとの報告がある。

甲状腺髄様癌の既往のある患者及び甲状腺髄様癌又は多発性内分泌腫瘍症 2 型の家族歴のある患者に対する、本剤の安全性は確立していない。［8.6 参照］

16. 薬物動態

16.1 血中濃度

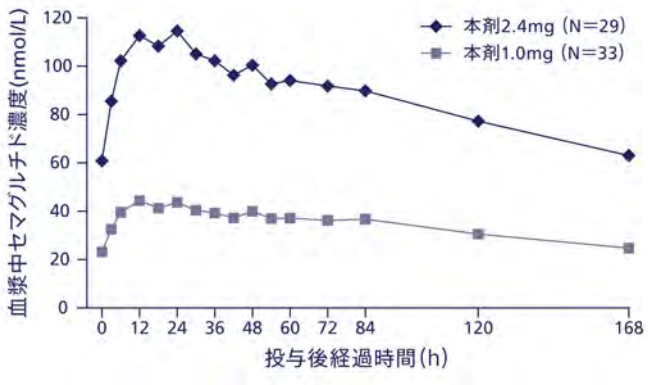
肥満者を対象に本剤を週 1 回、21 週間反復皮下投与後の薬物動態プロファイルを検討した。本剤は、週 1 回 0.25mg で投与を開始し、4 週間間隔で 0.5mg、1.0mg、1.7mg 及び 2.4mg へ増量した。定常状態における本剤 1.0mg 及び 2.4mg 投与時の薬物動態パラメータ及び血漿中濃度推移を以下に示す[7]（外国人データ）。

用量	N	$AUC_{0\text{-}168h}$ (nmol・h/L)	C_{max} (nmol/L)	t_{max}[注] (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_{ss}/F (L)
1.0mg	33	5783 (20.7)	46.8 (29.1)	18 (6-42)	—	0.042 (20.7)	—
2.4mg	29	14698 (22.6)	119 (26.3)	24 (3-48)	155 (9.8)	0.040 (22.6)	9.8 (23.4)

幾何平均（変動係数%）

CL/F：見かけの総クリアランス、V_{ss}/F：見かけの分布容積

注）中央値（最小値-最大値）



16.2 吸収

外国人健康成人 10 例に本剤 0.5mg を単回皮下投与したときの絶対的バイオアベイラビリティは、89%であった[8]。

肥満症等の被験者 2366 例（日本人 408 例）を対象とした母集団薬物動態解析の結果、本剤を異なる投与部位（腹部、大腿部及び上腕部）に投与したとき、腹部への投与に対する大腿部及び上腕部への投与での定常状態の本剤曝露量の比の推定値及び 90%信頼区間は、0.99［0.96；1.01］及び 0.99［0.95；1.03］であった。

16.3 分布

本剤の血漿中のアルブミンに対する *in vitro* 結合率は 99%超であった[9) 10)]。

16.4 代謝

^{3}H でラベル化した本剤 0.5mg を外国人健康男性被験者 7 例に単回皮下投与した結果、本剤はペプチド骨格のタンパク質分解及び脂肪酸側鎖の β 酸化により代謝されると推定された[11)]。

本剤は、CYP 分子種に対して臨床上問題となる誘導（CYP1A2、CYP2B6 及び CYP3A4/5）あるいは阻害作用（CYP1A2、CYP2B6、CYP2C8、CYP2C9、CYP2C19、CYP2D6 及び CYP3A4/5）を示さなかった[12) 13)]（外国人データ、*in vitro* 試験）。

16.5 排泄

^{3}H でラベル化した本剤 0.5mg を外国人健康男性被験者 7 例に単回皮下投与した結果、最大 56 日までの総投与放射能に対する尿中及び糞中の放射能排泄率は 53.0%及び 18.6%であった。総投与放射能のうち、本剤未変化体の尿中放射能排泄率は 3.12%であった[11)]。

また、本剤は、ヒトトランスポーター（P-gp、BCRP、OATP1B1、OATP1B3、OAT1、OAT3 及び OCT2）に対して臨床上問題となる阻害作用を示さなかった[14)]（外国人データ、*in vitro* 試験）。

16.6 特定の背景を有する患者

16.6.1 腎機能障害被験者における薬物動態

腎機能障害の程度の異なる被験者（クレアチニンクリアランス（Ccr）による分類）における本剤 0.5mg 単回皮下投与後の薬物動態を、腎機能が正常な被験者（Ccr 80mL/min 超）と比較検討した結果を以下に示す[9]（外国人データ）。

腎機能	AUC_{0-inf}	C_{max}
	比の推定値［95%信頼区間］	比の推定値［90%信頼区間］
軽度/正常（軽度：Ccr 50 超～80mL/min）	0.99［0.85；1.16］	0.90［0.73；1.11］
中等度/正常（中等度：Ccr 30 超～50mL/min）	1.07［0.91；1.27］	0.79［0.64；0.99］
重度/正常（重度：Ccr 30mL/min 以下）	1.13［0.97；1.32］	0.86［0.70；1.06］
末期/正常（末期：血液透析を必要とする被験者）	1.10［0.94；1.28］	0.82［0.66；1.01］

被験者数：正常 14 例、軽度 10 例、中等度 11 例、重度 10 例、末期 9 例

注：比の推定値及び 95%信頼区間又は 90%信頼区間は、年齢、性別及び体重で調整した事後解析に基づく。

肥満症等の被験者 2366 例（日本人 408 例）を対象とした母集団薬物動態解析の結果、腎機能が正常な被験者に対する軽度腎機能障害を有する被験者及び中等度腎機能障害を有する被験者の定常状態の本剤曝露量の比の推定値及び 90%信頼区間は、1.04［1.02；1.06］及び 1.07［1.02；1.11］であった。

16.6.2 肝機能障害被験者における薬物動態

肝機能障害の程度の異なる被験者（Child-Pugh scores に基づく分類）における本剤 0.5mg 単回皮下投与後の薬物動態を、肝機能が正常な被験者と比較検討した結果を以下に示す[10]（外国人データ）。

肝機能	AUC_{0-inf}	C_{max}
	比の推定値［90%信頼区間］	比の推定値［90%信頼区間］
軽度/正常（軽度：Child-Pugh 分類 A）	0.95［0.77；1.16］	0.99［0.80；1.23］
中等度/正常（中等度：Child-Pugh 分類 B）	1.02［0.93；1.12］	1.02［0.88；1.18］
重度/正常（重度：Child-Pugh 分類 C）	0.97［0.84；1.12］	1.15［0.89；1.48］

被験者数：正常 18 例、軽度 8 例、中等度 10 例、重度 7 例

注：比の推定値及び 90%信頼区間は、年齢、性別及び体重で調整した。

16.6.3 高齢者における薬物動態

肥満症等の被験者 2366 例（日本人 408 例）を対象とした母集団薬物動態解析の結果、18 歳以上～65 歳未満の被験者に対する 65 歳以上～75 歳未満及び 75 歳以上の被験者の定常状態の本剤曝露量の比の推定値及び 90%信頼区間は、0.98［0.96；1.01］及び 0.96［0.89；1.02］であった。

16.7 薬物相互作用

本剤 1.0mg 又は 2.4mg の定常状態において、メトホルミン、ワルファリン、ジゴキシン、アトルバスタチン、経口避妊薬及びアセトアミノフェンを併用投与したときの薬物動態の結果を以下に示す[15)～18)]（外国人データ）。

経口薬	用量[a] mg		対象	N	AUC[b]比[c] ［90%信頼区間］[e]	C_{max} 比[c] ［90%信頼区間］[e]	t_{max} 差[d] ［90%信頼区間］
	併用薬	本剤					
ﾒﾄﾎﾙﾐﾝ	500	1.0	健康被験者	22	1.03［0.96；1.11］	0.90［0.83；0.98］	0.50［-0.38；1.25］
S-ﾜﾙﾌｧﾘﾝ	25		健康被験者	22	1.05［0.99；1.11］	0.91［0.85；0.98］	2.00［1.25；2.75］
R-ﾜﾙﾌｧﾘﾝ	25		健康被験者	22	1.04［0.98；1.10］	0.93［0.87；1.00］	1.75［0.88；2.50］
ｼﾞｺﾞｷｼﾝ	0.5		健康被験者	26	1.02［0.97；1.08］	0.93［0.84；1.03］	0.25［0.00；0.25］
ｱﾄﾙﾊﾞｽﾀﾁﾝ	40		健康被験者	26	1.02［0.93；1.12］	0.62［0.47；0.82］	1.75［1.00；2.50］
ｴﾁﾆﾙｴｽﾄﾗｼﾞｵｰﾙ	0.03		2型糖尿病	37	1.11［1.06；1.15］	1.04［0.98；1.10］	0.50［0.00；0.50］
ﾚﾎﾞﾉﾙｹﾞｽﾄﾚﾙ	0.15		2型糖尿病	40	1.20［1.15；1.26］	1.05［0.99；1.12］	0.50［0.25；0.75］
ﾊﾟﾗｾﾀﾓｰﾙ（ｱｾﾄｱﾐﾉﾌｪﾝ）	1500	1.0	肥満被験者	28	0.94［0.88；1.01］	0.77［0.67；0.88］	0.25［0.13；0.25］
	1500	2.4	肥満被験者	35	1.08［1.02；1.14］	0.94［0.82；1.07］	0.00［0.00；0.02］

注：a. 本剤：開始用量は 0.25mg。1.0mg の維持用量へは、0.25mg を 4 回、0.5mg を 4 回投与した後に増量し、2.4mg の維持用量へは 0.25mg を 4 回、0.5mg を 4 回、1.0mg を 4 回、1.7mg を 4 回投与した後に増量した。薬物相互作用は本剤 1.0mg を 4 回投与した後又は 2.4mg を 4 回投与した後に評価した。
併用薬：ﾜﾙﾌｧﾘﾝ、ｼﾞｺﾞｷｼﾝ、ｱﾄﾙﾊﾞｽﾀﾁﾝ及びﾊﾟﾗｾﾀﾓｰﾙは単回投与、ﾒﾄﾎﾙﾐﾝ（1 日 2 回、3.5 日）、ｴﾁﾆﾙｴｽﾄﾗｼﾞｵｰﾙ及びﾚﾎﾞﾉﾙｹﾞｽﾄﾚﾙ（いずれも 1 日 1 回、8 日）は反復投与。

b. AUC_{0-12h}：ﾒﾄﾎﾙﾐﾝ、AUC_{0-168}：S-及び R-ﾜﾙﾌｧﾘﾝ、AUC_{0-120h}：ｼﾞｺﾞｷｼﾝ、AUC_{0-72h}：ｱﾄﾙﾊﾞｽﾀﾁﾝ、AUC_{0-24h}：ｴﾁﾆﾙｴｽﾄﾗｼﾞｵｰﾙ及びﾚﾎﾞﾉﾙｹﾞｽﾄﾚﾙ、AUC_{0-5h}：ﾊﾟﾗｾﾀﾓｰﾙ

c. 併用薬の血中濃度に基づく薬物動態パラメータの本剤非併用時に対する本剤併用時の比

d. 中央値の差（h）（本剤併用時-本剤非併用時）（事後解析）

e. ﾊﾟﾗｾﾀﾓｰﾙについては 95%信頼区間

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 プラセボ対照二重盲検比較試験（高血圧、脂質異常症又は 2 型糖尿病を有する肥満症患者、国際共同第 III 相試験）

高血圧、脂質異常症又は 2 型糖尿病を有し、かつ BMI が 27.0kg/m^2 以上で高血圧、脂質異常症もしくは 2 型糖尿病も含めて 2 つ以上の肥満に関連する健康障害[注 1)]を有する又は BMI が 35.0kg/m^2 以上の肥満症患者 401 例を対象に無作為割り付けを行い、本剤 2.4mg、本剤 1.7mg 又はプラセボを週 1 回、68 週間皮下投与した（本剤 2.4mg：199 例（日本人：179 例）、本剤 1.7mg：101 例（日本人：92 例）、プラセボ：101 例（日本人：89 例））。なお、2 型糖尿病患者については、糖尿病網膜症又は黄斑症の状態が不安定となる可能性があると判断された患者は除外された。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を並行して行った。

注 1）肥満症診療ガイドライン 2016 で定義される肥満症の診断基準に必須の 11 の疾患とされ、組み入れられた被験者の割合は次のとおり。（1）耐糖能障害（2 型糖尿病・耐糖能異常など）：2 型糖尿病 24.7%、2 型糖尿病以外 41.6%、（2）脂質異常症：86.3%、（3）高血圧：74.6%、（4）高尿酸血症・痛風：35.2%、（5）冠動脈疾患：2.5%、（6）脳梗塞：1.5%、（7）非アルコール性脂肪性肝疾患：44.6%、（8）月経異常・不妊：2.5%、（9）閉塞性睡眠時無呼吸症候群・肥満低換気症候群：10.0%、（10）運動器疾患：10.2%、（11）肥満関連腎臓病：0.2%

本剤は、週 1 回 0.25mg で投与を開始し、本剤 1.7mg 群では 4 週間ごとに段階的に 0.5mg、1.0mg、1.7mg へ、本剤 2.4mg 群では 4 週間ごとに段階的に 0.5mg、1.0mg、1.7mg、2.4mg へ増量した。

主要評価項目であるベースラインから投与 68 週時までの体重変化率及び投与 68 週時に 5%以上の体重減少を達成した被験者の割合に関して、プラセボ群に対する本剤 2.4mg 群の優越性が示された（p<0.0001、下表参照）。

	本剤 1.7mg 群（101 例）	本剤 2.4mg 群（199 例）	ﾌﾟﾗｾﾎﾞ群（101 例）
ﾍﾞｰｽﾗｲﾝの体重(kg)	86.1±11.9（101例）	86.9±16.5（199例）	90.2±15.1（101例）
投与 68 週時の体重(kg)	77.8±13.9（98例）	75.1±17.0（193例）	88.6±15.5（100例）
投与 68 週時までの体重変化率(%)	-9.9±7.8（98例）	-13.4±8.6（193例）	-1.9±5.9（100例）
ﾌﾟﾗｾﾎﾞ群との群間差[a)] ［95%信頼区間］	-7.52［-9.62；-5.43］	-11.06［-12.88；-9.24］	-
5%以上体重減少達成割合[b)]	72.4（71/98）	82.9（160/193）	21.0（21/100）
ﾌﾟﾗｾﾎﾞ群とのｵｯｽﾞ比[c)] ［95%信頼区間］	11.08［5.53；22.22］	21.72［11.27；41.86］	-

平均値±標準偏差（評価例数）、割合%（該当例数/評価例数）

a）多重補完法を用いて欠測値を補完後、共分散分析により算出

b）投与 68 週時にベースラインから 5%以上の体重減少を達成した被験者の割合

c）多重補完法を用いて欠測値を補完後、ロジスティック回帰により算出

体重に関するその他の評価項目、血糖、血圧及び脂質パラメータに関する評価項目の結果を下表に示す。

体重に関するその他の評価項目

投与 68 週時	本剤 1.7mg 群（101 例）	本剤 2.4mg 群（199 例）	ﾌﾟﾗｾﾎﾞ群（101 例）
10%以上体重減少達成割合[a)]	41.8（41/98）	60.6（117/193）	5.0（5/100）
15%以上体重減少達成割合[b)]	24.5（24/98）	40.9（79/193）	3.0（3/100）

割合%（該当例数/評価例数）

a）ベースラインから 10%以上の体重減少を達成した被験者の割合

b）ベースラインから 15%以上の体重減少を達成した被験者の割合

血糖、血圧及び脂質パラメータに関する評価項目

		本剤 1.7mg 群（101 例）	本剤 2.4mg 群（199 例）	ﾌﾟﾗｾﾎﾞ群（101 例）
HbA1c (%)	ﾍﾞｰｽﾗｲﾝ	6.4±1.1（101例）	6.4±1.2（199例）	6.4±1.1（101例）
	投与 68 週時までの変化量	-0.9±0.8（98例）	-1.0±1.0（193例）	0.0±0.8（100例）
空腹時血糖 (mg/dL)	ﾍﾞｰｽﾗｲﾝ	111.7±26.2（101例）	111.2±27.2（199例）	112.7±29.5（100例）
	投与 68 週時までの変化量	-18.3±21.9（97例）	-19.3±22.6（192例）	1.7±26.1（98例）
収縮期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	135±13（101例）	133±14（199例）	133±14（101例）
	投与 68 週時までの変化量	-12±13（98例）	-11±15（193例）	-5±15（100例）
拡張期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	85±10（101例）	83±11（199例）	86±12（101例）
	投与 68 週時までの変化量	-5±10（98例）	-5±10（193例）	-3±9（100例）

		本剤 1.7mg 群 (101 例)	本剤 2.4mg 群 (199 例)	ﾌﾟﾗｾﾎﾞ群 (101 例)
総ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	207.1±39.9 (101例)	200.4±35.6 (199例)	206.2±36.4 (101例)
	投与 68 週時 までの変化率(%)	-6.0±16.1 (98例)	-7.8±12.3 (193例)	1.2±12.2 (100例)
LDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	124.89±33.53 (101例)	120.60±31.77 (199例)	126.96±31.50 (101例)
	投与 68 週時 までの変化率(%)	-7.1±28.8 (98例)	-11.8±20.3 (193例)	-2.8±18.5 (99例)
HDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	51.7±12.3 (101例)	52.2±12.3 (199例)	49.8±10.9 (101例)
	投与 68 週時 までの変化率(%)	8.0±18.3 (98例)	9.5±15.9 (193例)	7.1±13.2 (100例)
ﾄﾘｸﾞﾘｾﾘﾄﾞ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	163.65±120.06 (101例)	140.83±68.20 (199例)	154.70±108.98 (101例)
	投与 68 週時 までの変化率(%)	-12.2±54.7 (98例)	-13.6±39.0 (193例)	13.3±42.4 (99例)

平均値±標準偏差（評価例数）

副作用は、本剤 2.4mg 群 108 例(54.3%)、本剤 1.7mg 群 68 例(68.0%)、プラセボ群 20 例（19.8%）で報告された。主な副作用（発現した被験者の割合 5%以上）は、本剤 2.4mg 群では便秘 24.1%、悪心 15.6%、下痢 13.1%、嘔吐 7.5%、食欲減退 6.5%、腹部不快感 6.0%、本剤 1.7mg では下痢 19.0%、便秘 18.0%、悪心 15.0%、腹部不快感 9.0%、嘔吐 8.0%、腹部膨満 7.0%、消化不良 6.0%、食欲減退 5.0%であった。プラセボ群では、発現した被験者の割合が 5%以上の副作用は認められなかった。2 型糖尿病を有さない被験者では低血糖に関する有害事象は報告されなかった。2 型糖尿病を有する被験者では重大な又は血糖値確定（56mg/dL 未満）症候性低血糖[注 2)]は報告されなかった[19]。[11.1.1 参照]

注 2）重大な低血糖（米国糖尿病学会分類による）又は低血糖症状を伴う血糖値（血漿）が 56mg/dL 未満の低血糖。

17.1.2 プラセボ対照二重盲検比較試験（国際共同第 III 相試験）

BMI が 27.0kg/m^2 以上で高血圧、脂質異常症、閉塞性睡眠時無呼吸症候群もしくは心血管系疾患を有する又は BMI が 30.0kg/m^2 以上の被験者 1961 例を対象に無作為割り付けを行い、本剤 2.4mg 又はプラセボを週 1 回、68 週間皮下投与した（本剤 2.4mg：1306 例（日本人：67 例）、プラセボ：655 例（日本人：33 例））。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を並行して行った。

本剤は、週 1 回 0.25mg で投与を開始し、4 週間ごとに段階的に 0.5mg、1.0mg、1.7mg、2.4mg へ増量した。

主要評価項目であるベースラインから投与 68 週時までの体重変化率及び投与 68 週時に 5%以上の体重減少を達成した被験者の割合に関して、プラセボ群に対する本剤 2.4mg 群の優越性が示された(p＜0.0001、下表参照)。

	本剤 2.4mg 群 (1306 例)	プラセボ群 (655 例)
ﾍﾞｰｽﾗｲﾝの体重(kg)	105.4±22.1 (1306 例)	105.2±21.5 (655 例)
投与 68 週時の体重(kg)	89.0±22.7 (1212 例)	101.9±22.0 (577 例)
投与 68 週時までの 体重変化率(%)	-15.6±10.1 (1212 例)	-2.8±6.5 (577 例)
ﾌﾟﾗｾﾎﾞ群との群間差 a) [95%信頼区間]	-12.44 [-13.37；-11.51]	-
5%以上体重減少達成割合 b)	86.4 (1047/1212)	31.5 (182/577)
ﾌﾟﾗｾﾎﾞ群とのｵｯｽﾞ比 c) [95%信頼区間]	11.22 [8.88；14.19]	-

平均値±標準偏差（評価例数）、割合%（該当例数/評価例数）
a) 多重補完法を用いて欠測値を補完後、共分散分析により算出
b) 投与 68 週時にベースラインから 5%以上の体重減少を達成した被験者の割合
c) 多重補完法を用いて欠測値を補完後、ロジスティック回帰により算出

体重に関するその他の評価項目、血糖、血圧及び脂質パラメータに関する評価項目の結果を下表に示す。

体重に関するその他の評価項目

投与 68 週時	本剤 2.4mg 群 (1306 例)	プラセボ群 (655 例)
10%以上体重減少達成割合 a)	69.1 (838/1212)	12.0 (69/577)
15%以上体重減少達成割合 b)	50.5 (612/1212)	4.9 (28/577)

割合%（該当例数/評価例数）
a) ベースラインから 10%以上の体重減少を達成した被験者の割合
b) ベースラインから 15%以上の体重減少を達成した被験者の割合

血糖、血圧及び脂質パラメータに関する評価項目

		本剤 2.4mg 群 (1306 例)	プラセボ群 (655 例)
HbA1c (%)	ﾍﾞｰｽﾗｲﾝ	5.7±0.3 (1306 例)	5.7±0.3 (655 例)
	投与 68 週時 までの変化量	-0.5±0.3 (1197 例)	-0.2±0.3 (563 例)
空腹時血糖 (mg/dL)	ﾍﾞｰｽﾗｲﾝ	95.4±10.7 (1291 例)	94.7±10.5 (649 例)
	投与 68 週時 までの変化量	-9.2±10.9 (1175 例)	-0.4±12.7 (557 例)
収縮期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	126±14 (1306 例)	127±14 (655 例)
	投与 68 週時 までの変化量	-7±14 (1210 例)	-1±13 (574 例)
拡張期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	80±10 (1306 例)	80±10 (655 例)
	投与 68 週時 までの変化量	-3±9 (1210 例)	-1±9 (574 例)
ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	193.4±38.7 (1301 例)	195.8±39.0 (649 例)
	投与 68 週時 までの変化率(%)	-2.6±14.8 (1196 例)	1.3±15.0 (561 例)
LDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	115.30±33.23 (1300 例)	117.14±33.33 (648 例)
	投与 68 週時 までの変化率(%)	0.0±28.1 (1192 例)	4.4±25.9 (558 例)
HDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	51.0±13.2 (1300 例)	51.0±12.7 (648 例)
	投与 68 週時 までの変化率(%)	6.6±17.2 (1192 例)	3.0±15.5 (558 例)
ﾄﾘｸﾞﾘｾﾘﾄﾞ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	140.99±80.54 (1300 例)	146.36±131.68 (649 例)
	投与 68 週時 までの変化率(%)	-17.5±32.1 (1194 例)	-2.8±33.9 (561 例)

平均値±標準偏差（評価例数）

副作用は、本剤 2.4mg 群 926 例（70.9%）、プラセボ群 295 例（45.0%）で報告された。主な副作用（発現した被験者の割合 5%以上）は、本剤 2.4mg 群では悪心 42.1%、下痢 27.5%、嘔吐 21.7%、便秘 19.8%、消化不良 9.4%、食欲減退 9.2%、おくび 8.3%、腹痛 8.0%、上腹部痛 7.9%、腹部膨満 6.6%、頭痛 6.6%、プラセボ群では悪心 15.3%、下痢 12.5%、便秘 7.5%、嘔吐 5.0%であった。

低血糖に関する有害事象は、本剤 2.4mg 群で 8 例（0.6%）15 件、プラセボ群で 5 例（0.8%）7 件報告された[20]。[11.1.1 参照]

17.1.3 プラセボ対照二重盲検比較試験（国際共同第 III 相試験）

2 型糖尿病を有する BMI が 27.0kg/m^2 以上の被験者 1210 例を対象に無作為割り付けを行い、本剤 2.4mg、本剤 1.0mg 又はプラセボを週 1 回、68 週間皮下投与した(本剤 2.4mg：404 例（日本人：42 例)、本剤 1.0mg：403 例（日本人：36 例)、プラセボ：403 例（日本人：47 例））。なお、糖尿病網膜症又は黄斑症の状態が不安定となる可能性があると判断された患者は除外された。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を並行して行った。

本剤は、週 1 回 0.25mg で投与を開始し、本剤 1.0mg 群では 4 週間ごとに段階的に 0.5mg、1.0mg へ、本剤 2.4mg 群では 4 週間ごとに段階的に 0.5mg、1.0mg、1.7mg、2.4mg へ増量した。

主要評価項目であるベースラインから投与 68 週時までの体重変化率及び投与 68 週時に 5%以上の体重減少を達成した被験者の割合に関して、プラセボ群に対する本剤 2.4mg 群の優越性が示された(p＜0.0001、下表参照)。

	本剤 1.0mg 群 (403 例)	本剤 2.4mg 群 (404 例)	プラセボ群 (403 例)
ﾍﾞｰｽﾗｲﾝの体重(kg)	99.0±21.1 (403 例)	99.9±22.5 (404 例)	100.5±20.9 (403 例)
投与 68 週時の体重(kg)	92.3±20.7 (380例)	89.6±21.0 (388 例)	96.8±20.3 (376 例)
投与 68 週時までの 体重変化率(%)	-7.2±6.6 (380 例)	-9.9±8.0 (388 例)	-3.3±5.5 (376 例)
ﾌﾟﾗｾﾎﾞ群との群間差 a) [95%信頼区間]	-	-6.21 [-7.28;-5.15]	-
本剤 1.0mg 群との群間差 a) [95%信頼区間]	-	-2.65 [-3.66;-1.64]	-
5%以上体重減少達成割合 b)	57.1 (217/380)	68.8 (267/388)	28.5 (107/376)
ﾌﾟﾗｾﾎﾞ群とのｵｯｽﾞ比 c) [95%信頼区間]	-	4.88 [3.58;6.64]	-
本剤 1.0mg 群とのｵｯｽﾞ比 c) [95%信頼区間]	-	1.62 [1.21;2.18]	-

平均値±標準偏差（評価例数）、割合%（該当例数/評価例数）
a) 多重補完法を用いて欠測値を補完後、共分散分析により算出
b) 投与 68 週時にベースラインから 5%以上の体重減少を達成した被験者の割合
c) 多重補完法を用いて欠測値を補完後、ロジスティック回帰により算出

体重に関するその他の評価項目、血糖、血圧及び脂質パラメータに関する評価項目の結果を下表に示す。

体重に関するその他の評価項目

投与 68 週時	本剤 1.0mg 群 (403 例)	本剤 2.4mg 群 (404 例)	プラセボ群 (403 例)
10%以上体重減少達成割合 a)	28.7 (109/380)	45.6 (177/388)	8.2 (31/376)
15%以上体重減少達成割合 b)	13.7 (52/380)	25.8 (100/388)	3.2 (12/376)

割合% (該当例数/評価例数)
a) ベースラインから 10%以上の体重減少を達成した被験者の割合
b) ベースラインから 15%以上の体重減少を達成した被験者の割合

血糖、血圧及び脂質パラメータに関する評価項目

		本剤 1.0mg 群 (403 例)	本剤 2.4mg 群 (404 例)	プラセボ群 (403 例)
HbA1c (%)	ﾍﾞｰｽﾗｲﾝ	8.1±0.8 (403 例)	8.1±0.8 (404 例)	8.1±0.8 (403 例)
	投与 68 週時までの変化量	-1.5±1.1 (376 例)	-1.7±1.2 (381 例)	-0.3±1.3 (374 例)
空腹時血糖 (mg/dL)	ﾍﾞｰｽﾗｲﾝ	155.7±41.5 (395 例)	152.7±40.9 (396 例)	157.9±42.1 (400 例)
	投与 68 週時までの変化量	-36.5±45.1 (367 例)	-37.9±45.9 (375 例)	-2.3±53.1 (370 例)
収縮期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	130±14 (403 例)	130±13 (404 例)	130±13 (403 例)
	投与 68 週時までの変化量	-3±15 (379 例)	-4±14 (387 例)	0±15 (376 例)
拡張期血圧 (mmHg)	ﾍﾞｰｽﾗｲﾝ	80±9 (403 例)	80±9 (404 例)	80±9 (403 例)
	投与 68 週時までの変化量	-1±9 (379 例)	-2±9 (387 例)	-1±9 (376 例)
総ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	177.0±42.5 (399 例)	175.1±38.8 (402 例)	175.4±40.8 (402 例)
	投与 68 週時までの変化率(%)	-1.2±19.6 (372 例)	0.2±18.4 (380 例)	1.8±19.0 (373 例)
LDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	96.60±35.90 (399 例)	95.87±33.23 (402 例)	95.87±33.35 (402 例)
	投与 68 週時までの変化率(%)	11.2±170.1 (372 例)	4.8±32.5 (376 例)	4.5±28.5 (369 例)
HDL ｺﾚｽﾃﾛｰﾙ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	44.2±10.9 (399 例)	46.0±10.8 (402 例)	45.1±11.4 (402 例)
	投与 68 週時までの変化率(%)	7.1±18.2 (372 例)	8.2±17.0 (375 例)	5.1±16.3 (369 例)
ﾄﾘｸﾞﾘｾﾘﾄﾞ (mg/dL)	ﾍﾞｰｽﾗｲﾝ	196.74±136.93 (399 例)	177.67±111.72 (402 例)	181.70±105.21 (402 例)
	投与 68 週時までの変化率(%)	-12.3±35.6 (372 例)	-14.0±40.5 (380 例)	1.7±57.3 (373 例)

平均値±標準偏差 (評価例数)

副作用は、本剤 2.4mg 群 257 例(63.8%)、本剤 1.0mg 群 222 例(55.2%)、プラセボ群 129 例 (32.1%) で報告された。主な副作用 (発現した被験者の割合 5%以上) は、本剤 2.4mg 群では悪心 33.3%、嘔吐 19.1%、下痢 16.9%、便秘 13.9%、食欲減退 9.4%、消化不良 5.7%、腹部膨満 5.5%、本剤 1.0mg では悪心 31.8%、下痢 17.9%、嘔吐 12.2%、便秘 10.0%、食欲減退 7.0%、消化不良 5.5%、プラセボ群では下痢 7.7%、悪心 6.7%であった。

重大な低血糖は、本剤 2.4mg 群で 1 件報告された。重大な又は血糖値確定 (56mg/dL 未満) 症候性低血糖は、本剤 2.4mg 群で 23 例 (5.7%) 51 件、本剤 1.0mg 群で 22 例 (5.5%) 29 件、プラセボ群で 12 例 (3.0%) 18 件報告された [21]。[11.1.1 参照]

18. 薬効薬理

18.1 作用機序

本剤はヒト GLP-1 アナログであり、内因性 GLP-1 が標的とする GLP-1 受容体と選択的に結合し、cAMP 放出量を増加させる GLP-1 受容体作動薬として作用する。

本剤はアルブミンと結合して代謝による分解の遅延及び腎クリアランスの低下を示すと考えられており、またアミノ酸置換により DPP-4 による分解に対して抵抗性を示すことにより、作用が持続する。

18.2 薬理作用

非臨床試験から、本剤は GLP-1 受容体を介して食事摂取の恒常的調節に関与する脳領域である視床下部及び脳幹に直接作用するものと考えられる。また、中隔、視床及び扁桃体を含む脳領域における直接的及び間接的作用を介して、報酬系にも作用する可能性もある [22]。

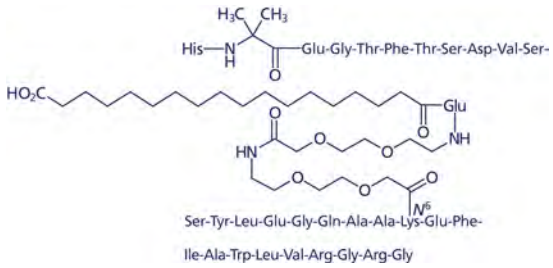
食餌誘発性肥満モデル (マウス及びラット) に本剤をそれぞれ投与した結果、溶媒群に比較して体重及び摂餌量の減少が認められた [22]。

過体重又は肥満の外国人被験者において、本剤 2.4mg (週 1 回投与) を 68 週間投与した結果、プラセボ群に比較して本剤群で体重の減少が認められ、脂肪量の減少が除脂肪体重の減少よりも大きかった [20]。

また、肥満の外国人被験者において、本剤 2.4mg (週 1 回投与) を 20 週間投与した結果、自由裁量の食事時のエネルギー摂取量がプラセボ群に比較して 35%低下した [18]。

19. 有効成分に関する理化学的知見

一般名：セマグルチド (遺伝子組換え) (JAN)
Semaglutide (Genetical Recombination) (JAN)
分子式：$C_{187}H_{291}N_{45}O_{59}$
分子量：4113.58
構造式：



本質記載：セマグルチドは、遺伝子組換えヒトグルカゴン様ペプチド-1 (GLP-1) 類縁体であり、ヒト GLP-1 の 7～37 番目のアミノ酸に相当し、2 番目の Ala 及び 28 番目の Lys は、それぞれ 2-アミノ-2-メチルプロパン酸及び Arg に置換され、1,18-オクタデカン二酸が 1 個の Glu 及び 2 個の 8-アミノ-3,6-ジオキサオクタン酸で構成されるリンカーを介して 20 番目の Lys に結合している。セマグルチドは、31 個のアミノ酸残基からなる修飾ペプチドである。

20. 取扱い上の注意

個装箱等により遮光し、凍結を避け、冷蔵庫 (2～8℃) に保管すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

〈0.25mg〉
0.5mL×2 本
〈0.5mg〉
0.5mL×2 本
〈1.0mg〉
0.5mL×2 本
〈1.7mg〉
0.75mL×2 本
〈2.4mg〉
0.75mL×2 本

23. 主要文献

1) 社内資料：ラットを用いた受胎能及び EFD 試験 (2018 年 3 月 23 日承認, CTD2.6.6.6.1)
2) 社内資料：ウサギを用いた EFD 試験 (2018 年 3 月 23 日承認, CTD2.6.6.6.2)
3) 社内資料：カニクイザルを用いた EFD 試験 (2018 年 3 月 23 日承認, CTD2.6.6.6.3)
4) 社内資料：カニクイザルを用いた EFD 及び PPND 試験 (2018 年 3 月 23 日承認, CTD2.6.6.6.3)
5) 社内資料：ラットを用いた 104 週間反復皮下投与がん原性試験 (2018 年 3 月 23 日承認, CTD2.6.6.5)
6) 社内資料：マウスを用いた 104 週間反復皮下投与がん原性試験 (2018 年 3 月 23 日承認, CTD2.6.6.5)
7) 社内資料:第 1 相臨床試験 (NN9536-4590) (2023 年 3 月 27 日承認, CTD 2.7.6.1)
8) 社内資料:第 1 相臨床試験 (NN9535-3687) (2018 年 3 月 23 日承認, CTD2.7.2.3)
9) Marbury T.C., et al. : Clin Pharmacokinet. 2017 ; 56 (11) : 1381-90
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24. 文献請求先及び問い合わせ先

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Tel 0120-180363（フリーダイアル）

25. 保険給付上の注意

本剤は新医薬品であるため、厚生労働省告示第 107 号（平成 18 年 3 月 6 日付）に基づき 2024 年 11 月末日までは、投薬は 1 回 14 日分を限度とされている。

26. 製造販売業者等

26.1 製造販売元

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＊2024年8月改訂（第2版）
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1．警告

1.1 本剤の主要な薬理学的特性はアンフェタミン類と類似しており、本剤を投与する際は、依存性について留意すること。また、海外においては食欲抑制剤の多くで数週間以内に薬物耐性がみられるとの報告がある。［11.1.1参照］

1.2 本剤の適用にあたっては、使用上の注意に留意し、用法及び用量、効能又は効果を厳守すること。

2．禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 閉塞隅角緑内障の患者［眼圧が上昇するおそれがある。］
2.3 重症の心障害のある患者［症状が悪化するおそれがある。］
2.4 重症の膵障害のある患者［インスリン分泌抑制作用を有する。］
2.5 重症の腎・肝障害のある患者［9.2.1、9.3.1参照］
2.6 重症高血圧症の患者［カテコラミンの昇圧作用を増強する。］
2.7 脳血管障害のある患者［症状が悪化するおそれがある。］
2.8 不安・抑うつ・異常興奮状態の患者及び統合失調症等の精神障害のある患者［症状が悪化するおそれがある。］
2.9 薬物・アルコール乱用歴のある患者［一般に依存性、乱用が起こりやすいと考えられる。］
＊2.10 MAO阻害剤（セレギリン塩酸塩、ラサギリンメシル酸塩及びサフィナミドメシル酸塩）投与中又は投与中止後2週間以内の患者［10.1参照］
2.11 妊婦又は妊娠している可能性のある女性［9.5参照］
2.12 小児［9.7参照］

3．組成・性状

3.1 組成

販売名	サノレックス錠0.5mg
有効成分	1錠中マジンドール0.50mg
添加剤	ステアリン酸マグネシウム、ポビドン、トウモロコシデンプン、部分アルファー化デンプン、乳糖水和物

3.2 製剤の性状

販売名	サノレックス錠0.5mg		
色・剤形	白色の素錠		
外形			
識別コード	LG		
大きさ（約）	直径：5.0mm　厚さ：2.0mm　質量：0.055g		

4．効能又は効果

あらかじめ適用した食事療法及び運動療法の効果が不十分な高度肥満症（肥満度が+70%以上又はBMIが35以上）における食事療法及び運動療法の補助

5．効能又は効果に関連する注意

5.1 肥満症治療の基本である食事療法及び運動療法をあらかじめ適用し、その効果が不十分な高度肥満症患者にのみ、本剤の使用を考慮すること。
5.2 本剤は肥満度が+70%以上又はBMIが35以上の高度肥満症であることを確認した上で適用を考慮すること。
肥満度（%）＝（実体重 - 標準体重）／標準体重×100
BMI（Body Mass Index）＝ 体重（kg）／身長（m）^{2}
5.3 内分泌性肥満、遺伝性肥満、視床下部性肥満等の症候性（二次性）肥満患者においては、原疾患の治療を優先させること。

6．用法及び用量

本剤は肥満度が+70%以上又はBMIが35以上の高度肥満症患者に対して、食事療法及び運動療法の補助療法として用いる。
通常、成人には、マジンドールとして0.5mg（1錠）を1日1回昼食前に経口投与する。1日最高投与量はマジンドールとして1.5mg（3錠）までとし、2～3回に分けて食前に経口投与するが、できる限り最小有効量を用いること。
投与期間はできる限り短期間とし、3ヵ月を限度とする。なお、1ヵ月以内に効果のみられない場合は投与を中止すること。

7．用法及び用量に関連する注意

7.1 本剤投与中に肺高血圧症があらわれたとの報告があり、また、海外で、食欲抑制剤の長期投与により肺高血圧症の発症の危険性が増加するとの報告があるので、本剤を3ヵ月を超えて投与しないこと。［11.1.2参照］
7.2 本剤は、睡眠障害を引き起こすことがあるので夕刻の投与は避けること。

8．重要な基本的注意

8.1 急激な減量による心血管系の合併症のリスクを避けるため本剤投与中は体重の推移に注意すること。
8.2 食事量、体重の推移、食生活等に留意の上、常に投与継続の可否、投与量について注意すること。
8.3 本剤投与中の患者には、自動車の運転等危険を伴う機械の操作に従事させないように注意すること。

9．特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 糖尿病の患者
インスリン、経口糖尿病剤の必要量が変化することがある。［10.2参照］

9.1.2 精神病の既往歴のある患者
症状が悪化するおそれがある。

9.1.3 てんかん又はその既往歴のある患者
本剤の副作用で痙攣が報告されており、発作を誘発するおそれがある。

9.1.4 開放隅角緑内障の患者
眼圧が上昇するおそれがある。

9.2 腎機能障害患者

9.2.1 重症の腎障害のある患者
投与しないこと。排泄が遅延するおそれがある。［2.5参照］

9.3 肝機能障害患者

9.3.1 重症の肝障害のある患者
投与しないこと。代謝又は排泄が遅延するおそれがある。［2.5参照］

9.5 妊婦

妊婦又は妊娠している可能性のある女性には投与しないこと。動物実験（ラット）で母獣に毒性のあらわれる大量投与により胎児毒性（体重増加の抑制、出生率の低下等）が報告されている。[2.11参照]

9.6 授乳婦

授乳しないことが望ましい。動物実験（ラット）で乳汁中へ移行することが報告されている。

9.7 小児等

投与しないこと。小児等を対象とした臨床試験は実施していない。[2.12参照]

9.8 高齢者

市販後調査で収集した安全性解析対象症例において、高齢者における副作用発現症例率は、65歳未満の症例に比べて高い傾向が認められている。

10. 相互作用

10.1 併用禁忌（併用しないこと）

薬剤名等	臨床症状・措置方法	機序・危険因子
＊MAO阻害剤 セレギリン塩酸塩（エフピー） ラサギリンメシル酸塩（アジレクト） サフィナミドメシル酸塩（エクフィナ） [2.10参照]	高血圧クリーゼを起こすことがあるので、MAO阻害剤投与中又はMAO阻害剤投与中止後2週間は、本剤を投与しないこと。	本剤は、交感神経刺激作用を有し、MAO阻害剤の作用を増強すると考えられる。

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
昇圧アミン アドレナリン ノルアドレナリン等	昇圧アミンの作用を増強することがあるので、観察を十分に行うこと。	本剤は神経終末におけるカテコラミンの再吸収を抑制するため、昇圧アミンの作用を増強する。
グアネチジン系薬剤 グアネチジン ベタニジン ラウオルフィア製剤 レセルピン等 クロニジン メチルドパ	降圧効果を減弱することがある。	本剤は、交感神経刺激作用を有するため、グアネチジン系薬剤、ラウオルフィア製剤、クロニジン、メチルドパの交感神経遮断作用に拮抗する。
インスリン 経口糖尿病剤 [9.1.1参照]	インスリン、経口糖尿病剤の必要量が変化することがある。	インスリン分泌抑制作用が認められること、また肥満の改善により、インスリン、経口糖尿病剤の必要量が変化するため。
アルコール（飲酒）	めまい、眠気等の副作用が増強されるおそれがある。	併用により、中枢神経系の刺激が増強されるため。
ハロゲン系吸入麻酔剤 ハロタン等	不整脈等を引き起こすおそれがある。	本剤の交感神経刺激の効果により、ハロゲン系吸入麻酔剤の心筋の感受性を高めるため。
中枢神経刺激剤 アマンタジン等	幻覚、睡眠障害等の副作用が増強されるおそれがあるので、用量に注意すること。	いずれも中枢神経刺激作用を有するため。
甲状腺ホルモン	本剤の中枢神経刺激作用を増強するおそれがある。	甲状腺ホルモンが、カテコラミンのレセプターの感受性を増大すると考えられているため。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 依存性（頻度不明）

本剤の主要な薬理学的特性はアンフェタミン類と類似しており、サルでの静脈内薬物自己摂取試験においては摂取頻度の増加がみられ、精神依存の形成が認められている。

イヌでの22ヵ月間経口投与による慢性毒性試験においては幻覚様異常行動がみられている。

この点に関し、ヒトにおける長期投与による依存性・精神症状の発現は明確ではないが、本剤を投与する際は、依存性について留意すること。アンフェタミンをはじめとする中枢興奮剤は耐性及び精神依存を形成することが知られている。[1.1参照]

11.1.2 肺高血圧症（頻度不明）

労作性呼吸困難、胸痛、失神等の症状があらわれた場合には投与を中止し、適切な処置を行うこと。[7.1参照]

11.2 その他の副作用

	5%以上[注)]	0.1%～5%未満[注)]	0.1%未満[注)]	頻度不明
精神神経系	口渇感	睡眠障害、頭痛、脱力感、めまい、けん怠感、いらいら感、眠気、ふらつき	—	神経過敏、激越、抑うつ、精神障害、振戦、幻覚、知覚異常、不安、痙攣
消化器	便秘	悪心・嘔吐、胃部不快感、腹部膨満感、腹痛、下痢	—	—
循環器	—	動悸	—	頻脈、胸痛、血圧上昇、脳卒中、狭心症、心筋梗塞、不整脈、心不全、心停止、顔面潮紅
過敏症	—	発疹	—	そう痒感
肝臓	—	AST、ALTの上昇	—	—
泌尿器	—	排尿困難	頻尿	—
その他	—	口中苦味感、発汗、性欲減退、脱毛、さむけ	咽頭不快感、月経異常	—

注）臨床試験と承認後の市販後調査を合算した発現頻度

13. 過量投与

13.1 症状

悪心、嘔吐、頭痛、頻脈、不整脈、呼吸困難、排尿障害、興奮、痙攣発作、昏睡

13.2 処置

興奮及び痙攣発作が認められる場合には、短時間作用型バルビツール酸誘導体又はベンゾジアゼピン系薬剤を投与する。

14. 適用上の注意

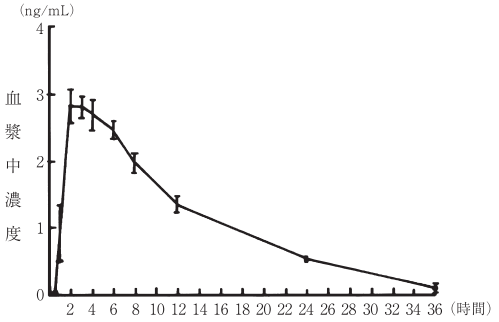
14.1 薬剤交付時の注意

PTP包装の薬剤はPTPシートから取り出して服用するよう指導すること。PTPシートの誤飲により、硬い鋭角部が食道粘膜へ刺入し、更には穿孔をおこして縦隔洞炎等の重篤な合併症を併発することがある。

16. 薬物動態

16.1 血中濃度

健康成人にマジンドール2mgを1回経口投与[注)]し、マジンドール未変化体の血漿中濃度を検討した。最高血漿中濃度は投与2時間後に得られ、その値は約2.81ng/mLであった。また、血漿中半減期は約9時間であった。



健康成人にマジンドール2mgを経口投与[注]後の平均血漿中濃度の推移（n=12、mean±S.E.）

16.5 排泄

健康成人にマジンドール2mgを1回経口投与[注]し、マジンドール未変化体の尿中排泄量を検討した。尿中排泄は投与後72時間でほぼ終了し、未変化体の総排泄量は投与量の約4.5%であった。

注）本剤の用法及び用量は、通常、1日1回0.5mgで、1日最高投与量は1.5mgである。

17．臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 国内臨床試験

二重盲検比較試験を含む本剤の臨床試験成績の概要は次のとおりである。高度肥満症患者（BMIが35以上）44例中における本剤の臨床効果判定は、食欲抑制効果及び体重減少効果等を調査して行った。全般改善度は中等度改善以上で43.2%（19/44例）、軽度改善以上で75.0%（33/44例）であった。また、プラセボを対照とした二重盲検比較試験の結果、本剤の有用性が確認された[1)~8)]。

18．薬効薬理

18.1 作用機序

本剤は、主として視床下部にある食欲中枢に作用し、摂食行動を抑制する。マジンドールは摂食調節中枢であるVMH及び視床下部外側野（LHA）への直接作用[9) 10)]及び神経終末におけるモノアミン（ノルアドレナリン、ドパミン、セロトニン）の再吸収抑制[11)~13)]を介した機序により、摂取エネルギー抑制（摂食抑制、消化吸収抑制）[14)~19)]及び消費エネルギー促進（グルコース利用、熱産生促進）[20)~22)]をもたらし、更に肥満時にみられる代謝変動を改善[16) 17) 19)]することにより肥満症を是正するものと考えられる。

18.2 摂食行動に対する作用

1回及び1日摂餌量の減少、食事後食事間間隔の延長及び体重減少が認められる（ラット）[14) 15)]。また、肥満動物モデルである視床下部腹内側核（VMH）破壊ラットにおいて正常ラットに対して影響を及ぼさない用量で摂餌量及び体重減少が認められる[16) 17)]。

18.3 消化吸収に対する作用

唾液（イヌ）及び胃酸分泌（ラット）の抑制が認められる[18)]。また、肥満動物モデルであるgoldthioglucose（GTG）投与マウスにおいて増大した小腸の絨毛表面積縮小及び消化酵素（スクラーゼ、エステラーゼ）活性の低下が認められる[19)]。

18.4 グルコース利用促進

骨格筋等へのグルコースの取り込み促進が認められ、組織におけるグルコース利用の増加が示唆されている（ラット）[20)]。

18.5 熱産生促進

ラット及び肥満型糖尿病モデルであるYellow KKマウスにおいて褐色脂肪組織（BAT）のミトコンドリア蛋白含量及びBAT熱産生能の指標であるguanosine 5'-diphosphate（GDP）結合能の増加等、BATの活性化が示唆されている[21) 22)]。

18.6 肥満時の代謝変動に対する作用

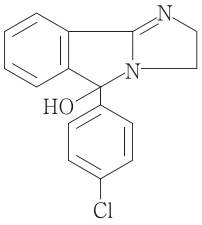
肥満時に認められる肝及び血中の脂質（コレステロール、中性脂肪、リン脂質、遊離脂肪酸等）、血中インスリン、脂肪組織重量、脂肪細胞容積等の増加を抑制する（VMH破壊ラット[16) 17)]、GTG投与マウス[19)]）。

19．有効成分に関する理化学的知見

一般名：マジンドール（Mazindol）

化学名：(±)-5-(*p*-Chlorophenyl)-2,5-dihydro-3*H*-imidazo[2,1-*a*]isoindol-5-ol

構造式：



分子式：$C_{16}H_{13}ClN_2O$

分子量：284.74

性　状：白色の結晶又は結晶性の粉末で、においはないか、又はわずかに特異なにおいがある。酢酸（100）に溶けやすく、メタノール、エタノール（95）、クロロホルム又は*N*,*N*-ジメチルホルムアミドに溶けにくく、アセトン又はジエチルエーテルに極めて溶けにくく、水又はヘキサンにはほとんど溶けない。

融　点：177～184℃（分解）

22．包装

100錠［10錠（PTP）×10］

23．主要文献

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5）井上修二：医学と薬学．1985；13（4）：837-845
6）谷口　中ほか：医学と薬学．1985；13（5）：1209-1213
7）藤岡滋典ほか：基礎と臨床．1985；19（9）：4767-4773
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10）Sikdar,S.K.et al.：Brain Res.Bull．1985；15（1）：33-38
11）Engstrom,R.G,et al.：Arch.Int.Pharmacodyn．1975；214（2）：308-321
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15）藤本一眞ほか：日薬理誌．1984；83（5）：425-432
16）井上修二ほか：日薬理誌．1984；83（5）：441-449
17）宇佐美勝ほか：日薬理誌．1985；85（4）：297-303
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20）Nagai,K.et al.：Eur.J.Pharmacol．1994；260（1）：29-37
21）Wyllie,M.G.et al.：Int.J.Obes．1984；8（Suppl.1）：85-92
22）吉田俊秀ほか：第15回日本肥満学会記録．1994；111-113

24．文献請求先及び問い合わせ先

富士フイルム富山化学株式会社　製品情報センター
電話番号　0120-502-620
〒104-0031　東京都中央区京橋2-14-1　兼松ビル

25．保険給付上の注意

本剤は厚生労働省告示第97号（平成20年3月19日付）に基づき、投薬期間は1回14日間分を限度とされている。

26．製造販売業者等

26.1 製造販売元

FUJIFILM　富士フイルム富山化学株式会社
〒104-0031　東京都中央区京橋2-14-1　兼松ビル

ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

1.8　添付文書（案）

日本イーライリリー株式会社

目次

1.8　添付文書（案）

1.8.1　添付文書（案）

ゼップバウンド皮下注 2.5mg アテオス、同 5mg アテオス、同 7.5mg アテオス、同 10mg アテオス、同 12.5mg アテオス及び同 15mg アテオスの添付文書（案）を以下に示す。

202X 年 X 月作成（第 1 版）

肥満症治療剤　持続性 GIP/GLP-1 受容体作動薬
チルゼパチド注射液

日本標準商品分類番号
87 2499

貯　　法:2～8℃で保存
有効期間:24 ヵ月

ゼップバウンド®皮下注 2.5mg アテオス®
ゼップバウンド®皮下注 5mg アテオス®
ゼップバウンド®皮下注 7.5mg アテオス®
ゼップバウンド®皮下注 10mg アテオス®
ゼップバウンド®皮下注 12.5mg アテオス®
ゼップバウンド®皮下注 15mg アテオス®

最適使用推進ガイドライン対象品目

Zepbound® Subcutaneous Injection ATEOS®

劇薬
処方箋医薬品[注)]
注）注意－医師等の処方箋により使用すること

	2.5mg	5mg	7.5mg	10mg	12.5mg	15mg
承認番号						
販売開始	－					

2. 禁忌（次の患者には投与しないこと）

2.1 本剤の成分に対し過敏症の既往歴のある患者
2.2 糖尿病性ケトアシドーシス、糖尿病性昏睡又は前昏睡、1 型糖尿病の患者［インスリン製剤による速やかな治療が必須となるので、本剤を投与すべきでない。］
2.3 2 型糖尿病を有する患者における重症感染症、手術等の緊急の場合［インスリン製剤による血糖管理が望まれるので、本剤の投与は適さない。］

3. 組成・性状

3.1 組成

販売名	有効成分	添加剤	
ゼップバウンド皮下注 2.5mg アテオス	1 キット中 チルゼパチド 2.5mg		
ゼップバウンド皮下注 5mg アテオス	1 キット中 チルゼパチド 5mg	リン酸水素二ナトリウム七水和物	0.7mg
ゼップバウンド皮下注 7.5mg アテオス	1 キット中 チルゼパチド 7.5mg	塩化ナトリウム	4.1mg
ゼップバウンド皮下注 10mg アテオス	1 キット中 チルゼパチド 10mg	塩酸	適量
ゼップバウンド皮下注 12.5mg アテオス	1 キット中 チルゼパチド 12.5mg	水酸化ナトリウム	適量
ゼップバウンド皮下注 15mg アテオス	1 キット中 チルゼパチド 15mg		

3.2 製剤の性状

販売名	形態	性状・剤形	pH	浸透圧比（生理食塩液に対する比）
ゼップバウンド皮下注 2.5mg アテオス	固定注射針付きシリンジを注入器にセットしたコンビネーション製品（キット製品）	無色～微黄色～微褐色の澄明又はわずかに乳白光を呈する液（注射剤）	6.5～7.5	約 1
ゼップバウンド皮下注 5mg アテオス				
ゼップバウンド皮下注 7.5mg アテオス				
ゼップバウンド皮下注 10mg アテオス				
ゼップバウンド皮下注 12.5mg アテオス				
ゼップバウンド皮下注 15mg アテオス				

4. 効能又は効果

肥満症
ただし、高血圧、脂質異常症又は 2 型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。
・BMI が 27kg/m² 以上であり、2 つ以上の肥満に関連する健康障害を有する
・BMI が 35kg/m² 以上

5. 効能又は効果に関連する注意

本剤の適用にあたっては、あらかじめ肥満症治療の基本である食事療法・運動療法を行っても、十分な効果が得られない場合で、薬物治療の対象として適切と判断された患者のみを対象とすること。肥満に関連する健康障害は、臨床試験に組み入れられた患者背景を参考に判断すること。［17.1.1 参照］

6. 用法及び用量

通常、成人には、チルゼパチドとして週 1 回 2.5mg から開始し、4 週間の間隔で 2.5mg ずつ増量し、週 1 回 10mg を皮下注射する。なお、患者の状態に応じて適宜増減するが、週 1 回 5mg まで減量、又は 4 週間以上の間隔で 2.5mg ずつ週 1 回 15mg まで増量できる。

7. 用法及び用量に関連する注意

7.1 本剤の用量調節に際しては、以下の点に留意すること。
・胃腸障害等の発現により忍容性が得られない患者では減量又は漸増の延期を考慮すること。
・患者の体重減少の程度や本剤に対する忍容性に応じて、週 1 回 5mg で治療を継続することも考慮すること。［17.1.2 参照］
7.2 本剤は週 1 回投与する薬剤であり、同一曜日に投与させること。
7.3 投与を忘れた場合は、次回投与までの期間が 3 日間（72 時間）以上であれば、気づいた時点で直ちに投与し、その後はあらかじめ定めた曜日に投与すること。次回投与までの期間が 3 日間（72 時間）未満であれば投与せず、次のあらかじめ定めた曜日に投与すること。なお、週 1 回投与の曜日を変更する必要がある場合は、前回投与から少なくとも 3 日間（72 時間）以上間隔を空けること。

8. 重要な基本的注意

8.1 本剤投与中は食事療法・運動療法を継続すること。定期的に体重、血糖、血圧、脂質等を確認し、本剤を 3～4 ヵ月間投与しても改善傾向が認められない場合には、本剤の投与を中止すること。本剤を 3～4 ヵ月間投与して改善傾向が認められた場合、その後も定期的に体重、血糖、血圧、脂質等を確認して患者の状態を十分に観察し、効果が不十分な場合には本剤の投与中止を検討すること。
8.2 本剤は持続性製剤であり、本剤中止後も効果が持続する可能性があるため、血糖値の変動や副作用予防、副作用発現時の処置について十分留意すること。［16.1 参照］

8.3 急性膵炎が発現することがあるので、急性膵炎の初期症状（嘔吐を伴う持続的な激しい腹痛等）があらわれた場合は、使用を中止し、速やかに医師の診断を受けるよう指導すること。［9.1.2、11.1.2 参照］
8.4 胃腸障害が発現した場合、急性膵炎の可能性を考慮し、必要に応じて画像検査等による原因精査を考慮するなど、慎重に対応すること。［9.1.2、11.1.2 参照］
8.5 下痢、嘔吐から脱水を続発し、急性腎障害に至るおそれがあるので、患者の状態に注意すること。
8.6 本剤投与中は、甲状腺関連の症候の有無を確認し、異常が認められた場合には、専門医を受診するよう指導すること。［15.2 参照］
8.7 胆石症、胆嚢炎、胆管炎又は胆汁うっ滞性黄疸が発現するおそれがあるので、腹痛等の腹部症状がみられた場合には、必要に応じて画像検査等による原因精査を考慮するなど、適切に対応すること。［11.1.3 参照］
8.8 血圧低下がみられた場合には患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。
8.9 本剤の自己注射にあたっては、患者に十分な教育訓練を実施した後、患者自ら確実に投与できることを確認した上で、医師の管理指導のもと実施すること。また、器具の安全な廃棄方法について指導を徹底すること。添付されている取扱説明書を必ず読むよう指導すること。
8.10 本剤は血糖降下作用を有するが、インスリンの代替薬ではない。2 型糖尿病を有する患者に対する本剤の投与に際しては、患者のインスリン依存状態を確認し、投与の可否を判断すること。インスリン依存状態の患者で、インスリンから GLP-1 受容体作動薬に切り替え、急激な高血糖及び糖尿病性ケトアシドーシスが発現した症例が報告されている。
8.11 本剤の使用にあたっては、患者に対し、低血糖症状及びその対処方法について十分説明すること。［9.1.3、11.1.1 参照］
8.12 低血糖を起こすことがあるので、高所作業、自動車の運転等に従事している患者に投与するときは注意すること。［11.1.1 参照］
8.13 急激な血糖コントロールの改善に伴い、糖尿病網膜症の顕在化又は増悪があらわれることがあるので、注意すること。［9.1.4 参照］
8.14 本剤はチルゼパチドを含有しているため、マンジャロ等他のチルゼパチド含有製剤あるいはその他の GLP-1 受容体作動薬等の GLP-1 受容体に対するアゴニスト作用を有する薬剤と併用しないこと。
8.15 本剤と DPP-4 阻害剤はいずれも GLP-1 受容体及び GIP 受容体を介した血糖降下作用を有している。2 型糖尿病を有する患者において両剤を併用した際の臨床試験成績はなく、有効性及び安全性は確認されていない。

9. 特定の背景を有する患者に関する注意

9.1 合併症・既往歴等のある患者

9.1.1 重症胃不全麻痺等の重度の胃腸障害のある患者

胃腸障害の症状が悪化するおそれがある。

9.1.2 膵炎の既往歴のある患者

［8.3、8.4、11.1.2 参照］

9.1.3 低血糖を起こすおそれがある以下の患者又は状態

・脳下垂体機能不全又は副腎機能不全
・栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態
・激しい筋肉運動
・過度のアルコール摂取
［8.11、11.1.1 参照］

9.1.4 増殖糖尿病網膜症、糖尿病黄斑浮腫、急性期治療を要する非増殖糖尿病網膜症を合併する患者又はこれらの既往歴のある患者

［8.13 参照］

9.4 生殖能を有する者

妊娠する可能性のある女性には、本剤投与中及び最終投与後 1 ヵ月間において避妊する必要性及び適切な避妊法について説明すること。［9.5 参照］

9.5 妊婦

妊婦又は妊娠している可能性のある女性には本剤を投与しないこと。
生殖発生毒性試験において、妊娠ラットに本剤を投与した場合、臨床最大用量でヒトに投与したときの本剤の曝露量を下回る用量（臨床最大用量での C_{max} 比較において 0.64 倍、AUC 比較において 0.22 倍）で、胎児毒性（骨格奇形、内臓奇形等）が認められた。これらの所見は母動物の摂餌量の低値及び体重の低値を伴うものであった[1)]。［9.4 参照］

9.6 授乳婦

治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行は不明である。

9.7 小児等

小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。

9.8 高齢者

患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。投与に際しては、臨床試験に組み入れられた患者背景を参考にすること。［17.1.1 参照］

10. 相互作用

10.2 併用注意（併用に注意すること）

薬剤名等	臨床症状・措置方法	機序・危険因子
糖尿病用薬 ビグアナイド系薬剤 スルホニルウレア剤 速効型インスリン分泌促進剤 α-グルコシダーゼ阻害剤 チアゾリジン系薬剤 DPP-4阻害剤 インスリン製剤 SGLT2阻害剤等 ［11.1.1 参照］	低血糖の発現に注意すること。特にスルホニルウレア剤、速効型インスリン分泌促進剤又はインスリン製剤と併用する場合、低血糖のリスクが増加するおそれがある。これらの薬剤と併用する場合、低血糖のリスクを軽減するため、これらの薬剤の減量を検討すること。	血糖降下作用が増強される。
経口避妊薬 ［16.7参照］	特に投与開始初期又は漸増後初期では併用する経口避妊薬の効果を減弱させるおそれがある。	本剤の胃内容物排出遅延作用による。
クマリン系薬剤 ワルファリンカリウム	GLP-1受容体作動薬との併用によりワルファリンの t_{max} が遅延したとの報告があり、エキセナチドで出血を伴うINR増加が報告されている。	本剤の胃内容物排出遅延作用による。

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 低血糖（頻度不明）

低血糖症状（脱力感、高度の空腹感、冷汗、顔面蒼白、動悸、振戦、頭痛、めまい、嘔気、視覚異常等）があらわれることがある。また、2 型糖尿病患者においてインスリン製剤又はスルホニルウレア剤との併用時に重篤な低血糖症状があらわれ意識消失を来す例も報告されている。
低血糖症状が認められた場合は、糖質を含む食品を摂取するなど適切な処置を行うこと。ただし、α-グルコシダーゼ阻害剤との併用時はブドウ糖を投与すること。［8.11、8.12、9.1.3、10.2、17.1.1-17.1.3 参照］

11.1.2 急性膵炎（0.1%未満）

嘔吐を伴う持続的な激しい腹痛等の異常が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。また、膵炎と診断された場合は、再投与は行わないこと。［8.3、8.4、9.1.2 参照］

11.1.3 胆嚢炎（頻度不明）、胆管炎（0.1%未満）、胆汁うっ滞性黄疸（頻度不明）

［8.7 参照］

11.1.4 アナフィラキシー、血管性浮腫（いずれも頻度不明）

11.2 その他の副作用

副作用分類	5%以上	1～5%未満	1%未満
循環器			心拍数増加[注]、低血圧、血圧低下
消化器	悪心、嘔吐、下痢、便秘、腹痛、消化不良、食欲減退	腹部膨満、胃食道逆流性疾患、おくび、鼓腸	
肝胆道			胆石症
眼			糖尿病網膜症
注射部位	注射部位反応（紅斑、そう痒感、疼痛、腫脹等）		
免疫系			過敏症(湿疹、発疹、そう痒性皮疹等)
精神神経系			味覚不全、異常感覚
臨床検査			膵アミラーゼ増加、リパーゼ増加、体重減少
その他		疲労、浮動性めまい、脱毛症	

注）心拍数の増加が持続的にみられた場合には患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。

14. 適用上の注意

14.1 薬剤投与前の注意

注入器の破損又は異常がないこと、薬液の変色や浮遊物がないことを確認すること。

14.2 薬剤投与時の注意

皮下注射は、腹部、大腿部又は上腕部に行う。同じ部位の中で注射する場合、毎回注射する場所を変更すること。静脈内及び筋肉内に投与しないこと。

15. その他の注意

15.1 臨床使用に基づく情報

国内外の第 III 相試験 5 試験（3704 例）において、抗薬物抗体が評価可能な 3596 例のうち、抗チルゼパチド抗体が 65.5%（2357 例）に発現した。また、交差抗体及び中和抗体が評価可能な 3573 例のうち、内因性 GIP 又は GLP-1 に対する交差抗体はそれぞれ 42.8%（1531 例）及び 18.7%（668 例）に、内因性 GIP 又は GLP-1 に対する中和抗体はそれぞれ 0.8%（28 例）及び 0.1%（3 例）に、チルゼパチドの GIP 受容体又は GLP-1 受容体の活性化に対する中和抗体はそれぞれ 2.4%（85 例）及び 2.2%（78 例）に発現した。

15.2 非臨床試験に基づく情報

雌雄ラットを用いた 2 年間がん原性試験において、本剤を 0.15、0.50 及び 1.5mg/kg の用量（それぞれ臨床最大用量をヒトに皮下投与した際の AUC の 0.11、0.31 及び 0.88 倍の AUC をもたらす用量）で週 2 回皮下投与したところ、対照群と比較して、甲状腺 C 細胞腫瘍（腺腫及び癌）の発生頻度の増加がすべての用量でみられた。rasH2 トランスジェニックマウスを用いた 6 ヵ月間がん原性試験において、本剤を 1、3 及び 10mg/kg の用量で週 2 回皮下投与したところ、甲状腺 C 細胞の過形成あるいは腫瘍の発生頻度に増加は認められなかった [1]。甲状腺髄様癌の既往のある患者及び甲状腺髄様癌又は多発性内分泌腫瘍症 2 型の家族歴のある患者に対する本剤の安全性は確立していない。［8.6 参照］

16. 薬物動態

16.1 血中濃度

日本人 2 型糖尿病患者 29 例に本剤 5mg、10mg 又は 15mg を週 1 回皮下投与（いずれの用量においても週 1 回 2.5mg で投与を開始し、以後 4 週間ごとに 2.5mg ずつ増量）したとき、32 週目投与後の薬物動態を評価した。本剤 32 週目投与後の t_{max} の中央値は約 24 時間、半減期（$t_{1/2}$）は約 5～6 日であり、C_{max} 及び $AUC_{(0-168hr)}$ の幾何平均値は概ね用量比例的に増加した。［8.2 参照］

薬物動態パラメータ及び血漿中濃度推移を以下に示す [2]。

表 1）血漿中チルゼパチドの薬物動態パラメータ

投与量（例数）	t_{max} (hr) [a]	$t_{1/2}$ (hr) [b]	C_{max} (ng/mL)	$AUC_{(0-168hr)}$ (ng・hr/mL)	CL/F (L/hr)	V_z/F (L)
5mg (N=7)	24.63 (8.00-48.00)	146 (121-269) [c]	835 (23)	94800 (16) [d]	0.0528 (16) [d]	11.1 (51) [c]
10mg (N=10)	23.57 (8.00-72.00)	121 (104-156) [d]	1730 (46)	197000 (36)	0.0507 (36)	9.47 (48) [d]
15mg (N=9)	24.08 (8.00-47.50)	122 (103-148) [d]	2370 (21)	288000 (21)	0.0502 (22) [e]	9.43 (19) [d]

CL/F:見かけのクリアランス、V_z/F:見かけの分布容積

幾何平均値（幾何変動係数%）

a）中央値（範囲）

b）幾何平均値（範囲）

c）N=5

d）N=6

e）N=7

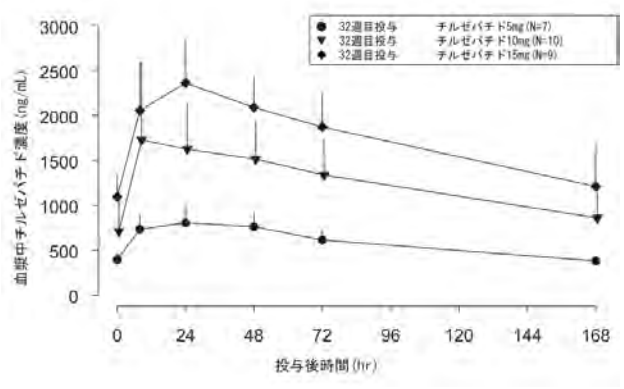


図 1）日本人 2 型糖尿病患者の血漿中チルゼパチド濃度（算術平均値+標準偏差）

第 III 相国内試験（I8F-JE-GPHZ 試験）より得られた 149 例を対象とした母集団薬物動態解析の結果、日本人肥満症患者の定常状態での薬物動態パラメータの推定値は表 2 のとおりであった [3]。

表 2）血漿中チルゼパチドの薬物動態パラメータの推定値

投与量（例数）	体重 (kg) [a]	C_{max} (ng/mL) [b]	$AUC_{(0-168hr)}$ (ng・hr/mL) [b]
10mg (N=72)	92 (15)	1540 (17)	190000 (18)
15mg (N=77)	92 (15)	2310 (14)	288000 (17)

a）算術平均値（標準偏差）

b）幾何平均値（幾何変動係数%）

16.2 吸収

健康成人 54 例に 3 つの異なる投与部位（腹部、上腕部及び大腿部）に本剤 5mg を単回皮下投与したとき、腹部投与に対する上腕部及び大腿部投与での $AUC_{(0-\infty)}$ の最小二乗幾何平均値の比［90%信頼区間］は、0.99［0.97,1.01］及び 0.95［0.94,0.97］であった [4]（外国人データ）。健康成人 20 例に本剤 5mg を単回皮下投与したときの絶対的バイオアベイラビリティの推定値は 80%であった [5]（外国人データ）。

16.3 分布

本剤は主に血漿アルブミンと強く結合（結合率:99.06%）する [6]。

16.4 代謝

本剤の代謝経路は、一般的なタンパク質の異化経路によるペプチド骨格の分解、C20 脂肪酸部分のβ酸化及びアミド加水分解である。

16.5 排泄

本剤は代謝され主に尿中及び糞便中に排泄される。未変化体は尿中及び糞便中には認められなかった [7]。

16.6 特定の背景を有する患者

16.6.1 腎機能障害患者

腎機能正常被験者（eGFR≧90mL/min/1.73m²）14 例、軽度腎機能障害患者（eGFR:60～89mL/min/1.73m²）8 例、中等度腎機能障害患者（eGFR:30～59mL/min/1.73m²）8 例、重度腎機能障害患者（eGFR＜30mL/min/1.73m²）7 例及び末期腎疾患患者（3 ヵ月以上血液透析を受けている）8 例に本剤 5mg を単回皮下投与した試験において、腎機能正常被験者に対する軽度、中等度、重度腎機能障害患者及び末期腎疾患患者の本剤の $AUC_{(0-\infty)}$ の最小二乗幾何平均値の比［90%信頼区間］は、それぞれ 1.05［0.86,1.27］、1.29［1.07,1.56］、1.03［0.84,1.27］及び 1.16［0.96,1.40］であった。また、C_{max} の最小二乗幾何平均値の比［90%信頼区間］は、それぞれ 1.04［0.84,1.30］、1.09［0.87,1.36］、1.23［0.97,1.56］及び 1.02［0.82,1.27］であった [8]（外国人データ）。

16.6.2 肝機能障害患者

肝機能正常被験者 13 例、軽度肝機能障害患者（Child-Pugh 分類 A）6 例、中等度肝機能障害患者（Child-Pugh 分類 B）6 例、重度肝機能障害患者（Child-Pugh 分類 C）7 例に本剤 5mg を単回皮下投与した試験において、肝機能正常被験者に

対する軽度、中等度及び重度肝機能障害患者の本剤の $AUC_{(0-\infty)}$ の最小二乗幾何平均値の比［90%信頼区間］は、それぞれ1.08［0.88,1.32］、0.96［0.79,1.17］及び0.85［0.70,1.04］であった。また、C_{max}の最小二乗幾何平均値の比［90%信頼区間］は、それぞれ 0.92［0.73,1.16］、1.00［0.80,1.25］及び 0.97［0.78,1.21］であった[9]（外国人データ）。

16.6.3 高齢者

第 III 相国際共同試験（I8F-MC-GPHK 試験）より得られた 1864 例（65 歳以上:114 例、65 歳未満:1750 例）を対象とした母集団薬物動態解析の結果、年齢はチルゼパチドの見かけのクリアランス及び見かけの分布容積の有意な共変量ではなかった[10]。

16.7 薬物相互作用

本剤と経口避妊薬又はアセトアミノフェンを併用した薬物相互作用試験の結果を表 3 に示す[11),12)]（外国人データ）。［10.2 参照］

表3）本剤と経口避妊薬又はアセトアミノフェンを併用した薬物相互作用試験の結果

併用薬	本剤投与量	本剤投与	例数	併用薬に対する影響		
				C_{max}比［90%信頼区間］	AUC比［90%信頼区間］	t_{max}差(hr)［90%信頼区間］
健康成人女性に本剤を単回投与						
経口避妊薬[a)]						
ノルエルゲストロミン[b)]	5mg	単回	25/25	0.45［0.40,0.51］	0.78［0.71,0.84］	4.50［1.50,5.00］
エチニルエストラジオール			24/24	0.41［0.36,0.47］	0.79[c)]［0.73,0.85］	4.23［1.50,6.50］
2型糖尿病を有するBMIが27kg/m²以上の患者に本剤を週1回反復投与						
アセトアミノフェン1g[d)]	5mg	1回目	18/18	0.44［0.36,0.53］	0.88［0.77,1.00］	0.25［0.00,2.28］
	15mg[e)]	6回目	15/18	0.57［0.47,0.70］	1.08［0.94,1.25］	0.50［0.25,1.25］
BMIが27kg/m²以上の患者(糖尿病患者を除く)に本剤を週1回反復投与						
アセトアミノフェン1g[d)]	5mg	1回目	18/18	0.45［0.38,0.55］	0.89［0.78,1.01］	1.50［0.25,2.50］
	15mg[e)]	6回目	15/18	0.80［0.66,0.98］	1.23［1.07,1.42］	0.50［0.00,1.00］

例数:本剤併用投与時/本剤非投与時

AUC:経口避妊薬は $AUC_{(0-\tau)}$、アセトアミノフェンは $AUC_{(0-last)}$

C_{max} 比及び AUC 比:プラセボ群に対する本剤群の最小二乗幾何平均値の比

t_{max} 差:プラセボ群に対する本剤群の中央値の差

a）ノルゲスチメート 0.25mg（国内未承認）、エチニルエストラジオール 0.035mg

b）ノルゲスチメートの活性代謝物

c）例数:21/21

d）アセトアミノフェンは、本剤初回投与 24 時間後及び本剤 6 回目投与 24 時間後に投与された

e）本剤 5、5、10、10、10、15mg の順に週 1 回投与

17. 臨床成績

17.1 有効性及び安全性に関する試験

17.1.1 プラセボ対照二重盲検比較試験（第 III 相国内試験:I8F-JE-GPHZ 試験）

BMI が 27kg/m² 以上で 2 つ以上の肥満に関連する健康障害[注1)]を有する又は BMI が 35kg/m² 以上で1つ以上の肥満に関連する健康障害[注1)]を有する肥満症患者225例[注2),注3)]を対象に、二重盲検下で本剤 10mg、15mg 又はプラセボを週 1 回、72 週間皮下投与した（本剤10mg群:73例、本剤15mg群:77例、プラセボ群:75例）。なお、糖尿病患者は除外された。本剤は、いずれの用量においても週 1 回 2.5mg で投与を開始し、以後 4 週間ごとに 2.5mg ずつ増量した。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を併せて行った。

注 1）組み入れ基準では、耐糖能異常（空腹時血糖 110～125mg/dL 又は 75g 経口ブドウ糖負荷試験の血糖 2 時間値 140～199mg/dL）、高トリグリセリド血症（空腹時トリグリセリド 150mg/dL 以上）又は非アルコール性脂肪性肝疾患（肝臓脂肪含有率 5%以上）とした。

注2）組み入れられた被験者において、肥満症診療ガイドラインで定義された肥満症の診断に必須の 11 の疾患を有する症例の割合は次のとおりであった。（1）耐糖能障害（2 型糖尿病・耐糖能異常等）:65.8%（耐糖能異常のみ）、（2）脂質異常症:89.3%、（3）高血圧:53.3%、（4）高尿酸血症・痛風:35.6%、（5）冠動脈疾患:2.2%、（6）脳梗塞:0%、（7）非アルコール性脂肪性肝疾患:98.2%、（8）月経異常・不妊:2.2%、（9）閉塞性睡眠時無呼吸症候群・肥満低換気症候群:8.9%、（10）運動器疾患:8.0%、（11）肥満関連腎臓病:4.0%

注 3）組み入れられた被験者において、65 歳以上の症例の割合はプラセボ群で 13.3%（10/75 例）、本剤 10mg 群で 6.8%（5/73 例）、本剤 15mg 群で 9.1%（7/77 例）であり、75 歳以上の症例の割合は本剤 10mg 群で 1.4%（1/73 例）であった。

主要評価項目（co-primary endpoints）であるベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合のいずれについても、本剤 10mg 及び本剤 15mg のプラセボに対する優越性が検証された（$p<0.001$）[13)]。

表 1）ベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合

	本剤 10mg 群（73 例）	本剤 15mg 群（77 例）	プラセボ群（75 例）
ベースラインの体重（kg）	92.5±15.15（71 例）	91.9±14.84（76 例）	92.0±15.25（75 例）
投与 72 週時の体重（kg）	76.3±16.07（59 例）	71.9±14.70（65 例）	90.5±16.01（66 例）
投与 72 週時の体重変化率(%)	-18.4±7.61（59 例）	-22.6±8.90（65 例）	-1.8±4.94（66 例）
プラセボ群との群間差[a)]［95%信頼区間］	-16.1[c)]［-18.7,-13.5］	-21.1[c)]［-23.6,-18.5］	-
5%以上体重減少達成割合(%)	94.9（56/59）	96.9（63/65）	21.2（14/66）
プラセボ群とのオッズ比[b)]［95%信頼区間］	119.65[c)]［29.06,492.67］	153.57[c)]［36.03,654.53］	-

平均値±標準偏差（評価例数）又は割合%（該当例数/評価例数）、群間差は最小二乗平均の差［95%信頼区間］、-:該当なし

a）投与群、評価時点、投与群と評価時点の交互作用、ベースラインの体重、スクリーニング時の耐糖能異常の有無、スクリーニング時の高トリグリセリド血症の有無、スクリーニング時の非アルコール性脂肪性肝疾患の有無及び性別を説明変数とし、被験者内誤差に無構造を仮定した mixed-effects model for repeated measures（MMRM）により算出。

b）a）の MMRM により算出された体重変化率の予測値を用いて欠測値を補完後、投与群、ベースラインの体重、スクリーニング時の耐糖能異常の有無、スクリーニング時の高トリグリセリド血症の有無、スクリーニング時の非アルコール性脂肪性肝疾患の有無及び性別を説明変数とする Firth 補正を用いたロジスティック回帰により算出。

c）本剤 10mg 群とプラセボ群の比較及び本剤 15mg 群とプラセボ群の比較にそれぞれ両側有意水準 2.5%が用いられた。

主な副次評価項目の結果を下表に示す。

表 2）投与 72 週時に 10%、15%又は 20%以上の体重減少を達成した被験者の割合

	本剤 10mg 群（73 例）	本剤 15mg 群（77 例）	プラセボ群（75 例）
10%以上	88.1(52/59)	92.3(60/65)	4.6(3/66)
15%以上	67.8(40/59)	83.1(54/65)	1.5(1/66)
20%以上	44.1(26/59)	66.2(43/65)	0.0(0/66)

割合%（該当例数/評価例数）

表 3）血糖、血圧及び脂質パラメータに関する評価項目

		本剤 10mg 群（73 例）	本剤 15mg 群（77 例）	プラセボ群（75 例）
HbA1c(%)	ベースライン	5.65±0.34（70 例）	5.67±0.35（75 例）	5.66±0.32（74 例）
	投与 72 週時の変化量	-0.54±0.35（59 例）	-0.61±0.29（65 例）	0.01±0.27（66 例）
空腹時血糖(mg/dL)	ベースライン	96.13±9.14（66 例）	97.55±10.94（73 例）	97.20±9.85（72 例）
	投与 72 週時の変化量	-11.36±9.16（59 例）	-9.84±10.27（65 例）	3.08±11.40（66 例）
収縮期血圧(mmHg)	ベースライン	125.4±12.99（71 例）	125.5±11.97（76 例）	125.0±12.95（75 例）
	投与 72 週時の変化量	-11.4±13.37（59 例）	-12.1±13.04（65 例）	1.7±9.08（66 例）
拡張期血圧(mmHg)	ベースライン	79.3±9.05（71 例）	79.7±8.28（76 例）	80.0±9.65（75 例）
	投与 72 週時の変化量	-6.2±10.35（59 例）	-6.3±8.80（65 例）	0.3±8.25（66 例）
総コレステロール(mg/dL)	ベースライン	210.1±38.40（66 例）	213.7±35.82（73 例）	212.5±36.48（72 例）
	投与 72 週時の変化率(%)	-8.40±14.27（59 例）	-11.95±13.54（65 例）	0.07±10.44（66 例）
LDL コレステロール(mg/dL)	ベースライン	132.1±33.92（66 例）	133.7±31.14（73 例）	132.8±31.55（72 例）
	投与 72 週時の変化率(%)	-8.6±26.52（59 例）	-13.3±19.14（65 例）	1.8±15.05（66 例）
HDL コレステロール(mg/dL)	ベースライン	49.8±12.05（66 例）	49.3±10.42（73 例）	50.9±11.47（72 例）
	投与 72 週時の変化率(%)	15.4±17.77（59 例）	17.5±21.55（65 例）	3.7±12.34（66 例）
空腹時トリグリセリド(mg/dL)	ベースライン	180.9±89.16（66 例）	191.4±91.88（73 例）	179.4±90.71（72 例）
	投与 72 週時の変化率(%)	-33.1±29.43（59 例）	-42.4±23.73（65 例）	-3.7±34.40（66 例）

平均値±標準偏差（評価例数）

副作用発現割合は、本剤 10mg 群で 56.2%（41/73 例）、本剤 15mg 群で 63.6%（49/77 例）及びプラセボ群で 10.7%（8/75 例）であった。主な副作用は本剤

10mg 群では悪心 13.7%（10/73 例）、便秘 13.7%（10/73 例）及び食欲減退 12.3%（9/73 例）、本剤 15mg 群では便秘 23.4%（18/77 例）及び悪心 22.1%（17/77 例）であった。なお、プラセボ群における便秘、食欲減退及び悪心の発現割合は、それぞれ 2.7%（2/75 例）、1.3%（1/75 例）及び 0%（0/75 例）であった。
血糖値 54mg/dL 未満の低血糖は、本剤 10mg 群で 5.5%（4/73 例）、本剤 15mg 群で 9.1%（7/77 例）及びプラセボ群で 1.3%（1/75 例）認められ、重症低血糖は認められなかった。［5.、9.8、11.1.1 参照］

17.1.2 プラセボ対照二重盲検比較試験（第 III 相国際共同試験：I8F-MC-GPHK 試験）

BMI が 27kg/m^2 以上で高血圧、脂質異常症、閉塞性睡眠時無呼吸症候群若しくは心血管疾患のいずれかを有する被験者又は BMI が 30kg/m^2 以上の被験者 2517 例を対象に、二重盲検下で本剤 5mg、10mg、15mg 又はプラセボを週 1 回、72 週間皮下投与した（本剤 5mg 群:624 例（日本人:24 例）、本剤 10mg 群:628 例（日本人:22 例）、本剤 15mg 群:628 例（日本人:29 例）、プラセボ群:637 例（日本人:27 例））。なお、糖尿病患者は除外された。本剤は、いずれの用量においても週 1 回 2.5mg で投与を開始し、以後 4 週間ごとに 2.5mg ずつ増量した。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を併せて行った。
主要評価項目（co-primary endpoints）であるベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合のいずれについても、本剤 10mg 及び本剤 15mg のプラセボに対する優越性が検証された（p<0.001）[14]。

表 4）ベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合

	本剤 5mg 群（624 例）	本剤 10mg 群（628 例）	本剤 15mg 群（628 例）	プラセボ群（637 例）
ベースラインの体重(kg)	103.2±20.68（617 例）	106.2±23.29（621 例）	105.6±22.96（623 例）	104.9±21.45（629 例）
投与 72 週時の体重(kg)	86.0±20.58（535 例）	83.2±23.35（526 例）	81.8±21.87（533 例）	101.5±22.77（466 例）
投与 72 週時の体重変化率(%)	−16.5±9.13（535 例）	−21.9±10.16（526 例）	−22.9±10.16（533 例）	−3.3±6.96（466 例）
プラセボ群との群間差 a)［95%信頼区間］	−13.5［−14.6,−12.4］	−18.9 c)［−20.0,−17.8］	−20.1 c)［−21.2,−18.9］	−
5%以上体重減少達成割合(%)	90.3（483/535）	96.4（507/526）	96.3（513/533）	34.1（159/466）
プラセボ群とのオッズ比 b)［95%信頼区間］	23.41［17.00,32.23］	74.84 c)［47.39,118.17］	74.08 c)［46.97,116.82］	−

平均値±標準偏差（評価例数）又は割合%（該当例数/評価例数）、群間差は最小二乗平均の差［95%信頼区間］、−:該当なし
a）投与群、評価時点、投与群と評価時点の交互作用、ベースラインの体重、無作為化時の前糖尿病の有無、地域及び性別を説明変数とし、被験者内誤差に無構造を仮定した MMRM により算出。
b）a）の MMRM により算出された体重変化率の予測値を用いて欠測値を補完後、投与群、ベースラインの体重、無作為化時の前糖尿病の有無、地域及び性別を説明変数とする Firth 補正を用いたロジスティック回帰により算出。
c）本剤 10mg 群とプラセボ群の比較及び本剤 15mg 群とプラセボ群の比較にそれぞれ両側有意水準 2.5%が用いられた。

主な副次評価項目の結果を下表に示す。

表 5）投与 72 週時に 10%、15%、20%又は 25%以上の体重減少を達成した被験者の割合

	本剤 5mg 群（624 例）	本剤 10mg 群（628 例）	本剤 15mg 群（628 例）	プラセボ群（637 例）
10%以上	75.0（401/535）	86.1（453/526）	90.2（481/533）	17.4（81/466）
15%以上	53.5（286/535）	74.3（391/526）	78.2（417/533）	7.3（34/466）
20%以上	34.0（182/535）	56.8（299/526）	64.0（341/533）	1.5（7/466）
25%以上	17.8（95/535）	36.9（194/526）	41.3（220/533）	0.4（2/466）

割合%（該当例数/評価例数）

表 6）血糖、血圧及び脂質パラメータに関する評価項目

		本剤 5mg 群（624 例）	本剤 10mg 群（628 例）	本剤 15mg 群（628 例）	プラセボ群（637 例）
HbA1c(%)	ベースライン	5.56±0.36（602 例）	5.55±0.37（600 例）	5.55±0.41（606 例）	5.57±0.38（606 例）
	投与 72 週時の変化量	−0.41±0.30（527 例）	−0.49±0.32（516 例）	−0.51±0.36（524 例）	−0.08±0.30（459 例）
空腹時血糖(mg/dL)	ベースライン	95.34±9.84（603 例）	95.58±10.77（599 例）	95.18±10.27（606 例）	95.77±9.57（606 例）
	投与 72 週時の変化量	−7.70±13.47（524 例）	−9.98±12.02（517 例）	−10.40±12.63（521 例）	0.66±13.50（457 例）
収縮期血圧(mmHg)	ベースライン	123.6±12.52（618 例）	123.8±12.86（621 例）	122.9±12.91（623 例）	122.7±12.60（628 例）
	投与 72 週時の変化量	−7.5±12.85（535 例）	−9.1±12.98（526 例）	−8.0±13.03（533 例）	−1.1±11.70（466 例）
拡張期血圧(mmHg)	ベースライン	79.2±8.17（618 例）	79.9±8.32（621 例）	79.3±8.21（623 例）	79.5±7.91（628 例）
	投与 72 週時の変化量	−5.2±8.76（535 例）	−6.0±8.82（526 例）	−4.7±9.23（533 例）	−1.2±8.23（466 例）
総コレステロール(mg/dL)	ベースライン	191.0±40.03（603 例）	194.4±38.75（599 例）	190.9±37.88（606 例）	190.0±38.67（606 例）
	投与 72 週時の変化率(%)	−3.68±16.31（523 例）	−4.60±17.05（517 例）	−6.46±15.96（520 例）	0.52±18.09（458 例）
LDL コレステロール(mg/dL)	ベースライン	113.3±32.30（584 例）	116.3±32.83（574 例）	114.0±32.66（582 例）	113.2±33.29（573 例）
	投与 72 週時の変化率(%)	−1.70±26.60（514 例）	−3.55±26.37（511 例）	−5.97±24.89（515 例）	3.05±28.63（456 例）
HDL コレステロール(mg/dL)	ベースライン	49.2±13.14（589 例）	48.9±12.73（577 例）	49.0±12.62（584 例）	48.0±12.61（576 例）
	投与 72 週時の変化率(%)	8.68±20.19（518 例）	10.13±20.77（515 例）	9.96±20.65（519 例）	2.82±17.42（458 例）
空腹時トリグリセリド(mg/dL)	ベースライン	150.1±151.96（603 例）	144.0±87.89（599 例）	142.6±82.01（606 例）	146.4±82.81（606 例）
	投与 72 週時までの変化率(%)	−18.4±34.76（522 例）	−19.2±38.52（515 例）	−24.8±37.73（518 例）	0.5±44.65（457 例）

平均値±標準偏差（評価例数）

副作用発現割合は、本剤 5mg 群で 55.6%（347/624 例）、本剤 10mg 群で 62.3%（391/628 例）、本剤 15mg 群で 61.1%（384/628 例）及びプラセボ群で 30.5%（194/637 例）であった。主な副作用は本剤 5mg 群では悪心 21.0%（131/624 例）、下痢 15.4%（96/624 例）及び便秘 13.5%（84/624 例）、本剤 10mg 群では悪心 30.7%（193/628 例）、下痢 17.8%（112/628 例）、便秘 14.0%（88/628 例）、食欲減退 11.0%（69/628 例）及び嘔吐 10.0%（63/628 例）、本剤 15mg 群では悪心 28.5%（179/628 例）、下痢 19.1%（120/628 例）、嘔吐 10.7%（67/628 例）及び便秘 10.0%（63/628 例）であった。なお、プラセボ群における悪心、下痢、便秘、食欲減退及び嘔吐の発現割合は、それぞれ 8.0%（51/637 例）、5.7%（36/637 例）、4.1%（26/637 例）、3.0%（19/637 例）及び 0.8%（5/637 例）であった。
血糖値 54mg/dL 未満の低血糖（重症低血糖を含む）は、本剤 5mg 群で 1.4%（9/624 例）、本剤 10mg で 1.6%（10/628 例）、本剤 15mg 群で 1.6%（10/628 例）及びプラセボ群で 0.2%（1/637 例）認められ、そのうち重症低血糖は本剤 5mg 群の 1 例で認められた。［7.1、11.1.1 参照］

17.1.3 プラセボ対照二重盲検比較試験（第 III 相国際共同試験：I8F-MC-GPHL 試験）

2 型糖尿病を有する BMI が 27.0kg/m^2 以上の被験者 912 例を対象に、二重盲検下で本剤 10mg、15mg 又はプラセボを週 1 回、72 週間皮下投与した（本剤 10mg 群:302 例（日本人:14 例）、本剤 15mg 群:303 例（日本人:14 例）、プラセボ群:307 例（日本人:13 例））。本剤は、いずれの用量においても週 1 回 2.5mg で投与を開始し、以後 4 週間ごとに 2.5mg ずつ増量した。試験期間中、被験者は食事のカロリー制限及び身体活動の増加を併せて行った。

主要評価項目（co-primary endpoints）であるベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合のいずれについても、本剤 10mg 及び本剤 15mg のプラセボに対する優越性が検証された（p<0.001）[15]。

表 7）ベースラインから投与 72 週時までの体重変化率及び投与 72 週時に 5%以上の体重減少を達成した被験者の割合

	本剤 10mg 群 (302 例)	本剤 15mg 群 (303 例)	プラセボ群 (307 例)
ベースラインの体重(kg)	101.7± 20.84 (299 例)	99.8±20.10 (301 例)	102.1± 22.27 (303 例)
投与 72 週時の体重(kg)	88.5±20.36 (274 例)	84.1±19.51 (259 例)	97.3±22.49 (256 例)
投与 72 週時の体重変化率(%)	-13.3±8.38 (274 例)	-16.0±9.70 (259 例)	-3.5±5.87 (256 例)
プラセボ群との群間差 a) [95%信頼区間]	-10.3 c) [-11.7,-8.9]	-12.4 c) [-13.8,-11.1]	-
5%以上体重減少達成割合(%)	82.1 (225/274)	87.6 (227/259)	33.6 (86/256)
プラセボ群とのオッズ比 b) [95%信頼区間]	11.03 c) [7.42,16.39]	14.92 c) [9.80,22.71]	-

平均値±標準偏差（評価例数）又は割合%（該当例数/評価例数）、群間差は最小二乗平均の差［95%信頼区間］、-:該当なし
a）投与群、評価時点、投与群と評価時点の交互作用、ベースラインの体重、無作為化時に使用していた血糖降下薬の種類、地域及び性別を説明変数とし、被験者内誤差に無構造を仮定した MMRM により算出。
b）a）の MMRM により算出された体重変化率の予測値を用いて欠測値を補完後、投与群、ベースラインの体重、無作為化時に使用していた血糖降下薬の種類、地域及び性別を説明変数とする Firth 補正を用いたロジスティック回帰により算出。
c）本剤 10mg 群とプラセボ群の比較及び本剤 15mg 群とプラセボ群の比較にそれぞれ両側有意水準 2.5%が用いられた。

主な副次評価項目の結果を下表に示す。

表 8）投与 72 週時に 10%、15%、20%又は 25%以上の体重減少を達成した被験者の割合

	本剤 10mg 群 (302 例)	本剤 15mg 群 (303 例)	プラセボ群 (307 例)
10%以上	63.1(173/274)	71.0(184/259)	10.2(26/256)
15%以上	41.2(113/274)	54.1(140/259)	3.1(8/256)
20%以上	21.9(60/274)	34.4(89/259)	1.2(3/256)
25%以上	8.8(24/274)	17.4(45/259)	0.4(1/256)

割合%（該当例数/評価例数）

表 9）血糖、血圧及び脂質パラメータに関する評価項目

		本剤 10mg 群 (302 例)	本剤 15mg 群 (303 例)	プラセボ群 (307 例)
HbA1c(%)	ベースライン	8.02±0.83 (291 例)	8.07±1.00 (293 例)	7.96±0.84 (282 例)
	投与 72 週時の変化量	-2.22± 1.00 (265 例)	-2.29± 1.12 (249 例)	-0.59± 1.04 (165 例)
空腹時血糖(mg/dL)	ベースライン	158.23± 42.52 (290 例)	161.87± 50.20 (293 例)	157.41± 45.61 (282 例)
	投与 72 週時の変化量	-50.24±44.36 (264 例)	-53.22±44.93 (250 例)	-9.34± 39.89 (162 例)
収縮期血圧(mmHg)	ベースライン	130.6± 12.19 (299 例)	130.2± 12.23 (301 例)	131.3± 11.77 (303 例)
	投与 72 週時の変化量	-6.0± 14.55 (274 例)	-7.9± 13.25 (259 例)	-1.2± 13.65 (256 例)
拡張期血圧(mmHg)	ベースライン	80.1±8.14 (299 例)	79.8±8.67 (301 例)	79.5±8.39 (303 例)
	投与 72 週時の変化量	-2.4±8.67 (274 例)	-2.9±9.78 (259 例)	-0.2±7.75 (256 例)
総コレステロール(mg/dL)	ベースライン	177.5± 43.23 (286 例)	170.9± 42.01 (286 例)	179.3± 41.86 (284 例)
	投与 72 週時の変化率(%)	-1.33± 21.65 (272 例)	1.47± 23.73 (257 例)	3.31± 20.73 (255 例)
LDL コレステロール(mg/dL)	ベースライン	96.0± 35.20 (286 例)	92.3± 35.23 (286 例)	97.9± 33.72 (284 例)
	投与 72 週時の変化率(%)	10.57± 75.67 (272 例)	12.45± 48.15 (256 例)	10.80± 39.07 (255 例)
HDL コレステロール(mg/dL)	ベースライン	45.2± 12.42 (286 例)	42.9± 10.31 (286 例)	43.9± 11.42 (284 例)
	投与 72 週時の変化率(%)	8.04± 18.96 (272 例)	12.78± 25.76 (257 例)	2.58± 18.24 (255 例)
空腹時トリグリセリド(mg/dL)	ベースライン	187.0± 143.42 (286 例)	182.5± 131.03 (286 例)	191.4± 117.88 (284 例)
	投与 72 週時の変化率(%)	-19.8± 36.77 (272 例)	-21.7± 40.79 (257 例)	1.0±43.14 (255 例)

平均値±標準偏差（評価例数）

副作用発現割合は、本剤 10mg 群で 48.7%（147/302 例）、本剤 15mg 群で 47.2%（143/303 例）及びプラセボ群で 27.0%（83/307 例）であった。主な副作用は本剤 10mg 群では悪心 17.5%（53/302 例）及び下痢 14.9%（45/302 例）、本剤 15mg 群では悪心 19.5%（59/303 例）、下痢 17.2%（52/303 例）及び嘔吐 11.2%（34/303 例）であった。なお、プラセボ群における下痢、悪心及び嘔吐の発現割合は、それぞれ 6.8%（21/307 例）、5.2%（16/307 例）及び 2.6%（8/307 例）であった。
血糖値 54mg/dL 未満の低血糖は、本剤 10mg 群で 3.6%（11/302 例）、本剤 15mg で 5.0%（15/303 例）及びプラセボ群で 1.3%（4/307 例）認められ、重症低血糖は認められなかった。［11.1.1 参照］

18. 薬効薬理

18.1 作用機序

本剤は GIP 受容体及び GLP-1 受容体のアゴニストである。本剤は中枢神経系において GIP 受容体及び GLP-1 受容体に作用することにより食欲を調節し、また、脂肪細胞の GIP 受容体に作用することにより脂質等の代謝を亢進させることで、体重減少作用を示すと考えられる。
本剤は C20 脂肪酸側鎖を含む 39 個のアミノ酸からなるペプチドであり、内因性アルブミンと結合して消失半減期が延長することにより作用が持続する。

18.2 薬理作用

18.2.1 GIP 受容体及び GLP-1 受容体アゴニスト活性

本剤は、*in vitro* 試験において、GIP 受容体及び GLP-1 受容体に結合して活性化し、いずれの受容体に対しても細胞内 cAMP を増加させるアゴニスト活性を示した[16]。

18.2.2 体重減少作用

食餌誘発性肥満マウスに本剤を反復投与した結果、溶媒群と比較して体重が低値を示した[16]。
BMI が 27kg/m^2 以上の被験者に対して、本剤 5mg、10mg 又は 15mg を週 1 回 72 週間投与した結果、プラセボ群と比較して本剤群で体重減少の程度が大きく、脂肪量の減少が除脂肪体重の減少よりも大きかった[14]。

18.2.3 食欲の調節

食餌誘発性肥満マウスに本剤を反復投与した結果、溶媒群と比較して摂餌量が低値を示した[16]。また、本剤は、マウスの高脂肪食への嗜好性を低下させ、総摂取カロリーを減少させた[17]。

18.2.4 脂肪代謝の調節

ヒト脂肪細胞を用いた *in vitro* 試験において、本剤は、リポタンパクリパーゼ活性を上昇させ、脂肪酸の細胞内への取り込み及び脂肪分解を促進した[17]。また、食餌誘発性肥満マウスに対して食餌制限後に本剤を投与した結果、エネルギー消費量及び脂肪消費量が溶媒群と比較して大きかった[17]。

19. 有効成分に関する理化学的知見

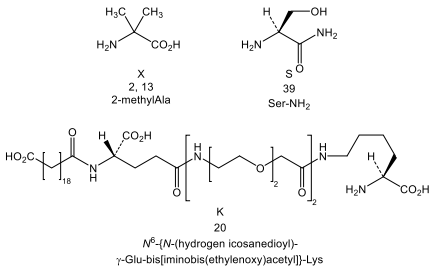
一般的名称：　チルゼパチド（Tirzepatide）〔JAN〕

分　子　式：　$C_{225}H_{348}N_{48}O_{68}$

分　子　量：　4813.45

性　　状：　白色の粉末である。

化学構造式：　YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS



本　　質　：　チルゼパチドは、ヒトグルコース依存性インスリン分泌刺激ポリペプチド（GIP）受容体及びヒトグルカゴン様ペプチド-1（GLP-1）受容体のアゴニストであり、2 及び 13 番目のアミノ酸残基は 2-methylAla、C 末端はアミド化された Ser である。さらに、1,20-イコサン二酸が 1 個の Glu 及び 2 個の 8-アミノ-3,6-ジオキサオクタン酸で構成されるリンカーを介して 20 番目の Lys に結合している。チルゼパチドは 39 個のアミノ酸残基からなる合成ペプチドである。

20. 取扱い上の注意

20.1 凍結を避け、2～8℃で遮光保存すること。凍結した場合は、使用しないこと。

20.2 室温で保存する場合は、30℃を超えない場所で外箱から出さずに保存し、21 日以内に使用すること。

21. 承認条件

医薬品リスク管理計画を策定の上、適切に実施すること。

22. 包装

〈ゼップバウンド皮下注 2.5mg アテオス〉
0.5mL×2 キット
〈ゼップバウンド皮下注 5mg アテオス〉
0.5mL×2 キット
〈ゼップバウンド皮下注 7.5mg アテオス〉
0.5mL×2 キット
〈ゼップバウンド皮下注 10mg アテオス〉
0.5mL×2 キット
〈ゼップバウンド皮下注 12.5mg アテオス〉
0.5mL×2 キット
〈ゼップバウンド皮下注 15mg アテオス〉
0.5mL×2 キット

23. 主要文献

1)社内資料：チルゼパチドの毒性試験(2022 年 9 月 26 日承認、CTD2.6.6)
2)社内資料：日本人 2 型糖尿病患者の薬物動態(2022 年 9 月 26 日承認、CTD2.7.2.2.2.1.2)
3)社内資料：母集団薬物動態解析補遺
4)社内資料：投与部位の影響を評価した試験(2022 年 9 月 26 日承認、CTD2.7.1.2.3)
5)社内資料：絶対的バイオアベイラビリティを評価した試験(2022 年 9 月 26 日承認、CTD2.7.1.2.1)
6)社内資料：血漿蛋白結合(2022 年 9 月 26 日承認、CTD2.7.2.2.1.1)
7)社内資料：マスバランス試験(2022 年 9 月 26 日承認、CTD2.7.2.2.2.3.1)
8)Urva S, et al.: Clin. Pharmacokinet. 2021; 60(8): 1049-1059
9)Urva S, et al.: Clin. Pharmacokinet. 2022; 61(7): 1057-1067
10)社内資料：母集団薬物動態解析
11)社内資料：経口避妊薬との薬物相互作用試験(I8F-MC-GPGR 試験)(2022 年 9 月 26 日承認、CTD2.7.2.2.2.5.1)
12)社内資料：アセトアミノフェンを用いた胃内容排出に対する影響を評価した試験(I8F-MC-GPHU 試験)
13)社内資料：肥満症患者を対象とした第 III 相国内試験(I8F-JE-GPHZ 試験)
14)社内資料：BMI が 27kg/m^{2}以上の患者（糖尿病患者を除く）を対象とした第 III 相国際共同試験(I8F-MC-GPHK 試験)
15)社内資料：2 型糖尿病を有する BMI が 27kg/m^{2}以上の患者を対象とした第 III 相国際共同試験(I8F-MC-GPHL 試験)
16)社内資料：チルゼパチドの薬理試験(2022 年 9 月 26 日承認、CTD2.6.2)
17)社内資料：チルゼパチドの薬理試験

24. 文献請求先及び問い合わせ先

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medical.lilly.com/jp

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〒541-8505　大阪市中央区道修町 3-2-10
TEL:0120-753-280（医療関係者向け）

26. 製造販売業者等

26.1 製造販売元

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26.2 販売元

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Ⓡ:登録商標
ZEP-I001(R1)

1.8.2　効能又は効果（案）及びその設定根拠

1.8.2.1　効能又は効果（案）

肥満症
ただし、高血圧、脂質異常症又は2型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。
・ BMIが27 kg/m^{2}以上であり、2つ以上の肥満に関連する健康障害を有する
・ BMIが35 kg/m^{2}以上

1.8.2.2　設定根拠

本申請効能又は効果（案）は、以下に示す肥満症診療ガイドライン 2016 に準じて実施したチルゼパチドの肥満症患者を対象とした国内第 3 相試験、及び日本人を含む肥満又は過体重の被験者を対象とした国際共同第 3 相試験より得られたチルゼパチドの有効性及び安全性成績に基づき設定した。

- 国内第3相試験
  - I8F-JE-GPHZ試験（以下、GPHZ試験）
- 国際共同第3相試験
  - I8F-MC-GPHK試験（以下、GPHK試験）
  - I8F-MC-GPHL試験（以下、GPHL試験）

GPHZ、GPHK、及び GPHL 試験で、主要評価項目である体重のベースラインからの変化率と5%以上の体重減少を達成した被験者の割合は、いずれのチルゼパチド群でもプラセボ群と比較して優越性を示した。いずれの試験でも、各チルゼパチド群で平均体重はベースライン後早期から減少し、投与72週時まで持続した。

2 型糖尿病（T2D）の有無にかかわらず、すべてのチルゼパチド群でプラセボ群と比較して、10%及び 15%以上の体重減少を達成した被験者の割合が有意に高かった。さらに、少なくとも20%の体重減少を達成した被験者の割合は GPHZ 試験のチルゼパチド 10 mg 群で約 3 分の 1 及び 15 mg 群で約 3 分の 2、GPHK 試験のチルゼパチド 10 mg 群及び 15 mg 群で約 2 分の 1、並びに GPHL 試験のチルゼパチド 15 mg 群で約 3 分の 1 であり、現在利用可能な薬物療法よりも複数の健康障害の改善に求められる高い減量目標値を達成した。また、T2D を有する GPHL 試験のチルゼパチド群では、HbA1c が臨床的に意味のある減少を示した。

また、GPHZ試験の投与72週時点で、肥満に関連する健康障害が改善した被験者の割合は、チルゼパチド10 mg群及び15 mg群でプラセボ群と比較して統計学的に有意に高かった。投与72週時点で耐糖能異常（IGT）、高脂血症、及び非アルコール性脂肪性肝疾患（NAFLD）の改善を達成した被験者の割合は、いずれもチルゼパチド10 mg群及び15 mg群でプラセボ群と比較して統計学的に有意に高かった。

GPHZ 試験では、肥満症の診断に必要な健康障害として、肥満症診療ガイドラインに規定されたその他の肥満に関連する健康障害パラメータでも、臨床的に意味のある改善が認められた。

また、日本人集団で、体重、腹囲、脂質関連パラメータ、血糖コントロール項目のいずれでもプラセボ群と比較して各チルゼパチド群で良好な結果が得られており、全体集団と同様の傾向が確認された。

全般的に、成人の肥満又は過体重に対する体重管理のための低カロリー食及び身体活動の増強に対する補助としてのチルゼパチドの安全性プロファイルは、T2D を有する成人でのチルゼパチドの既知の安全性プロファイルと一貫していた。

グルカゴン様ペプチド-1（GLP-1）受容体作動薬と同様に、チルゼパチドでは悪心及び下痢が全体で最も多く認められた有害事象であり、最も多く認められた治験薬の投与中止に至った有害事象でもあった。

臨床評価項目判定委員会で確定された急性膵炎の症例は少なく、プラセボ群とチルゼパチド群で同程度であった。類薬の GLP-1 受容体作動薬による急性膵炎のリスクは医療現場では良く知られており、現在 T2D で行っている医薬品安全性監視活動を通じての情報収集、及び添付文書などでの注意喚起を引き続き行うことで管理可能であると考える。

日本人が組み入れられた国際共同第3相試験であるGPHK及びGPHL試験で、TEAE（treatment-emergent adverse event）、重篤な有害事象、胃腸関連有害事象、及びバイタルサインを日本人集団と全体集団で比較した結果、脈拍数の増加を除き、いずれの試験でも日本人集団と全体集団で安全性の結果に大きな違いはなかった。また、いずれの試験でも、日本人集団のみで発現割合が顕著に高く、かつ臨床的に問題となる事象は認められなかった。日本人集団に特異的な安全性上の懸念は認められなかった。

このように、チルゼパチドは、肥満症、肥満、又は過体重の様々な臨床的症状を呈する被験者集団に対して、臨床的に意味のある体重減少をもたらし、肥満症の治療に対して承認されているインクレチン関連薬と同様の安全性プロファイルを有していることが示された。主要及び副次的なベネフィットが、すべての安全性事象の包括的な評価に基づくリスクを上回ることから、チルゼパチドは日本人肥満症患者にとって意味のある治療選択肢となり得る。

本効能又は効果でのチルゼパチドの投与は、以下の理由により適切と考えている。

日本肥満学会が推奨する肥満症診療ガイドライン 2022 に規定される 11 の健康障害は、内臓脂肪蓄積に起因あるいは関連する疾患として選定されており、減量による内臓脂肪の減少によって複数の疾患が一挙に改善するというエビデンスに基づいている。

肥満症の薬物治療では、体重減少により複数の健康障害を一挙に解決することが求められる。特に肥満に起因する糖尿病や脂質異常症、高血圧、非アルコール性脂肪性肝疾患、高尿酸血症などの疾患を個々別々に治療するのではなく、減量によってそれらを一挙に改善させることを推奨するものである。

GPHZ 試験では、チルゼパチドの主要評価項目である体重減少効果と共に、副次評価項目で体重減少による健康障害の改善効果を明確に評価するために、IGT、高脂血症、及び NAFLD のスクリーニング時における検査による診断を選択基準に含め、それらの改善効果の評価を副次評価項目に含めているが、実際には肥満症の診断に必要な 11 の健康障害のうち、10 種類の健康障害を持つ被験者が組み入れられていた。なお、11 の健康障害の一つである脳梗塞・一過性脳虚血発作の既往歴を有する被験者は、試験実施時の除外基準及び疾患の特異性の観点から試験に登録さ

れなかったが、病因が近似している心血管系疾患を併存する被験者、又は脳血管系疾患のリスク因子となる一部の健康障害（IGT、高血圧、脂質異常症など）を有する被験者が登録されている。減量によりその予防や病態改善が期待できるというエビデンスが一定程度以上蓄積されているものを診断に必要な健康障害として定義していることからも、GPHZ 試験において広く十分に肥満症の健康障害を有する被験者を評価できると考える。

GPHZ、GPHK、及び GPHL 試験で、主要評価項目である体重のベースラインからの変化率及び 5%以上の体重減少を達成した被験者の割合は、プラセボ群と比較してチルゼパチド群で優越性を示した。また、GPHZ 試験で肥満に関連する健康障害（IGT、高脂血症、及び NAFLD）が改善した被験者の割合はプラセボ群と比較してチルゼパチド群で統計学的に有意に高く、チルゼパチド投与による健康障害の改善が認められた。さらに、高血圧、高尿酸血症、腎臓病などの肥満に関連する複数の健康障害が、臨床検査値などの客観的指標に基づいて改善したことが確認された。加えて、将来的に健康障害の合併リスクとなる内臓脂肪蓄積にも影響を与えうる点が明らかとなった。これらのエビデンスは、日本肥満学会が肥満症治療薬に求める、安全に減量を加速させることにより肥満に起因する複数の健康障害の改善と肥満症治療における他剤併用の抑制と一貫するもので、チルゼパチドが肥満症治療、特に 11 の健康障害の改善に広く有効であることを支持するものと考えられた。

類薬であるウゴービは、日本肥満学会のガイドラインに則り、肥満症を効能又は効果として承認された日本初の GLP-1 受容体作動薬である。肥満症診療ガイドラインに規定された、肥満症又は高度肥満症の患者に対する薬物療法に必要な健康障害の種類及び併存数を考慮して、組み入れ基準の高血圧、脂質異常症、及び T2D の 3 疾患のいずれかが肥満症に関連する健康障害として含まれており、その改善効果を臨床検査値で示している。GPHZ 試験では、肥満症診療ガイドラインの基準案に記載されている副次評価項目をより重要視して、選択基準である 3 つの健康障害に対する本剤の効果を精緻に確認した。したがって、チルゼパチドもウゴービの効能又は効果、及びチルゼパチドで実施したこれまでの臨床試験の肥満に関連する健康障害を持つ患者背景、及び客観的指標による健康障害の改善効果を踏まえ、組み入れ基準の 3 疾患である耐糖能障害、脂質異常症、及び NAFLD のいずれかを併存していれば、2 つ目の健康障害の種類は肥満症診療ガイドラインに規定されたその他の健康障害から選択するという同様の効能又は効果が肥満症診療ガイドラインに基づき適切と考える。

一方、チルゼパチドの投与対象として適切な効能又は効果で規定する健康障害について PMDA との協議の結果、以下のとおり効能又は効果を再検討した。

「肥満」はメタボリックドミノの上流に位置し、糖尿病や脂質異常症をはじめとした代謝性疾患や、それらを基盤として発症する冠動脈疾患や脳血管疾患等の肥満に関連する健康障害の発症及び進展を助長させる因子となる。効能又は効果で規定する健康障害は、薬剤の有効性及び安全性プロファイルに応じて選定することが科学的に適切と考える。一方で、肥満症自体に薬剤介入することの臨床的意義を明確にする必要があるとも考える。したがって、IGT 及び NAFLD は、薬剤介入に一定の科学的及び臨床的意義はあると考えるものの、現時点では薬剤介入の臨床的意

義が診療ガイドライン等で確立している状況ではないことを考慮し、効能又は効果で規定する健康障害には含めないこととする。

高血圧について、GPHZ 試験では 53.3%、GPHK 試験では 32.0%、GPHL 試験では 66.6%の高血圧を有する被験者が組み入れられており、すべての試験でプラセボ群と比較してチルゼパチド群で収縮期血圧及び拡張期血圧の改善が認められた。高血圧は心血管系疾患の代表的な危険因子で、生命予後や健康寿命を保つために肥満症に合併する高血圧症の治療及び管理は重要であり、体重減少は降圧の主要な治療法であることから、高血圧を効能又は効果で規定する健康障害に含めることは適切と考える。

GPHZ、GPHK、及び GPHL 試験には一定の割合で脂質異常症を有する被験者が組み入れられており、試験ごとに各脂質パラメータで改善傾向が認められたことから、脂質異常症を効能又は効果で規定する健康障害に含めることは適切と考える。また、GPHL 試験では T2D を有する肥満の被験者に対するチルゼパチド投与により、臨床的に意味のある減量と HbA1c の減少を示したことから、T2D を効能又は効果で規定する健康障害に含めることは適切と考える。

以上より、本剤の投与対象として効能又は効果で規定する健康障害は、高血圧、脂質異常症又は 2 型糖尿病とし、第 1.8.2.1 項の効能又は効果（案）を設定した。

1.8.3　用法及び用量（案）並びにその設定根拠

1.8.3.1　用法及び用量（案）

通常、成人には、チルゼパチドとして週 1 回 2.5 mg から開始し、4 週間の間隔で 2.5 mg ずつ増量し、週 1 回 10 mg を皮下注射する。
なお、患者の状態に応じて適宜増減するが、週 1 回 5 mg まで減量、又は 4 週間以上の間隔で 2.5 mg ずつ週 1 回 15 mg まで増量できる。

＜用法及び用量に関連する注意（案）＞　注：5 mg での治療継続及び投与を忘れた場合の注意のみ抜粋
7.1 本剤の用量調節に際しては、以下の点に留意すること。
・　患者の体重減少の程度や本剤に対する忍容性に応じて、週 1 回 5 mg で治療を継続することも考慮すること。［17.1.2 参照］
7.3 投与を忘れた場合は、次回投与までの期間が 3 日間（72 時間）以上であれば、気づいた時点で直ちに投与し、その後はあらかじめ定めた曜日に投与すること。次回投与までの期間が 3 日間（72 時間）未満であれば投与せず、次のあらかじめ定めた曜日に投与すること。なお、週 1 回投与の曜日を変更する必要がある場合は、前回投与から少なくとも 3 日間（72 時間）以上間隔を空けること。

1.8.3.2　設定根拠

1.8.3.2.1　用法及び用量（案）の設定根拠

本申請用法及び用量（案）は、国内第 3 相試験（GPHZ 試験）、及び日本人を含む国際共同第 3 相試験（GPHK 試験、GPHL 試験）より得られたチルゼパチドの有効性及び安全性成績に基づき設定した。

GPHZ、GPHK、及び GPHL 試験でのチルゼパチドの開始用量は 2.5 mg の週 1 回投与であり、維持用量まで 4 週間隔で 2.5 mg ずつ漸増することとした。チルゼパチドの維持用量は、GPHK 試

験では 5 mg、10 mg、又は 15 mg の週 1 回投与とし、GPHZ 及び GPHL 試験では 10 mg 又は 15 mg の週 1 回投与とした。

GPHZ 試験では、主要評価項目である投与 72 週時点の体重の変化率及び 5%以上の体重減少を達成した被験者の割合について、多重性の調整のもとでチルゼパチド 10 mg 群及び 15 mg 群のプラセボ群に対する優越性が示された。2 用量のうち低用量のチルゼパチド 10 mg 群でも、主要評価項目で臨床的に意味のある有効性が認められた。

また、高用量のチルゼパチド15 mg群では、10 mg群よりも体重の変化率がさらに大きく、15%以上や 20%以上といった大きな体重減少を達成した被験者の割合が高かった。実臨床での減量目標は、合併する健康障害の状態に応じて設定される。より高い減量目標を必要とする健康障害を有する肥満症患者にとって、チルゼパチド 15 mg 投与が有用となる可能性が考えられる。

GPHK 試験のチルゼパチド 5 mg 群、10 mg 群、及び 15 mg 群、並びに GPHL 試験のチルゼパチド 10 mg 群及び 15 mg 群でも、体重の変化率、並びに 5%、10%、15%、及び 20%（GPHK 試験では加えて 25%）以上体重が減少した被験者の割合でプラセボ群に対する優越性が示された。GPHZ 試験と同様に、チルゼパチド 10 mg 群で臨床的に意味のある有効性が認められ、高用量であるほどより高い有効性が認められた。

GPHZ、GPHK、及び GPHL 試験のいずれでも、体重に加えて、腹囲、脂質関連パラメータ、血圧、及び患者報告アウトカムで、チルゼパチド 10 mg 群及び 15 mg 群の有効性が認められた。

GPHZ、GPHK、及び GPHL 試験の安全性プロファイルはおおむね良好であった。

胃腸関連有害事象の忍容性改善のため、チルゼパチドを 2.5 mg の低用量から用量漸増する用法とした。悪心、嘔吐、及び下痢（GPHZ 試験では悪心、嘔吐、下痢及び便秘）の発現割合はチルゼパチドの用量漸増期間で高く、維持用量に達した後（すなわち、割り付けられた維持用量に到達後 4 週間以降）は低下した。この結果は、チルゼパチドを 2.5 mg の低用量から開始し、その後 4 週間ごとに 2.5 mg ずつ緩やかに用量漸増することで、胃腸関連有害事象の忍容性が改善することを支持していた。

なお、GPHK 及び GPHL 試験の日本人集団の有効性は全体集団と一貫しており、日本人集団と全体集団の安全性プロファイルに臨床的に問題となるような重要な違いは認められず、日本人及び外国人の薬物動態（PK）は類似していたことから、第 3 相試験で用いた用法及び用量を日本人肥満症患者にも適用することは妥当であると考えられた。

以上、GPHZ、GPHK、及び GPHL 試験の結果より、肥満症に対するチルゼパチド 10 mg、及び 15 mg の有効性並びに良好な安全性プロファイルが示され、良好なベネフィット・リスクプロファイルが認められたことから、維持用量として 10 mg は適切と判断した。また、10 mg 及び 15 mg はいずれも臨床用量として適切と判断した。

臨床診療では、より高い減量目標を必要とする健康障害を有する肥満症患者にとって、チルゼパチド 15 mg 投与が有用となる可能性が考えられる。忍容性などの観点から低い用量を必要とす

る患者もいることが予想される。そのため、チルゼパチドの異なる用量が利用可能であれば、患者中心の治療アプローチの観点で、医療従事者は個々の患者の必要性に応じてチルゼパチドの投与量を調整することが可能となる。

以上より、第 1.8.3.1 項の用法及び用量（案）を設定した。

1.8.3.2.2　用法及び用量に関連する注意（案）の設定根拠

＜5 mg での治療継続について＞

審査中の PMDA との協議の結果、GPHK 試験における因果関係を否定できない有害事象及び投与中止に至った有害事象の発現割合はチルゼパチド 5 mg 群と比較してチルゼパチド 10 mg 群及び 15 mg 群で高かったことを考慮し、患者の状況に応じて、チルゼパチドを 10 mg には増量せずに 5 mg での治療を継続することも可能とすることとした。そのため、第 1.8.3.1 項の用法及び用量に関連する注意（案）7.1 に記載する「患者の体重減少の程度や本剤に対する忍容性に応じて、週 1 回 5 mg で治療を継続することも考慮すること」を設定した。

＜投与を忘れた場合の注意について＞母集団 PK 解析で構築した最終モデルを用いて、投与忘れの影響をシミュレーションして検討した。

予定した投与日からの経過日数が 4 日間以内（すなわち、次回投与までの期間が 3 日間［72 時間］以上）の場合、気づいた時点で直ちに忘れた回のチルゼパチドを投与すると、次の予定された投与により一過性の血漿中チルゼパチド濃度の増加が認められるが、その程度は約 15%である。予定した投与日からの経過日数が 5 日間以上の場合、忘れた回のチルゼパチドを投与すると、その次の投与により、曝露量が約 20%以上増加する可能性がある。

このことから、投与を忘れた場合は次回投与までの期間が 3 日間（72 時間）以上であれば、気づいた時点で直ちに投与する。また、次回投与までの期間が 3 日間（72 時間）未満であれば忘れた回は投与せず、次のあらかじめ定めた曜日に投与することが適切であると考えられた。いずれの場合も、患者はその後、通常の週 1 回の投薬スケジュールを再開する。また、週 1 回投与の曜日を変更する必要がある場合は、前回投与から少なくとも 3 日間（72 時間）以上間隔を空けることが適切であると考えられた。

以上より、第 1.8.3.1 項の用法及び用量に関連する注意（案）7.3 を設定した。

1.8.4　使用上の注意（案）及びその設定根拠

本剤の使用上の注意（案）は、本剤の臨床試験結果、企業中核データシート［Company Core Data Sheet（CCDS）］、医薬品リスク管理計画書（案）及び国内で承認されているグルカゴン様ペプチド-1（GLP-1）受容体作動薬及びマンジャロの使用上の注意を踏まえて設定した。

使用上の注意（案）	設定根拠
2. 禁忌（次の患者には投与しないこと） 2.1 本剤の成分に対し過敏症の既往歴のある患者 2.2 糖尿病性ケトアシドーシス、糖尿病性昏睡又は前昏睡、1 型糖尿病の患者［インスリン製剤による速やかな治療が必須となるので、本剤を投与すべきでない。］ 2.3 2 型糖尿病を有する患者における重症感染症、手術等の緊急の場合［インスリン製剤による血糖管理が望まれるので、本剤の投与は適さない。］	2.1 CCDS 及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。 2.2 本剤は肥満症治療を適応としているが、2 型糖尿病を有する肥満症患者に本剤の血糖降下作用を目的として使用されることも考えられる。そのため、マンジャロ及び GLP-1 受容体作動薬と同様の禁忌を設定すべきと考えた。これらの患者はインスリン製剤による治療が必須であり、CCDS 及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。 2.3 2.2 と同様に、これらの状態にある 2 型糖尿病を有する患者ではインスリン製剤による血糖管理が必要であるため、マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
5. 効能又は効果に関連する注意 本剤の適用にあたっては、あらかじめ肥満症治療の基本である食事療法・運動療法を行っても、十分な効果が得られない場合で、薬物治療の対象として適切と判断された患者のみを対象とすること。肥満に関連する健康障害は、臨床試験に組み入れられた患者背景を参考に判断すること。［17.1.1 参照］	肥満症治療における基本的な考え方及び臨床試験に組み入れられた患者背景に基づき設定した。
7. 用法及び用量に関連する注意 7.1 本剤の用量調節に際しては、以下の点に留意すること。 ・胃腸障害等の発現により忍容性が得られない患者では減量又は漸増の延期を考慮すること。 ・患者の体重減少の程度や本剤に対する忍容性に応じて、週 1 回 5mg で治療を継続することも考慮すること。［17.1.2 参照］	・胃腸障害が用量依存的に多くなる傾向が認められることから、胃腸障害への忍容性を考慮の上で、増量や減量の必要性を検討する旨の注意喚起を設定した。 ・1.8.3.2.2 項参照。
7.2 本剤は週 1 回投与する薬剤であり、同一曜日に投与させること。	本剤は週 1 回投与の薬剤であることから、本剤の薬物動態プロファイルに基づき設定した。
7.3 投与を忘れた場合は、次回投与までの期間が 3 日間（72 時間）以上であれば、気づいた時点で直ちに投与し、その後はあらかじめ定めた曜日に投与すること。次回投与までの期間が 3 日間（72 時間）未満であれば投与せず、次のあらかじめ定めた曜日に投与すること。なお、週 1 回投与の曜日を変更する必要がある場合は、前回投与から少なくとも 3 日間（72 時間）以上間隔を空けること。	1.8.3.2.2 項参照。
8. 重要な基本的注意 8.1 本剤投与中は食事療法・運動療法を継続すること。定期的に体重、血糖、血圧、脂質等を確認し、本剤を 3～4 ヵ月間投与しても改善傾向が認められない場合には、本剤の投与を中止すること。本剤を 3～4 ヵ月間投与して改善傾向が認められた場合、その後も定期的に体重、血糖、血圧、脂質等を確認して患者の状態を十分に観察し、効果が不十分な場合には本剤の投与中止を検討すること。	肥満症治療に対する基本的な考え方に基づき設定した。
8.2 本剤は持続性製剤であり、本剤中止後も効果が持続する可能性があるため、血糖値の変動や副作用予防、副作用発現時の処置について十分留意すること。［16.1 参照］	本剤は持続性 GIP/GLP-1 受容体作動薬であり、本剤の投与中止後もその効果が持続する可能性があることから、マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。

使用上の注意（案）	設定根拠
8.3 急性膵炎が発現することがあるので、急性膵炎の初期症状（嘔吐を伴う持続的な激しい腹痛等）があらわれた場合は、使用を中止し、速やかに医師の診断を受けるよう指導すること。［9.1.2、11.1.2 参照］	CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.4 胃腸障害が発現した場合、急性膵炎の可能性を考慮し、必要に応じて画像検査等による原因精査を考慮するなど、慎重に対応すること。［9.1.2、11.1.2 参照］	CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.5 下痢、嘔吐から脱水を続発し、急性腎障害に至るおそれがあるので、患者の状態に注意すること。	CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.6 本剤投与中は、甲状腺関連の症候の有無を確認し、異常が認められた場合には、専門医を受診するよう指導すること。［15.2 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.7 胆石症、胆嚢炎、胆管炎又は胆汁うっ滞性黄疸が発現するおそれがあるので、腹痛等の腹部症状がみられた場合には、必要に応じて画像検査等による原因精査を考慮するなど、適切に対応すること。［11.1.3 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.8 血圧低下がみられた場合には患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。	CCDS 及びマンジャロの使用上の注意を参考に設定した。
8.9 本剤の自己注射にあたっては、患者に十分な教育訓練を実施した後、患者自ら確実に投与できることを確認した上で、医師の管理指導のもと実施すること。また、器具の安全な廃棄方法について指導を徹底すること。添付されている取扱説明書を必ず読むよう指導すること。	自己注射に対する基本的注意として設定した。
8.10 本剤は血糖降下作用を有するが、インスリンの代替薬ではない。2 型糖尿病を有する患者に対する本剤の投与に際しては、患者のインスリン依存状態を確認し、投与の可否を判断すること。インスリン依存状態の患者で、インスリンから GLP-1 受容体作動薬に切り替え、急激な高血糖及び糖尿病性ケトアシドーシスが発現した症例が報告されている。	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.11 本剤の使用にあたっては、患者に対し、低血糖症状及びその対処方法について十分説明すること。［9.1.3、11.1.1 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.12 低血糖を起こすことがあるので、高所作業、自動車の運転等に従事している患者に投与するときは注意すること。［11.1.1 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.13 急激な血糖コントロールの改善に伴い、糖尿病網膜症の顕在化又は増悪があらわれることがあるので、注意すること。［9.1.4 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.14 本剤はチルゼパチドを含有しているため、マンジャロ等他のチルゼパチド含有製剤あるいはその他の GLP-1 受容体作動薬等の GLP-1 受容体に対するアゴニスト作用を有する薬剤と併用しないこと。	GLP-1 受容体作動薬の使用上の注意を参考に設定した。
8.15 本剤と DPP-4 阻害剤はいずれも GLP-1 受容体及び GIP 受容体を介した血糖降下作用を有している。2 型糖尿病を有する患者において両剤を併用した際の臨床試験成績はなく、有効性及び安全性は確認されていない。	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
9. 特定の背景を有する患者に関する注意 **9.1 合併症・既往歴等のある患者** **9.1.1 重症胃不全麻痺等の重度の胃腸障害のある患者** 胃腸障害の症状が悪化するおそれがある。	これらの患者を対象とした臨床試験は実施しておらず慎重に投与する必要があることから、CCDS に基づき設定した。

使用上の注意（案）	設定根拠
9.1.2 膵炎の既往歴のある患者 ［8.3、8.4、11.1.2 参照］	これらの患者を対象とした臨床試験は実施しておらず慎重に投与する必要があることから、CCDS に基づき設定した。
9.1.3 低血糖を起こすおそれがある以下の患者又は状態 ・脳下垂体機能不全又は副腎機能不全 ・栄養不良状態、飢餓状態、不規則な食事摂取、食事摂取量の不足又は衰弱状態 ・激しい筋肉運動 ・過度のアルコール摂取 ［8.11、11.1.1 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
9.1.4 増殖糖尿病網膜症、糖尿病黄斑浮腫、急性期治療を要する非増殖糖尿病網膜症を合併する患者又はこれらの既往歴のある患者 ［8.13 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
9.4 生殖能を有する者 妊娠する可能性のある女性には、本剤投与中及び最終投与後 1 ヵ月間において避妊する必要性及び適切な避妊法について説明すること。［9.5 参照］	「医薬品の投与に関連する避妊の必要性等に関するガイダンスについて」（令和 5 年 2 月 16 日付け薬生薬審発 0216 第 1 号、薬生安発 0216 第 1 号厚生労働省医薬・生活衛生局医薬品審査管理課長、医薬安全対策課長連名通知）に基づき、設定した。
9.5 妊婦 妊婦又は妊娠している可能性のある女性には本剤を投与しないこと。 生殖発生毒性試験において、妊娠ラットに本剤を投与した場合、臨床最大用量でヒトに投与したときの本剤の曝露量を下回る用量（臨床最大用量での C_{max} 比較において 0.64 倍、AUC 比較において 0.22 倍）で、胎児毒性（骨格奇形、内臓奇形等）が認められた。これらの所見は母動物の摂餌量の低値及び体重の低値を伴うものであった。［9.4 参照］	妊娠又は妊娠している可能性のある女性を対象とした臨床試験は実施しておらず、これらの患者における本剤の安全性は確立していないため、CCDS 及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
9.6 授乳婦 治療上の有益性及び母乳栄養の有益性を考慮し、授乳の継続又は中止を検討すること。本剤のヒト乳汁中への移行は不明である。	本剤のヒト乳汁中への移行は不明であり、CCDS に基づき設定した。
9.7 小児等 小児等を対象とした有効性及び安全性を指標とした臨床試験は実施していない。	18 歳未満の小児における有効性及び安全性は確立していないため、CCDS に基づき設定した。
9.8 高齢者 患者の状態を観察しながら慎重に投与すること。一般に生理機能が低下していることが多い。投与に際しては、臨床試験に組み入れられた患者背景を参考にすること。［17.1.1 参照］	マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。

<table>
<tr><th>使用上の注意（案）</th><th>設定根拠</th></tr>
<tr><td>

10. 相互作用

10.2 併用注意（併用に注意すること）

<table>
<tr><th>薬剤名等</th><th>臨床症状・措置方法</th><th>機序・危険因子</th></tr>
<tr><td>糖尿病用薬
ビグアナイド系薬剤
スルホニルウレア剤
速効型インスリン分泌促進剤
α-グルコシダーゼ阻害剤
チアゾリジン系薬剤
DPP-4阻害剤
インスリン製剤
SGLT2阻害剤等
［11.1.1 参照］</td><td>低血糖の発現に注意すること。特にスルホニルウレア剤、速効型インスリン分泌促進剤又はインスリン製剤と併用する場合、低血糖のリスクが増加するおそれがある。これらの薬剤と併用する場合、低血糖のリスクを軽減するため、これらの薬剤の減量を検討すること。</td><td>血糖降下作用が増強される。</td></tr>
<tr><td>経口避妊薬
［16.7参照］</td><td>特に投与開始初期又は漸増後初期では併用する経口避妊薬の効果を減弱させるおそれがある。</td><td>本剤の胃内容物排出遅延作用による。</td></tr>
<tr><td>クマリン系薬剤
ワルファリンカリウム</td><td>GLP-1 受容体作動薬との併用によりワルファリンの t_{max} が遅延したとの報告があり、エキセナチドで出血を伴う INR 増加が報告されている。</td><td>本剤の胃内容物排出遅延作用による。</td></tr>
</table>

</td><td>糖尿病用薬に関して、CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
経口避妊薬に関して、本剤との薬物相互作用試験で、本剤との併用により、経口避妊薬の曝露量の低下が認められていることから設定した。
ワルファリンに関して、本剤とワルファリンとの併用経験が限られていることから、既存の GLP-1 受容体作動薬でのワルファリンとの併用に関する使用上の注意を参考に設定した。</td></tr>
<tr><td>

11. 副作用

次の副作用があらわれることがあるので、観察を十分に行い、異常が認められた場合には投与を中止するなど適切な処置を行うこと。

11.1 重大な副作用

11.1.1 低血糖（頻度不明）

低血糖症状（脱力感、高度の空腹感、冷汗、顔面蒼白、動悸、振戦、頭痛、めまい、嘔気、視覚異常等）があらわれることがある。また、2 型糖尿病患者においてインスリン製剤又はスルホニルウレア剤との併用時に重篤な低血糖症状があらわれ意識消失を来す例も報告されている。

低血糖症状が認められた場合は、糖質を含む食品を摂取するなど適切な処置を行うこと。ただし、α-グルコシダーゼ阻害剤との併用時はブドウ糖を投与すること。［8.11、8.12、9.1.3、10.2、17.1.1-17.1.3 参照］

</td><td>CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。</td></tr>
<tr><td>

11.1.2 急性膵炎（0.1%未満）

嘔吐を伴う持続的な激しい腹痛等の異常が認められた場合には、本剤の投与を中止し、適切な処置を行うこと。また、膵炎と診断された場合は、再投与は行わないこと。［8.3、8.4、9.1.2 参照］

</td><td>マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。</td></tr>
<tr><td>

11.1.3 胆嚢炎（頻度不明）、**胆管炎**（0.1%未満）、**胆汁うっ滞性黄疸**（頻度不明）

［8.7 参照］

</td><td>マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。</td></tr>
<tr><td>

11.1.4 アナフィラキシー、血管性浮腫（いずれも頻度不明）

</td><td>マンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。</td></tr>
<tr><td>

11.2 その他の副作用

<table>
<tr><th>副作用分類</th><th>5%以上</th><th>1～5%未満</th><th>1%未満</th></tr>
<tr><td>循環器</td><td></td><td></td><td>心拍数増加注)、低血圧、血圧低下</td></tr>
<tr><td>消化器</td><td>悪心、嘔吐、下痢、便秘、腹痛、消化不良、食欲減退</td><td>腹部膨満、胃食道逆流性疾患、おくび、鼓腸</td><td></td></tr>
<tr><td>肝胆道</td><td></td><td></td><td>胆石症</td></tr>
<tr><td>眼</td><td></td><td></td><td>糖尿病網膜症</td></tr>
</table>

</td><td>マンジャロの使用上の注意及び臨床試験の結果から本剤投与との間に関連性があると判断された事象を CCDS に基づき副作用として設定した。
なお、事象の頻度は 3 種の評価試験（GPHZ 試験、GPHK 試験及び GPHL 試験）における頻度に基づき算出した。</td></tr>
</table>

使用上の注意（案）	設定根拠
<table><tr><td>注射部位</td><td>注射部位反応（紅斑、そう痒感、疼痛、腫脹等）</td><td></td><td></td></tr><tr><td>免疫系</td><td></td><td></td><td>過敏症(湿疹、発疹、そう痒性皮疹等)</td></tr><tr><td>精神神経系</td><td></td><td></td><td>味覚不全、異常感覚</td></tr><tr><td>臨床検査</td><td></td><td></td><td>膵アミラーゼ増加、リパーゼ増加、体重減少</td></tr><tr><td>その他</td><td></td><td>疲労、浮動性めまい、脱毛症</td><td></td></tr></table>注）心拍数の増加が持続的にみられた場合には患者の状態を十分に観察し、異常が認められた場合には適切な処置を行うこと。	
14. 適用上の注意 **14.1 薬剤投与前の注意** 注入器の破損又は異常がないこと、薬液の変色や浮遊物がないことを確認すること。	投与前に目視により本剤の品質に異常がないか確認することを記載した。
14.2 薬剤投与時の注意 皮下注射は、腹部、大腿部又は上腕部に行う。同じ部位の中で注射する場合、毎回注射する場所を変更すること。静脈内及び筋肉内に投与しないこと。	CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。
15. その他の注意 **15.1 臨床使用に基づく情報** 国内外の第 III 相試験 5 試験（3704 例）において、抗薬物抗体が評価可能な 3596 例のうち、抗チルゼパチド抗体が 65.5%（2357 例）に発現した。また、交差抗体及び中和抗体が評価可能な 3573 例のうち、内因性 GIP 又は GLP-1 に対する交差抗体はそれぞれ 42.8%（1531 例）及び 18.7%（668 例）に、内因性 GIP 又は GLP-1 に対する中和抗体はそれぞれ 0.8%（28 例）及び 0.1%（3 例）に、チルゼパチドの GIP 受容体又は GLP-1 受容体の活性化に対する中和抗体はそれぞれ 2.4%（85 例）及び 2.2%（78 例）に発現した。	肥満症患者を対象とした 5 つの第 3 相臨床試験の結果について、CCDS に基づき設定した。
15.2 非臨床試験に基づく情報 雌雄ラットを用いた 2 年間がん原性試験において、本剤を 0.15、0.50 及び 1.5mg/kg の用量（それぞれ臨床最大用量をヒトに皮下投与した際の AUC の 0.11、0.31 及び 0.88 倍の AUC をもたらす用量）で週 2 回皮下投与したところ、対照群と比較して、甲状腺 C 細胞腫瘍（腺腫及び癌）の発生頻度の増加がすべての用量でみられた。rasH2 トランスジェニックマウスを用いた 6 ヵ月間がん原性試験において、本剤を 1、3 及び 10mg/kg の用量で週 2 回皮下投与したところ、甲状腺 C 細胞の過形成あるいは腫瘍の発生頻度に増加は認められなかった。甲状腺髄様癌の既往のある患者及び甲状腺髄様癌又は多発性内分泌腫瘍症 2 型の家族歴のある患者に対する本剤の安全性は確立していない。［8.6 参照］	CCDS 及びマンジャロ及び GLP-1 受容体作動薬の使用上の注意を参考に設定した。 これらの患者を対象とした本剤の臨床試験は実施されていないことから設定した。

ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

1.9　一般的名称に係る文書

日本イーライリリー株式会社

薬生薬審発 0601 第１号
令 和 ３ 年 ６ 月 １ 日

各都道府県衛生主管部（局）長　殿

厚生労働省医薬・生活衛生局医薬品審査管理課長
（　　公　　印　　省　　略　　）

医薬品の一般的名称について

標記については、「医薬品の一般的名称の取扱いについて（平成 18 年３月 31 日薬食発第 0331001 号厚生労働省医薬食品局長通知）」等により取り扱っているところです。今般、我が国における医薬品の一般的名称（以下「JAN」という。）について、新たに別添のとおり定めたので、御了知の上、貴管下関係業者に周知方よろしく御配慮願います。

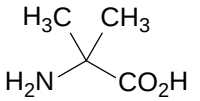
（参照）
「日本医薬品一般的名称データベース」https://jpdb.nihs.go.jp/jan/Default.aspx
（別添の情報のうち、JAN 以外の最新の情報は、当該データベースの情報で対応することとしています。）

別添

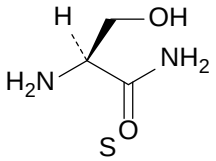
（別表２）INN に収載された品目の我が国における医薬品一般的名称
（平成 18 年 3 月 31 日薬食審査発第 0331001 号厚生労働省医薬食品局審査管理課長通知に示す別表２）

登録番号　302-4-B10
JAN（日本名）：チルゼパチド
JAN（英　名）：Tirzepatide

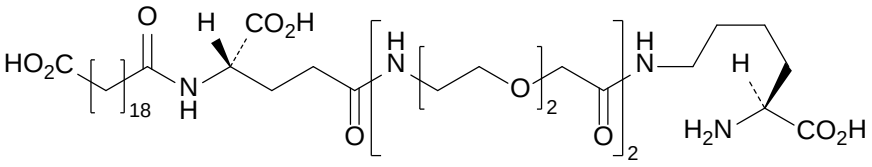
YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS



X
2, 13
2-methylAla



39
Ser-NH2



K
20
*N*6-{*N*-(hydrogen icosanedioyl)-
γ-Glu-bis[iminobis(ethylenoxy)acetyl]}-Lys

$C_{225}H_{348}N_{48}O_{68}$

チルゼパチドは，ヒトグルコース依存性インスリン分泌刺激ポリペプチド（GIP）受容体及びヒトグルカゴン様ペプチド-1（GLP-1）受容体のアゴニストであり，2 及び 13 番目のアミノ酸残基は 2-methylAla，C 末端はアミド化された Ser である．さらに，1,20-イコサン二酸が 1 個の Glu 及び 2 個の 8-アミノ-3,6-ジオキサオクタン酸で構成されるリンカーを介して 20 番目の Lys に結合している．チルゼパチドは 39 個のアミノ酸残基からなる合成ペプチドである．

Tirzepatide is an agonist of human glucose-dependent insulinotropic polypeptide (GIP) and human glucagon-like peptide-1 (GLP-1) receptors, whose amino acid residues at positions 2 and 13 are 2-methylAla, and the C-terminus is amidated Ser. A 1,20-icosanedioic acid is attached to Lys at position 20 via a linker which consists of a Glu and two 8-amino-3,6-dioxaoctanoic acids. Tirzepatide is a synthetic peptide consisting of 39 amino acid residues.

※　JAN 以外の情報は、参考として掲載しました。

Recommended International Nonproprietary Names (Rec. INN): List 63
Dénominations communes internationales recommandées (DCI Rec.): Liste 63
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 63
(WHO Drug Information, Vol. 24, No. 1, 2010)

p.62	*suprimáse*	*insertese*
	iodine (^{124}I) girentuximab	iodo (^{124}I) girentuximab

Recommended International Nonproprietary Names (Rec. INN): List 81
Dénominations communes internationales recommandées (DCI Rec.): Liste 81
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 81
(WHO Drug Information, Vol. 33, No. 1, 2019)

p.123 **tirzepatidum**

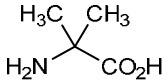
tirzepatide	*replace the structure by the following one*
tirzépatide	*remplacer la structure par la suivante*
tirzepatida	*sustitúyase la estructura por la siguiente*

Sequence / Séquence / Secuencia

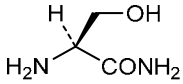
YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS 39

Modified residues / Résidus modifiés / Restos modificados

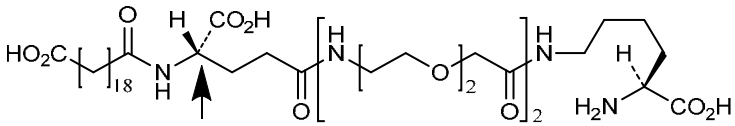
X (2, 13) 2-methylalanine (Aib)



S (39) L-serinamide



K (20): N^6-{*N*-(hydrogen icosanedioyl)-γ-Glu-bis[iminobis(ethylenoxy)acetyl]}-Lysine



Recommended International Nonproprietary Names (Rec. INN): List 83
Dénominations communes internationales recommandées (DCI Rec.): Liste 83
Denominaciones Comunes Internacionales Recomendadas (DCI Rec.): Lista 83
(WHO Drug Information, Vol. 34, No. 1, 2020)

p.34 **betibeglogenum autotemcelum #**

betibeglogene autotemcel	*replace the description by the following one*
bétibéglogène autotemcel	*remplacer la description par la suivante*
betibeglogén autotemcel	*sustitúyase la descripción por la siguiente*

autologous CD34+ hematopoietic stem cells **obtained from mobilised peripheral blood of patients with beta-thalassemia**, transduced *ex vivo* with *betibeglogene darolentivec (116)(78),* a self-inactivating human immunodeficiency virus-1 (HIV-1)-derived lentiviral vector encoding a T87Q-mutated form of the human hemoglobin subunit beta (HBB, beta-globin) gene under the control of a human β-globin promoter and a 3' β-globin enhancer.

cellules souches hématopoïétiques CD34+ autologues **obtenues à partir de sang périphérique mobilisé de patients atteints de bêta-thalassémie,** transduites *ex vivo*

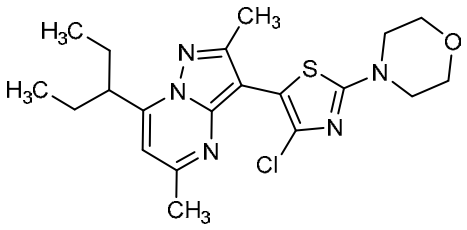
tildacerfontum

tildacerfont　3-[4-chloro-2-(morpholin-4-yl)-1,3-thiazol-5-yl]-2,5-dimethyl-7-(pentan-3-yl)pyrazolo[1,5-*a*]pyrimidine

tildacerfont　3-[4-chloro-2-(morpholin-4-yl)-1,3-thiazol-5-yl]-2,5-diméthyl-7-(pentan-3-yl)pyrazolo[1,5-*a*]pyrimidine

tildacerfont　3-[4-cloro-2-(morfolin-4-il)-1,3-tiazol-5-il]-2,5-dimetil-7-(pentan-3-il)pirazolo[1,5-*a*]pirimidina

$C_{20}H_{26}ClN_5OS$



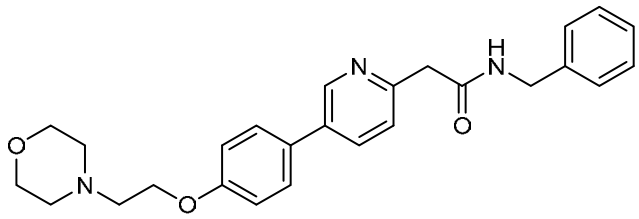
tirbanibulinum

tirbanibulin　*N*-benzyl-2-(5-{4-[2-(morpholin-4-yl)ethoxy]phenyl}pyridin-2-yl)acetamide

tirbanibuline　*N*-benzyl-2-(5-{4-[2-(morpholin-4-yl)éthoxy]phényl}pyridin-2-yl)acetamide

tirbanibulina　*N*-bencil-2-(5-{4-[2-(morfolin-4-il)etoxi]fenil}piridin-2-il)acetamida

$C_{26}H_{29}N_3O_3$



tirzepatidum

tirzepatide　L-tyrosyl-2-methylalanyl-L-α-glutamylglycyl-L-threonyl-L-phenylalanyl-L-threonyl-L-seryl-L-α-aspartyl-L-tyrosyl-L-seryl-L-isoleucyl-2-methylalanyl-L-leucyl-L-α-aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutaminyl-*N*^{6}-[(22*S*)-22,42-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracontan-1-oyl]-L-lysyl-L-alanyl-L-phenylalanyl-L-valyl-L-glutaminyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-alanylglycylglycyl-L-prolyl-L-seryl-L-serylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-serinamide

tirzépatide　L-tyrosyl-2-méthylalanyl-L-α-glutamylglycyl-L-thréonyl-L-phénylalanyl-L-thréonyl-L-séryl-L-α-aspartyl-L-tyrosyl-L-séryl-L-isoleucyl-2-méthylalanyl-L-leucyl-L-α-aspartyl-L-lysyl-L-isoleucyl-L-alanyl-L-glutaminyl-*N*^{6}-[(22*S*)-22,42-dicarboxy-10,19,24-trioxo-3,6,12,15-tétraoxa-9,18,23-triazadotétracontan-1-oyl]-L-lysyl-L-alanyl-L-phénylalanyl-L-valyl-L-glutaminyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-alanylglycylglycyl-L-prolyl-L-séryl-L-sérylglycyl-L-alanyl-L-prolyl-L-prolyl-L-prolyl-L-sérinamide

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tirzepatida

L-tirosil-2-metilalanil-L-α-glutamilglicil-L-treonil-L-fenilalanil-L-treonil-L-seril-L-α-aspartil-L-tirosil-L-seril-L-isoleucil-2-metilalanil-L-leucil-L-α-aspartil-L-lisil-L-isoleucil-L-alanil-L-glutaminil-N^6-[(22*S*)-22,42-dicarboxi-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracontan-1-oil]-L-lisil-L-alanil-L-fenilalanil-L-valil-L-glutaminil-L-triptofil-L-leucil-L-isoleucil-L-alanilglicilglicil-L-prolil-L-seril-L-serilglicil-L-alanil-L-prolil-L-prolil-L-prolil-L-serinamida

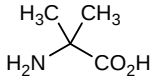
$C_{225}H_{348}N_{48}O_{68}$

Sequence / Séquence / Secuencia

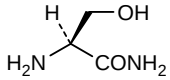
YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS 39

Modified residues / Résidus modifiés / Restos modificados

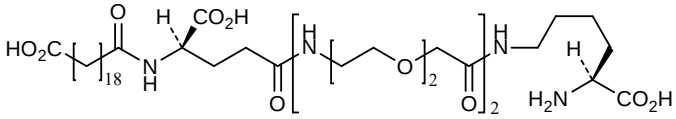
X (2 , 13) 2-methylalanine (Aib)



S (39) L-serinamide



K (20) N^6-{*N*-(hydrogen icosanedioyl)-γ-Glu-bis[iminobis(ethylenoxy)acetyl]}-Lysine



tofersenum

tofersen

all-P-ambo-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)adenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)guanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-5-methyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-deoxy-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methylcytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-*P*-thioadenylyl-(3'→5')-2'-*O*-(2-methoxyethyl)guanylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-methoxyethyl)-5-methyluridine

tofersen

tout-P-ambo-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)adénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioguanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)guanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-*P*-thioadénylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-désoxy-*P*-thioadénylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-5-méthyl-*P*-thiocytidylyl-(3'→5')-*P*-thiothymidylyl-(3'→5')-2'-désoxy-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthylcytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-*P*-thioadénylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)guanylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyl-*P*-thiocytidylyl-(3'→5')-2'-*O*-(2-méthoxyéthyl)-5-méthyluridine

ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

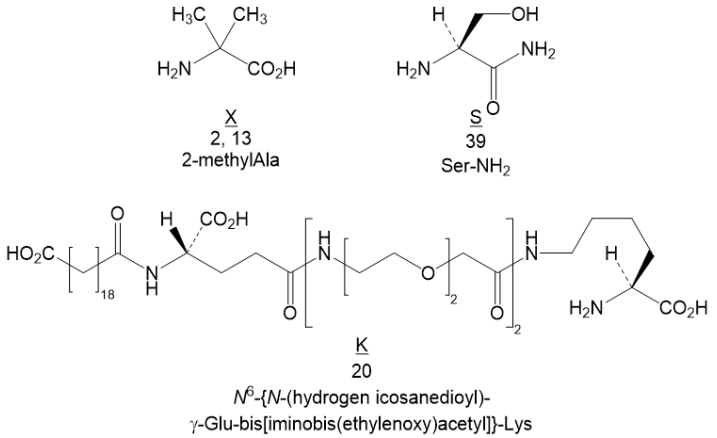
1.10　毒薬・劇薬等の指定審査資料のまとめ

日本イーライリリー株式会社

目次

1.10　毒薬・劇薬等の指定審査資料のまとめ

表 1.10-1 毒薬・劇薬等の指定審査資料のまとめ（現行）

化学名・別名	チルゼパチド及びその製剤
構造式	YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS 
効能・効果	2 型糖尿病
用法・用量	通常、成人には、チルゼパチドとして週 1 回 5mg を維持用量とし、皮下注射する。ただし、週 1 回 2.5mg から開始し、4 週間投与した後、週 1 回 5mg に増量する。 なお、患者の状態に応じて適宜増減するが、週 1 回 5 mg で効果不十分な場合は、4 週間以上の間隔で 2.5 mg ずつ増量できる。ただし、最大用量は週 1 回 15 mg までとする。
劇薬等の指定	劇薬、処方箋医薬品
市販名及び有効成分・分量	原体：チルゼパチド 製剤： マンジャロ皮下注 2.5mg アテオス（1 キット中チルゼパチド 2.5 mg 含有） マンジャロ皮下注 5mg アテオス（1 キット中チルゼパチド 5 mg 含有） マンジャロ皮下注 7.5mg アテオス（1 キット中チルゼパチド 7.5 mg 含有） マンジャロ皮下注 10mg アテオス（1 キット中チルゼパチド 10 mg 含有） マンジャロ皮下注 12.5mg アテオス（1 キット中チルゼパチド 12.5 mg 含有） マンジャロ皮下注 15mg アテオス（1 キット中チルゼパチド 15 mg 含有）

毒性

単回投与

動物種	性	投与経路	LD_0（単位）
マウス	♂♀	皮下	>30[a]
ラット	♂♀	皮下	>3[b]
サル	♂♀	皮下	>0.5[c]

[a]：4 週間反復投与毒性試験の初回投与後の所見に基づき推定。
[b]：6 カ月反復投与毒性試験の初回投与後の所見に基づき推定。
[c]：6 カ月反復投与毒性試験の初回投与後の所見に基づき推定。

反復投与（皮下投与）

動物種	投与期間	投与量 (mg/kg)	NOAEL (mg/kg)	特記すべき異常所見
マウス	4 週	1, 3, 30	30	≧1：体重↓、削痩(3 mg/kg 除く)、赤血球数↓(雌)、ヘモグロビン↓(雌)、ヘマトクリット↓(雌)、グルコース↓(雄)、尿素窒素↑(雄)、卵巣黄体数↓、子宮及び子宮頸部；萎縮、膣；上皮萎縮、副腎；皮質 X 帯の退縮及び空胞変性↓(雌)、顎下腺；顆粒管分泌枯渇(雌)、肝：グリコーゲン↓(雄)、肝重量↓(雄) ≧3：アルブミン↑(雄)、膵臓；腺房細胞におけるチモーゲン顆粒↓(雄)
ラット	1 カ月	0.15, 0.5, 1.5	1.5	≧0.15：体重↓、摂餌量↓、赤血球数↓(雌)、ヘモグロビン↓(雌)、ヘマトクリット↓(雌)、総タンパク↓(雄)、アルブミン↓(雄)、ALP↑(雄) ≧0.5：総タンパク↓(雌)、アルブミン↓(雌)、ALP↑(雌)、Ca↓、グロブリン↓(雄) 1.5：尿量↑(雄)、尿比重↓(雄)
ラット	6 カ月	0.5, 1.5, 3	3	≧0.5：体重↓、摂餌量↓、網状赤血球数↓、アミラーゼ↓(雌)、総タンパク↓、アルブミン↓、グロブリン↓、総コレステロール↓、トリグリセリド↓、Ca↓(雌)、膵臓；腺房細胞におけるチモーゲン枯渇/びまん性萎縮(雌)/膵島線維化↓(雄)/膵島色素↓(雄)、皮膚／皮下組織；脂肪細胞萎縮、大腿骨骨髄；脂肪細胞↓(雌) ≧1.5：アミラーゼ↓(雄)、膵臓；びまん性萎縮(雄)、脾臓；髄外造血↓、副腎；皮質空胞化↓(雄)、心臓；心筋症↓(雄) 3：円背位、大腿骨骨髄；脂肪細胞↓(雄)、心臓；心筋症↓(雌)
サル	1 カ月	0.05, 0.15, 0.5	0.15	≧0.05：摂餌量↓(雌)、心臓；脂肪組織委縮(雌)、皮膚/皮下組織；脂肪組織委縮(雌) ≧0.15：体重↓、摂餌量↓(雄)、心拍数↑(雄)、膵臓；腺房細胞におけるチモーゲン顆粒↓(雌)、大腿骨骨髄；脂肪組織委縮(雌)、心臓；脂肪組織委縮(雄)、皮膚/皮下組織；脂肪組織委縮(雄) 0.5：削痩(雌)、膵臓；腺房細胞におけるチモーゲン顆粒↓(雄)、大腿骨骨髄；脂肪組織委縮(雄)
サル	6 カ月	0.05, 0.15, 0.5	0.5	≧0.05：体重増加量↓(雄)、尿量↑(雄) ≧0.15：摂餌量↓(雌)、脱水、心拍数↑ 0.5：体重増加量↓(雌)、摂餌量↓(雄)、膵臓；チモーゲン顆粒↓(雌)

略語：↑＝増加、↓減少、ALP＝アルカリフォスファターゼ、Ca＝カルシウム、NOAEL＝無毒性量。

副作用

2 型糖尿病患者を対象とした国内第 3 相試験及び日本を含む国際共同第 3 相試験において、本剤を投与した 1638 例中（日本人症例 1048 例を含む）797 例（48.7%）に因果関係を否定できない有害事象（臨床検査値以上を含む）が認められた。

副作用の種類	例数（発現割合）
悪心	257（15.7%）

	食欲減退　182（11.1%） 下痢　154（9.4%） 便秘　152（9.3%） 嘔吐　99（6.0%） 臨床検査値異常の種類　例数（発現割合） リパーゼ増加　51（3.1%） 体重減少　28（1.7%） アミラーゼ増加　26（1.6%） 心拍数増加　11（0.7%） 膵酵素増加　6（0.4%）
会社	日本イーライリリー株式会社 製剤：輸入

表 1.10-2 毒薬・劇薬等の指定審査資料のまとめ（追加）

<table>
<tr><td>化学名・別名</td><td></td></tr>
<tr><td>構造式</td><td></td></tr>
<tr><td>効能・効果</td><td>肥満症
ただし、高血圧、脂質異常症又は 2 型糖尿病のいずれかを有し、食事療法・運動療法を行っても十分な効果が得られず、以下に該当する場合に限る。
・ BMI が 27 kg/m^2 以上であり、2 つ以上の肥満に関連する健康障害を有する
・ BMI が 35 kg/m^2 以上</td></tr>
<tr><td>用法・用量</td><td>通常、成人には、チルゼパチドとして週 1 回 2.5 mg から開始し、4 週間の間隔で 2.5 mg ずつ増量し、週 1 回 10 mg を皮下注射する。なお、患者の状態に応じて適宜増減するが、週 1 回 5 mg まで減量、又は 4 週間以上の間隔で 2.5 mg ずつ週 1 回 15 mg まで増量できる。</td></tr>
<tr><td>劇薬等の指定</td><td></td></tr>
<tr><td>市販名及び有効成分・分量</td><td>原体：チルゼパチド
製剤：
ゼップバウンド皮下注 2.5mg アテオス（1 キット中チルゼパチド 2.5 mg 含有）
ゼップバウンド皮下注 5mg アテオス（1 キット中チルゼパチド 5 mg 含有）
ゼップバウンド皮下注 7.5mg アテオス（1 キット中チルゼパチド 7.5 mg 含有）
ゼップバウンド皮下注 10mg アテオス（1 キット中チルゼパチド 10 mg 含有）
ゼップバウンド皮下注 12.5mg アテオス（1 キット中チルゼパチド 12.5 mg 含有）
ゼップバウンド皮下注 15mg アテオス（1 キット中チルゼパチド 15 mg 含有）</td></tr>
<tr><td>毒性</td><td></td></tr>
<tr><td>副作用</td><td>肥満症患者を対象とした国内第 3 相試験及び日本を含む国際共同第 3 相試験において、本剤を投与した 2635 例中（日本人症例 253 例を含む）1502 例（57.0%）に因果関係を否定できない有害事象（臨床検査値以上を含む）が認められた。
副作用の種類　例数（発現割合）
悪心　642（24.4%）
下痢　437（16.6%）
便秘　301（11.4%）
嘔吐　241（9.1%）
食欲減退　240（9.1%）

臨床検査値異常の種類　例数（発現割合）
アミラーゼ増加　22（0.8%）
リパーゼ増加　20（0.7%）
血中カルシトニン増加　17（0.6%）
膵酵素増加　11（0.4%）</td></tr>
</table>

	血中重炭酸塩減少　　10（0.4%）
会社	日本イーライリリー株式会社 製剤：輸入

ゼップバウンド皮下注 2.5mg アテオス
ゼップバウンド皮下注 5mg アテオス
ゼップバウンド皮下注 7.5mg アテオス
ゼップバウンド皮下注 10mg アテオス
ゼップバウンド皮下注 12.5mg アテオス
ゼップバウンド皮下注 15mg アテオス

1.12　添付資料一覧

日本イーライリリー株式会社

1.12 添付資料一覧

第3部（モジュール3）：品質に関する文書
3.2　データ又は報告書
3.2.S　原薬

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
3.2.S	Drug Substance	NA	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	NA	評価資料	無

3.2.P　製剤

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
3.2.P	Drug Product	NA	（20[redacted]年[redacted]月）	Eli Lilly and Company / [redacted]	国外	NA	評価資料	無

3.2.A　その他

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
3.2.A	Appendices	NA	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	NA	評価資料	無

3.2.R　各極の要求資料

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
3.2.R	Regional Information	NA	NA	NA	NA	NA	NA	－

第4部（モジュール4）：非臨床試験報告書
4.2　試験報告書
4.2.1　薬理試験
4.2.1.1　効力を裏付ける試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
4.2.1.1.1	ENDO190: Tirzepatide regulation of adipocyte function in vitro	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料	無
4.2.1.1.2	ENDO187: Brain Enrichment and Distribution of Peripherally Administered Tirzepatide-AlexaFluor647 in Lean, Male C57Bl/6 Mouse	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料	無
4.2.1.1.3	ENDO186: The In vivo Effect of LY3298176 on Immediate Early Gene c-Fos Expression in Mouse Brain	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料	無

4.2.1.1.4	ENDO179: Effect of LY3298176 on Feeding Behavior in Obese Mice In Vivo	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料	無
4.2.1.1.5	Geisler et al. 2023: Tirzepatide suppresses palatable food intake by selectively reducing preference for fat in rodents	－	（20[redacted]年[redacted]月）	Eli Lilly and Company /University of Pennsylvania	国外	－	参考資料	無
4.2.1.1.6	ENDO188: The in vivo effect of LY3289176 on fat utilization in diet-induced obese mice under calorie restriction.	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料	無

4.2.1.2 副次的薬理試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.1.3 安全性薬理試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.1.4 薬力学的薬物相互作用試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2 薬物動態試験

4.2.2.1 分析法及びバリデーション報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.2 吸収

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.3 分布

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.4 代謝

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.5 排泄

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.6 薬物動態学的薬物相互作用

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.2.7 その他の薬物動態試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3 毒性試験

4.2.3.1 単回投与毒性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.2 反復投与毒性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.3 遺伝毒性試験

4.2.3.3.1 In Vitro試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.3.2 In Vivo試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.4 がん原性試験

4.2.3.4.1 長期がん原性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.4.2 短期または中期がん原性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.4.3 その他の試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.5 生殖発生毒性試験

4.2.3.5.1 受胎能及び着床までの初期胚発生に関する試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.5.2 胚･胎児発生に関する試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.5.3 出生前及び出生後の発生並びに母体の機能に関する試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.5.4 新生児を用いた試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.6 局所刺激性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7 その他の毒性試験

4.2.3.7.1 抗原性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.2 免疫毒性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.3 毒性発現の機序に関する試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.4 依存性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.5 代謝物の毒性試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.6 不純物毒性の試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.2.3.7.7 その他の試験

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

4.3 参考文献

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	参考文献	申請電子データの提出有無
4.3.1	Glucose-Dependent Insulinotropic Polypeptide Receptor-Expressing Cells in the Hypothalamus Regulate Food Intake.	Adriaenssens AE et al.	－	－	－	Cell Metab. 2019 Nov 5;30(5):987-996.	参考文献	－
4.3.2	Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol.	Andersen A et al.	－	－	－	Nat Rev Endocrinol. 2018 Jul;14(7):390-403.	参考文献	－
4.3.3	Determination of lipoprotein lipase activity using a novel fluorescent lipase assay.	Basu D et al.	－	－	－	J Lipid Res. 2011 Apr;52(4):826-32.	参考文献	－
4.3.4	GIP Receptor Agonism Attenuates GLP-1 Receptor Agonist-Induced Nausea and Emesis in Preclinical Models.	Borner T et al.	－	－	－	Diabetes. 2021 Nov;70(11):2545-2553.	参考文献	－
4.3.5	LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: From discovery to clinical proof of concept.	Coskun T et al.	－	－	－	Mol Metab. 2018 Dec;18:3-14.	参考文献	－
4.3.6	Anorectic and aversive effects of GLP-1 receptor agonism are mediated by brainstem cholecystokinin neurons, and modulated by GIP receptor activation.	Costa A et al.	－	－	－	Mol Metab. 2022 Jan;55:101407.	参考文献	－
4.3.7	Tirzepatide suppresses palatable food intake by selectively reducing preference for fat in rodents.	Geisler CE et al.	－	－	－	Diabetes Obes Metab. 2023 Jan;25(1):56-67.	参考文献	－
4.3.8	Whole-brain activation signatures of weight-lowering drugs.	Hansen HH et al.	－	－	－	Mol Metab. 2021 May;47:101171.	参考文献	－
4.3.9	An Optimized Mouse Brain Atlas for Automated Mapping and Quantification of Neuronal Activity Using iDISCO+ and Light Sheet Fluorescence Microscopy.	Perens J et al.	－	－	－	Neuroinformatics. 2021 Jul;19(3):433-446.	参考文献	－

4.3.10	Differentiation of human subcutaneous adipocytes and measurement of lipolytic unction induced by GIP or LY3437943.	Regmi A et al.	－	－	－	STAR Protoc. 2023 May 12;4(2):102304.	参考文献	－
4.3.11	The glucose-dependent insulinotropic polypeptide (GIP) regulates body weight and food intake via CNS-GIPR signaling.	Zhang Q et al.	－	－	－	Cell Metab. 2021 Apr 6;33(4):833-844.e5.	参考文献	－

第5部（モジュール5）：臨床試験報告書

5.2　全臨床試験一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.2	全臨床試験一覧表	－	－	－	－	－	－	－

5.3　臨床試験報告書

5.3.1　生物薬剤学試験報告書

5.3.1.1　バイオアベイラビリティ（BA）試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.1.2　比較BA試験及び生物学的同等性（BE）試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.1.3　In Vitro-In Vivoの関連を検討した試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.1.4　生物学的及び理化学的分析法検討報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.1.4.1	バリデーション報告書: 151682. Method Validation for the Quantitation of LY3298176 (GIP707) in Human Plasma by HRAM LC/MS	－	（20[redacted]年[redacted]月 [Revision [redacted]]、20[redacted]年[redacted]月 [Revision [redacted]]）	[redacted]	国外	－	参考資料	無
5.3.1.4.2	バリデーション報告書: 191444. Partial Method Validation for the Quantitation of LY3298176 (GIP707) in Human Plasma by HRAM LC/MS	－	（20[redacted]年[redacted]月 [Original], 20[redacted]年[redacted]月 [Revision [redacted]]）	[redacted]	国外	－	参考資料	無
5.3.1.4.3	バリデーション報告書：400008. Quantification of LY3298176 in Human Plasma by LC/MS/MS	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無

5.3.1.4.4	バリデーション報告書：8226219. Validation of a Method for the Determination of Acetaminophen in Human Plasma by HPLC with MS/MS Detection	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無
5.3.1.4.5	バリデーション報告書：Summary Report of Statistical Analysis Results for Cross-Validation of Methods 190033PVDJS_EII (Q2 Solutions) with Method 19BASM161 V[redacted] ([redacted]) for the Determination of LY3298176 Human Plasma Concentrations	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	参考資料	無
5.3.1.4.6	Method History Report: A Summary of Assay Development and Validation for the Detection and Characterization of Anti Drug Antibodies to Tirzepatide (LY3298176)_version[redacted]	－	（20[redacted]年[redacted]月）	Lilly Research Laboratories	国外	－	参考資料	無
5.3.1.4.7	Method History Report: A Summary of the Development and Validation of Assays to Detect Neutralizing Anti-Drug Antibodies Associated with Tirzepatide (LY3298176)	－	（20[redacted]年[redacted]月[Version [redacted]、20[redacted]年[redacted]月）[Version [redacted]）	Lilly Research Laboratories	国外	－	参考資料	無
5.3.1.4.8	バリデーション報告書:[redacted]-15-061- 360. Anti - LY3298176 Antibody Assay Validation Report	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Amendment [redacted]、20[redacted]年[redacted]月[Amendment [redacted]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Addendum [redacted], Amendment [redacted]、20[redacted]年[redacted]月[Amendment [redacted]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Addendum [redacted]）	[redacted]	国外	－	参考資料	無
5.3.1.4.9	バリデーション報告書:[redacted]-20-061-1157. Anti-LY3298176 Antibody Assay In-Study Cut Point Report in Support of Clinical Protocols I8F-MC-GPGK(a), I8F-MC-GPGH(a), I8F-MC-GPGI, I8F-MC-GPGM, I8F-MC-GPGL, I8F-JE-GPGP, and I8F-JE-GPGO	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無

5.3.1.4.10	バリデーション報告書:[redacted]-21-061-1206. Anti-LY3298176 Antibody Assay Disease State Cut Point Report in Support of Clinical Protocols I8F-MC-GPHK	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無
5.3.1.4.11	バリデーション報告書: 19BASM188V[redacted]. Anti-LY3298176 Antibody Assay Validation Report	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Amendment [redacted]]、20[redacted]年[redacted]月[Amendment [redacted]]）	[redacted]	国外	－	参考資料	無
5.3.1.4.12	バリデーション報告書:[redacted]-17-061-585.GIP Receptor Neutralizing Antibody Assay for LY3298176 Validation Report	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Addendum [redacted]]、20[redacted]年[redacted]月[Addendum [redacted]]、20[redacted]年[redacted]月[Amendment [redacted]]、20[redacted]年[redacted]月[Addendum [redacted]]、20[redacted]年[redacted]月[Amendment [redacted]]）	[redacted]	国外	－	参考資料	無
5.3.1.4.13	バリデーション報告書:[redacted]-21-061-1182_1188_1196_1214. Anti-LY3298176 Neutralizing Antibody Assay In-Study Cut Point Report in Support of Clinical Protocols I8F-MC-GPHM, I8F-MC-GPHL, I8F-MC-GPHN, I8F-JE-GPHZ(b)	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Amendment [redacted]]）	[redacted]	国外	－	参考資料	無
5.3.1.4.14	バリデーション報告書:[redacted]-20-061-1158. Anti-LY3298176 Neutralizing Antibody Assay In-Study Cut PointReport in Support of Clinical Protocols I8F-MC -GPGK(a), I8F-MC -GPGH(a), I8F-MC -GPGI, I8F-MC -GPGM, I8F-MC -GPGL, I8F-JE -GPGP, I8F-JE -GPGO	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無
5.3.1.4.15	バリデーション報告書:[redacted]-21-061-1228. Anti-LY3298176 Neutralizing Antibody Assay Disease State Cut Point Report in Support of Clinical Protocol I8F-MC-GPHK	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無

5.3.1.4.16	バリデーション報告書:[redacted]-18-061-728. GLP-1 Receptor Neutralizing Antibody Assay for LY3298176 Validation Report	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Amendment [redacted]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Amendment [redacted]）	[redacted]	国外	－	参考資料	無
5.3.1.4.17	バリデーション報告書:[redacted]-18-061-750. Native GIP(1-42) Neutralizing Antibody Assay-Specific Validation Report	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無
5.3.1.4.18	バリデーション報告書:[redacted]-17-061-534. Native GIP(1-42) Neutralizing Antibody Assay-Specific Validation Report	－	（20[redacted]年[redacted]月[Amendment [redacted]、20[redacted]年[redacted]月[Addendm [redacted]、20[redacted]年[redacted]月[Addendm [redacted]）	[redacted]	国外	－	参考資料	無
5.3.1.4.19	バリデーション報告書:[redacted]-18-061-749. Anti-GLP-1 Neutralizing Antibody Assay Validation Report	－	（20[redacted]年[redacted]月）	[redacted]	国外	－	参考資料	無
5.3.1.4.20	バリデーション報告書:[redacted]-17-061-551. Anti-GLP-1 Neutralizing Antibody Assay for LY3298176 Validation Report	－	（20[redacted]年[redacted]月[Original]、20[redacted]年[redacted]月[Addendum [redacted]、20[redacted]年[redacted]月[Addendum [redacted]）	[redacted]	国外	－	参考資料	無
5.3.1.4.21	Cut Point Factor Analysis：Anti-LY3298176 (tirzepatide) In-Study (I8F-JE-GPHZ) Tier 1 Cut Point Factor Analysis	－	（20[redacted]年[redacted]月）	Lilly Research Laboratories	国外	－	参考資料	無

5.3.2　ヒト生体試料を用いた薬物動態関連の試験報告書

5.3.2.1　血漿蛋白結合試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.2.1.1	In Vitro Protein Binding of Fluorescent N-Labeled LY3298176 in Human Serum Albumin, Human Alpha-1-Acid Glycoprotein, Human Plasma, Rat Serum Albumin, Rat Plasma, Monkey Serum Albumin, and Monkey Plasma (Amendmenet [redacted])	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	参考資料	無

5.3.2.2　肝代謝及び薬物相互作用試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.2.3　他のヒト生体試料を用いた試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.3　臨床薬物動態（PK）試験報告書

5.3.3.1　健康被験者におけるPK及び初期忍容性試験報告

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.3.2　患者におけるPK及び初期忍容性試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.3.3　内因性要因を検討したPK試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.3.4　外因性要因を検討したPK試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.3.5　ポピュレーションPK試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.3.5.1	Population Pharmacokinetic Analysis and Exposure-Response Analyses of Tirzepatide for Chronic Weight Management	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料＊	有

5.3.3.5.2	Japan Addendum for Population Pharmacokinetic Analysis and Exposure-Response Analyses of Tirzepatide for Chronic Weight Management	－	（20[redacted]年[redacted]月）	Eli Lilly and Company	国外	－	評価資料 *	有
*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関で同意取得及び無作為割付された被験者を除いて実施したポピュレーションPK解析の報告書を、本承認申請の評価資料として用いた。								

5.3.4 臨床薬力学（PD）試験報告書

5.3.4.1 健康被験者におけるPD試験及びPK/PD試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.4.2 患者におけるPD試験及びPK/PD試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.4.2.1	治験総括報告書I8F-MC-GPHU試験：The Impact of Tirzepatide on Gastric Emptying (GE) in Overweight/Obese Non-diabetic Subjects and in Overweight/Obese Subjects with Type 2 Diabetes Mellitus	－	2020年9月～2021年1月	米国	国外	－	参考資料	有
5.3.4.2.2	治験総括報告書 I8F-MC-GPGT試験：The Effect of Tirzepatide on α and β Cell Function and Insulin Sensitivity in Patients with Type 2 Diabetes Mellitus	－	2019年6月～2021年4月	ドイツ	国外	－	参考資料	無
5.3.4.2.3	治験総括報告書 I8F-JE-GPGC試験：A Multiple-Ascending Dose Study in Japanese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of LY3298176	－	2017年11月～2018年[redacted]月	日本	国内	－	参考資料	無
5.3.4.2.4	治験総括報告書I8F-MC-GPHG試験：A Randomized, Placebo-Controlled, Crossover Study to Investigate the Effect of Once-Weekly Tirzepatide on the Counter-Regulatory Response to Hypoglycemia in Patients with Type 2 Diabetes Mellitus	－	2020年2月～2022年1月	オーストリア	国外	－	参考資料	無

5.3.4.2.5	治験総括報告書I8F-MC-GPGU試験：A Randomized, Placebo-Controlled, Parallel-Arm Study to Investigate the Effect of Once-Weekly Tirzepatide on Energy Expenditure and Food Intake in Obese Subjects	－	2020年7月～2022年5月	米国	国外	－	参考資料	無
5.3.4.2.6	治験総括報告書I8F-MC-GPHH試験：Effect of Tirzepatide on Energy Intake and Appetite- and Reward Related Brain Areas in Overweight/Obese Subjects: A Placebo Controlled 6 Week Study with Functional MRI	－	2020年8月～2022年12月	米国	国外	－	参考資料	無

5.3.5 有効性及び安全性試験報告書

5.3.5.1 申請する適応症に関する比較対照試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.1.1	治験総括報告書 I8F-MC-GPGB試験：A Phase 2 Study of Once-Weekly LY3298176 Compared with Placebo and Dulaglutide in Patients with Type 2 Diabetes Mellitus	－	2017年[redacted]月～2018年[redacted]月	米国、ポーランド他	国外	－	参考資料	有
5.3.5.1.2	治験総括報告書 I8F-JE-GPHZ試験：Efficacy and Safety of Once-Weekly Tirzepatide in Participants with Obesity Disease: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-J)	－	2021年5月～2023年6月	日本	国内	－	評価資料*	有
5.3.5.1.3	治験総括報告書I8F-MC-GPHK試験：Efficacy and Safety of Tirzepatide Once Weekly in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-1)	－	2019年12月～2022年4月	アルゼンチン、日本他	国内外	－	評価資料*	有
5.3.5.1.4	治験総括報告書I8F-MC-GPHL試験：Efficacy and Safety of Tirzepatide Once Weekly in Participants with Type 2 Diabetes Who Have Obesity or Are Overweight: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-2)	－	2021年3月～2023年4月	アルゼンチン、日本他	国内外	－	評価資料*	有

5.3.5.1.5	治験総括報告書I8F-MC-GPHM試験：Efficacy and Safety of Tirzepatide Once Weekly Versus Placebo After an Intensive Lifestyle Program in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double Blind, Placebo-Controlled Trial (SURMOUNT-3)	－	2021年3月～2023年5月	アルゼンチン、ブラジル他	国外	－	参考資料	無
5.3.5.1.6	治験総括報告書I8F-MC-GPHN試験：Efficacy and Safety of Tirzepatide Once Weekly versus Placebo for Maintenance of Weight Loss in Participants without Type 2 Diabetes Who Have Obesity or Are Overweight with Weight-Related Comorbidities: A Randomized, Double-Blind, Placebo-Controlled Trial (SURMOUNT-4)	－	2021年3月～2023年5月	アルゼンチン、ブラジル他	国外	－	参考資料	無
*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関でスクリーニングを受けた被験者を除いた治験総括報告書補遺を、本承認申請の評価資料として用いた。また、当初、申請時に提出した治験総括報告書は参考資料とした。								

5.3.5.2 非対照試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.5.3 複数の試験成績を併せて解析した報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.5.3.1	Integrated Summary of Safety Information Addendum	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	有
5.3.5.3.2	Integrated Summary of Immunogenicity Addendum	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	無
5.3.5.3.3	Integrated Summary of Safety Information (supplemental new drug application)	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	有
5.3.5.3.4	Integrated Summary of Immunogenicity (supplemtal new drug application)	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	無
5.3.5.3.5	Integrated Summary of Effectiveness Data	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	無
5.3.5.3.6	Integrated Summary of Immunogenicity	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	無
5.3.5.3.7	Analyses of Integrated Information for Japan	－	（20[redacted]年[redacted]月）	－	国外	－	評価資料	無

5.3.5.4　その他の試験報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.3.6　市販後の使用経験に関する報告書

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.6.1	第2回定期的安全性最新報告-定期的ベネフィット・リスク評価報告（調査期間：20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日）	－	（20[redacted]年[redacted]月）	－	国外	－	参考資料	無
5.3.6.2	第2回安全性定期報告（調査期間：20[redacted]年[redacted]月[redacted]日～20[redacted]年[redacted]月[redacted]日）	－	（20[redacted]年[redacted]月）	－	国内	－	参考資料	無
5.3.6.3	市販直後調査実施報告書	－	（20[redacted]年[redacted]月）	－	国内	－	参考資料	無

5.3.7　患者データ一覧表及び症例記録

5.3.7.1　症例一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.1.1	症例一覧表 I8F-JE-GPHZ試験	－	－	－	国内	－	評価資料*	無
5.3.7.1.2	症例一覧表 I8F-MC-GPHK試験	－	－	－	国内外	－	評価資料*	無
5.3.7.1.3	症例一覧表 I8F-MC-GPHL試験	－	－	－	国内外	－	評価資料*	無

*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関でスクリーニングを受けた被験者を除いた治験総括報告書補遺を、本承認申請の評価資料として用いた。また、当初、申請時に提出した治験総括報告書は参考資料とした。

5.3.7.2　有害事象発現症例一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.2.1	有害事象発現症例一覧表 I8F-JE-GPHZ試験	－	－	－	国内	－	評価資料*	無
5.3.7.2.2	有害事象発現症例一覧表 I8F-MC-GPHK試験	－	－	－	国内外	－	評価資料*	無
5.3.7.2.3	有害事象発現症例一覧表 I8F-MC-GPHL試験	－	－	－	国内外	－	評価資料*	無

*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関でスクリーニングを受けた被験者を除いた治験総括報告書補遺を、本承認申請の評価資料として用いた。また、当初、申請時に提出した治験総括報告書は参考資料とした。

5.3.7.3 重篤な有害事象発現症例一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.3.1	重篤な有害事象発現症例一覧表 I8F-JE-GPHZ試験	－	－	－	国内	－	評価資料*	無
5.3.7.3.2	重篤な有害事象発現症例一覧表 I8F-MC-GPHK試験	－	－	－	国内外	－	評価資料*	無
5.3.7.3.3	重篤な有害事象発現症例一覧表 I8F-MC-GPHL試験	－	－	－	国内外	－	評価資料*	無

*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関でスクリーニングを受けた被験者を除いた治験総括報告書補遺を、本承認申請の評価資料として用いた。また、当初、申請時に提出した治験総括報告書は参考資料とした。

5.3.7.4 臨床検査値異常症例一覧表

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
5.3.7.4.1	臨床検査値異常症例一覧表 I8F-JE-GPHZ試験	－	－	－	国内	－	評価資料*	無
5.3.7.4.2	臨床検査値異常症例一覧表 I8F-MC-GPHK試験	－	－	－	国内外	－	評価資料*	無
5.3.7.4.3	臨床検査値異常症例一覧表 I8F-MC-GPHL試験	－	－	－	国内外	－	評価資料*	無

*GPHZ、GPHK、及びGPHL試験に参加した1施設で治験施設支援機関によるGCP違反が認められた。当該実施医療機関でスクリーニングを受けた被験者を除いた治験総括報告書補遺を、本承認申請の評価資料として用いた。また、当初、申請時に提出した治験総括報告書は参考資料とした。

5.3.7.5 臨床検査値変動図

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	評価資料参考資料	申請電子データの提出有無
	該当なし							

5.4 参考文献

添付資料番号	タイトル	著者	試験実施期間（報告書承認年月）	試験実施場所	報種類（国内、国外）	掲載誌	参考文献	申請電子データの提出有無
5.4.1	Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Based on a systematic review from the Obesity Expert Panel, 2013.	American College of Cardiology/American Heart Association Task Force on Practice Guidelines, Obesity Expert Panel.	－	－	－	Obesity (Silver Spring). 2014;22(suppl 2):S5-S39.	参考文献	－
5.4.2	The role of quality of life instruments in obesity management: review.	Accardi R. et al.	－	－	－	Bariatr Surg Pract Patient Care. 2017;12(4):145-152.	参考文献	－
5.4.3	8. Obesity and weight management for the prevention and treatment of type 2 diabetes: standards of medical care in diabetes—2022.	American Diabetes Association.	－	－	－	Diabetes Care. 2022;45(suppl 1):S113-S124.	参考文献	－
5.4.4	Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake.	Adriaenssens AE. et al.	－	－	－	Cell Metab. 2019;30(5):987-996.	参考文献	－
5.4.5	Controlled release phentermine/topiramate in severely obese adults: a randomized, controlled trial (EQUIP).	Allison DB. et al.	－	－	－	Obesity (Silver Spring). 2012;20(2):330-342.	参考文献	－
5.4.6	Glucagon-like peptide 1 in health and disease.	Andersen A. et al.	－	－	－	Nat Rev Endocrinol. 2018;14(7):390-403.	参考文献	－
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5.4.10	Body mass index, abdominal fatness and the risk of gallbladder disease.	Aune D. et al.	−	−	−	Eur J Epidemiol. 2015;30(9):1009-1019.	参考文献	−
5.4.11	Incretin-based drugs and adverse pancreatic events: almost a decade later and uncertainty remains.	Azoulay L.	−	−	−	Diabetes Care. 2015;38(6):951-953.	参考文献	−
5.4.12	Higher liver fat content among Japanese in Japan compared with non-Hispanic whites in the United States.	Azuma K. et al.	−	−	−	Metabolism. 2009;58(8):1200-1207.	参考文献	−
5.4.13	Biology of incretins: GLP-1 and GIP.	Baggio LL. et al.	−	−	−	Gastroenterology. 2007;132(6):2131-2157.	参考文献	−
5.4.14	Sarcopenic obesity: time to meet the challenge.	Barazzoni R. et al.	−	−	−	Obes Facts. 2018;11(4):294-305.	参考文献	−
5.4.15	GIP receptor agonism attenuates GLP-1 receptor agonist–induced nausea and emesis in preclinical models.	Borner T. et al.	−	−	−	Diabetes. 2021;70(11):2545-2553.	参考文献	−
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5.4.17	Risk of suicide and self-harm is increased after bariatric surgery-a systematic review and meta-analysis.	Castaneda D. et al.	−	−	−	Obes Surg. 2019;29(1):322-333.	参考文献	−
5.4.18	Preserving healthy muscle during weight loss.	Cava E. et al.	−	−	−	Adv Nutr. 2017;8(3):511-519.	参考文献	−

5.4.19	LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept.	Coskun T. et al.	−	−	−	Mol Metab. 2018;18:3-14.	参考文献	−
5.4.20	Anorectic and aversive effects of GLP-1 receptor agonism are mediated by brainstem cholecystokinin neurons, and modulated by GIP receptor activation.	Costa A. et al.	−	−	−	Mol Metab. 2022;55:101407.	参考文献	−
5.4.21	Efficacy of liraglutide for weight loss among patients with type 2 diabetes: the SCALE diabetes randomized clinical trial.	Davies MJ. et al.	−	−	−	JAMA. 2015;314(7):687-699.	参考文献	−
5.4.22	Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial.	Davies M. et al.	−	−	−	Lancet. 2021;397(10278):971-984.	参考文献	−
5.4.23	The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications.	Drucker DJ.	−	−	−	Diabetes. 2018;67(9):1710-1719.	参考文献	−
5.4.24	Examination of the relationship between obesity and suicidal ideation.	Dutton GR. et al.	−	−	−	Int J Obes (Lond). 2013;37(9):1282-1286.	参考文献	−
5.4.25	Pancreatic safety of incretin-based drugs - FDA and EMA assessment.	Egan AG. et al.	−	−	−	N Engl J Med. 2014;370(9):794-797.	参考文献	−
5.4.26	Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomized, placebo-controlled, phase 3 trial.	Gadde KM. et al.	−	−	−	Lancet. 2011;377(9774):1341-1352.	参考文献	−
5.4.27	Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity.	Garvey WT. et al.	−	−	−	Endocr Pract. 2016;22(Suppl 3):1-203.	参考文献	−

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5.4.29	Cardiovascular risk in the Asia–Pacific region from a nutrition and metabolic point of view: abdominal obesity.	Gill TP.	−	−	−	Asia Pac J Clin Nutr. 2001;10(2):85-89.	参考文献	−
5.4.30	Beneficial health effects of modest weight loss.	Goldstein DJ.	−	−	−	Int J Obes Relat Metab Disord. 1992;16(6):397-415.	参考文献	−
5.4.31	Effect of naltrexone plus bupropion on weight loss in overweight and obese adults (COR-I): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial.	Greenway FL. et al.	−	−	−	Lancet. 2010;376(9741):595-605.	参考文献	−
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5.4.33	Association of glucagon-like peptide-1 receptor agonist use with risk of gallbladder and biliary diseases: a systematic review and meta-analysis of randomized clinical trials.	He L. et al.	−	−	−	JAMA Intern Med. 2022;182(5):513-519.	参考文献	−
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5.4.35	Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes.	Holman RR. et al.	−	−	−	N Engl J Med. 2017;377(13):1228-1239.	参考文献	−
5.4.36	Diabetes and depression.	Holt RIG. et al.	−	−	−	Curr Diab Rep. 2014;14(6):491.	参考文献	−
5.4.37	Perceptions, attitudes and barriers to obesity management: Japanese data from the ACTION-IO study.	Iwabu M. et al.	−	−	−	J Diabetes Investig. 2021;12(5):845-858.	参考文献	−
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5.4.39	Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue.	Jendle J. et al.	−	−	−	Diabetes Obes Metab. 2009;11(12):1163-1172.	参考文献	−
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5.4.45	Obesity and kidney disease: hidden consequences of the epidemic.	Kovesdy CP. et al.	−	−	−	Am J Nephrol. 2017;45(3):283-291.	参考文献	−
5.4.46	Medical weight loss versus bariatric surgery: does method affect body composition and weight maintenance after 15% reduction in body weight?	Kulovitz MG. et al.	−	−	−	Nutrition. 2014;30(1):49-54.	参考文献	−
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5.4.49	Differential effects of glucagon-like peptide-1 receptor agonists on heart rate.	Lorenz M. et al.	−	−	−	Cardiovasc Diabetol. 2017;16(1):6.	参考文献	−

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5.4.52	Semaglutide and cardiovascular outcomes in patients with type 2 diabetes.	Marso SP. et al.	−	−	−	N Engl J Med. 2016a;375(19):1834-1844.	参考文献	−
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5.4.58	The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update.	Nauck MA. et al.	−	−	−	Diabetes Obes Metab. 2021;23(Suppl 3):5-29.	参考文献	−
5.4.59	A randomized, controlled trial of 3.0 mg of liraglutide in weight management.	Pi-Sunyer X. et al.	−	−	−	N Engl J Med. 2015;373(1):11-22.	参考文献	−
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5.4.62	Energy expenditure before and during energy restriction in obese patients.	Ravussin E. et al.	−	−	−	Am J Clin Nutr. 1985;41(4):753-759.	参考文献	−
5.4.63	Weight loss and improvement in comorbidity: differences at 5%, 10%, 15%, and over.	Ryan DH. et al.	−	−	−	Curr Obes Rep. 2017;6(2):187-194.	参考文献	−
5.4.64	GIPR Function in the Central Nervous System: Implications and Novel Perspectives for GIP-Based Therapies in Treating Metabolic Disorders.	Samms RJ. et al.	−	−	−	Diabetes. 2021;70(9):1938-1944.	参考文献	−
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5.4.66	Obesity as a multisystem disease: trends in obesity rates and obesity-related complications.	Sarma S. et al.	−	−	−	Diabetes Obes Metab. 2021;23(Suppl 1):3-16.	参考文献	−
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5.4.69	Bariatric surgery versus intensive medical therapy for diabetes - 5-year outcomes.	Schauer PR. et al.	−	−	−	N Engl J Med. 2017;376(7):641-651.	参考文献	−
5.4.70	Bariatric surgery and long-term cardiovascular events.	Sjöström L. et al.	−	−	−	JAMA. 2012;307(1):56-65.	参考文献	−
5.4.71	Current pharmacotherapy for obesity.	Srivastava G. et al.	−	−	−	Nat Rev Endocrinol. 2018;14(1):12-24.	参考文献	−
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5.4.73	Excess body weight and gallstone disease.	Stokes CS. et al.	−	−	−	Visc Med. 2021;37(4):254-260.	参考文献	−
5.4.74	Incretin-mimetic therapies and pancreatic disease: a review of observational data.	Suarez EA. et al.	−	−	−	Curr Med Res Opin. 2014;30(12):2471-2481.	参考文献	−
5.4.75	Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis.	Sun F. et al.	−	−	−	Diabetes Res Clin Pract. 2015;110(1):26-37.	参考文献	−
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5.4.89	効果的な保健医療の実施に対する提言―肥満症を対象とした考察.	株式会社日本総合研究所リサーチ・コンサルティング部門.	－	－	－	－	参考文献	－