Mounjaro for Diabetes Treatment

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Executive Summary

Tirzepatide (Mounjaro) was approved in May 2022 for the treatment of T2D in adults. It is a dual acting GIP/GLP-1 receptor agonist given as a once weekly SC injection.

Acronyms	
A1c	Hemoglobin A1c
GI	Gastrointestinal
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like peptide-1
MEN 2	Multiple Endocrine Neoplasia syndrome type 2
MOA	Mechanism of action
SC	Subcutaneous
T2D	Type 2 Diabetes

Key Takeaways

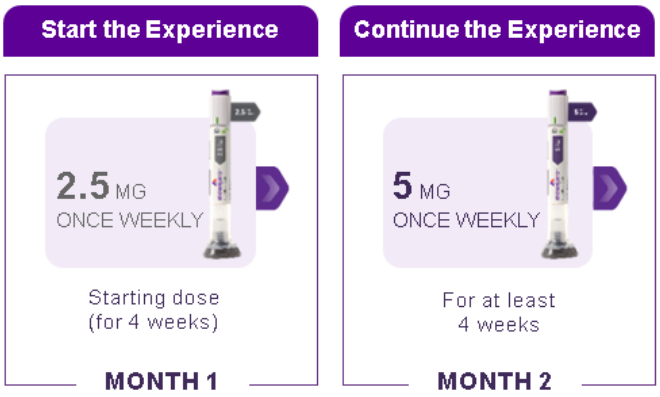
- Tirzepatide's MOA is similar to GLP-1 agonists such as semaglutide and dulaglutide, despite its action on GIP in addition to GLP-1
- Tirzepatide likely has similar A1c reduction compared to semaglutide 2 mg SC weekly, although no studies have directly compared tirzepatide to semaglutide 2 mg SC.
- Tirzepatide may be preferred over available GLP-1 agonists for patients seeking additional weight loss, however, it is important to keep in mind that cardiovascular safety data is not available yet.

Mechanism of Action:

Tirzepatide is a dual GIP and GLP-1 receptor agonist. GIP and GLP-1 are incretin hormones found in the GI tract that contribute to glucose dependent insulin secretion. Like GLP-1 agonists, tirzepatide's effects include:

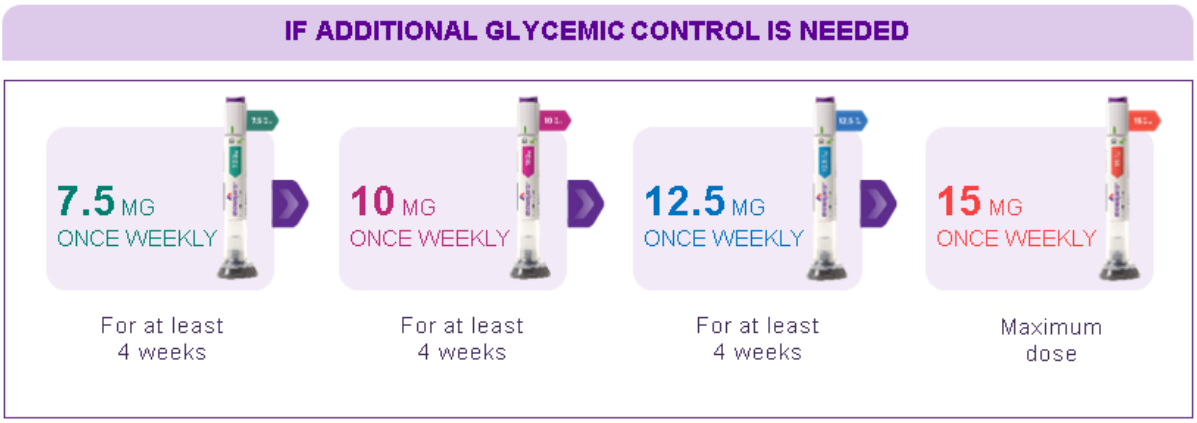
- Slow gastric emptying which may lead to decreased food intake and weight loss
- Decreased glucagon levels
- Increased insulin secretion and sensitivity

Dosing Information: Each dose comes in its own individual dosing pen.



Dose may be increased every 4 weeks as needed. Initial dose of 2.5 mg weekly does not provide effective glycemic control; it is intended to reduce GI symptoms.

Patients should be counseled on proper injection technique.

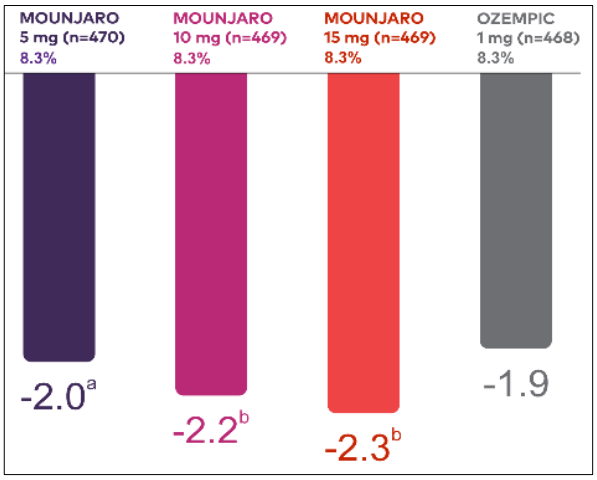


Safety and Efficacy

The safety and efficacy of tirzepatide was assessed in the SURPASS program, which consisted of 5 clinical trials. The SURPASS-2 trial compared tirzepatide to semaglutide 1 mg SC weekly and demonstrated that tirzepatide was superior with reduction in A1c after 40 weeks.

Subjects taking tirzepatide also had significantly more weight loss compared to the semaglutide group, with similar side effects between groups. Unfortunately, there are no studies comparing tirzepatide to semaglutide 2 mg SC weekly. However, results from the SUSTAIN-FORTE trial demonstrated an A1C reduction of 2.2% with semaglutide 2 mg SC, which is comparable to the effects seen with tirzepatide in the SURPASS-2 trial. See **Table 1** for a comparison of A1c reduction with other GLP-1 agonists.

Figure 1: SURPASS-2 Trial A1 Reduction



Source: Introduction to Mounjaro™. Lilly USA, LLC. 6/2022.

Figure 2: SURPASS-2 Trial Weight Changes (lbs)

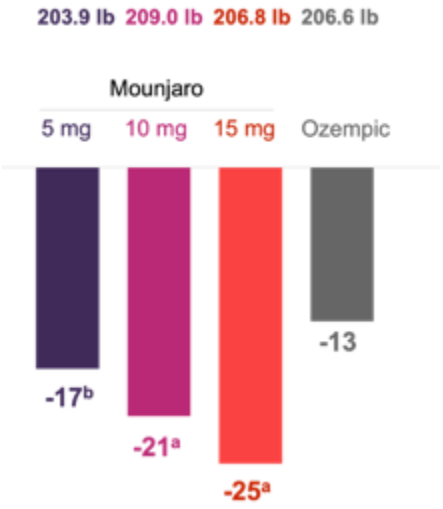


Table 1: Average A1c Reduction for GLP-1 Agonists

Medication	Dose	A1c Reduction
Tirzepatide (Mounjaro)	15mg	2.3%
Semaglutide (Ozempic)	2mg	2.2%
Dulaglutide (Trulicity)	4.5mg	1.8%
Liraglutide (Victoza)	1.8mg	1.0-1.5%
Exenatide ER (Bydureon BCise)	2mg	1.4%

Most reported side effects were GI related (nausea, vomiting, diarrhea). These were dose-dependent and improved over time.

Contraindications for use include personal or family history of medullary thyroid carcinoma, patients with MEN 2 and known hypersensitivity to ingredients.

Cardiovascular safety data is expected to be available fall 2024. It may be reasonable to avoid use in patients with known cardiovascular disease until data is available.

Access

Most insurance companies are requiring a prior authorization currently. There is a savings card available for patients with commercial insurance that will cap out-of-pocket costs at $25. Patients who are self-pay or have government insurance are not eligible. Avera Health Plans provides coverage without restriction after a member has been started on anti-diabetic medication, metformin.

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Prediabetes Treatments

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Executive Summary

Prediabetes is a condition of pancreatic beta cells failing to produce an adequate amount of insulin due to underlying insulin resistance. This is most caused by obesity. The risk of progression from prediabetes to T2D is highest for patients with a history of GDM, a strong family history of T2D and glycemia progressively increasing within the prediabetes range.

Within 3-5 years, approximately 25% of patients diagnosed with prediabetes will have progressed to T2D. Within their lifetime, as many as 70% of patients with prediabetes will progress to overt T2D if no changes are made. The first-line treatment for prediabetes is weight loss with lifestyle modifications, and medications for weight loss or bariatric surgery if necessary. It is also important to aggressively manage hypertension and dyslipidemia to decrease ASCVD risk. If weight loss alone is unsuccessful at reaching glycemic control, antidiabetic medications may be necessary to prevent the progression to T2D.

Acronyms	
A1c	Hemoglobin A1c
ASCVD	Atherosclerotic cardiovascular disease
BMI	Body mass index
BP	Blood pressure
DASH	Dietary Approaches to Stop Hypertension
GDM	Gestational diabetes mellitus
GLP-1 RA	Glucagon-like peptide 1 receptor agonist
LDL-C	Low-density lipoprotein cholesterol
NASH	Nonalcoholic steatohepatitis
OGTT	Oral glucose tolerance test
T2D	Type 2 diabetes

Key Takeaways

- Obesity is the most common cause of prediabetes, with 70% of prediabetic patients progressing to T2D if no changes are made to their condition.
- Lifestyle changes are the most effective way to prevent the progression to T2D with a focus on at least a 7% weight loss.
- No medications have been approved for the treatment of prediabetes or prevention of T2D, however several medications show a decreased progression to T2D.
- Metformin, GLP-1RA, or pioglitazone should be considered for the treatment of prediabetes when lifestyle interventions fail to achieve glycemic control.

Diagnosis of Prediabetes (at least one of the following):

Impaired fasting glucose	Impaired glucose tolerance	A1c
100 – 125 mg/dL	OGTT result of 140-199 mg/dL 2 hours after ingestion of 75 g of glucose	5.7% - 6.4%

Goals:

- Prevent progression to T2D
- Prevent progression to NASH
- Improve CVD risk factors via aggressive control of:
  - Elevated BP
  - Dyslipidemia
- Treat obesity or prevent excessive weight gain
- Improve functionality and quality of life

Lifestyle Interventions:

Lifestyle changes are the most effective way to prevent progression to T2D. Lifestyle modifications reduce progression to T2D by 58% compared to no intervention.

- Aerobic and resistance physical activity
  - ≥ 150 minutes/week of aerobic exercise, over 3-5 sessions
  - Resistance exercises using the major muscle groups 2-3 times per week
  - Reduction in overall sedentary behavior
- Diet
  - Mediterranean diet: shown to reduce rates of progression to T2D, independent of weight loss
  - DASH diet: most benefit seen for patients who are hypertensive at baseline and/or self-identify as African American
- Weight loss
  - The ADA recommends a goal to achieve and maintain at least 7% loss of initial body weight to lessen the risk of developing diabetes. Ideally, within the first 6 months of lifestyle intervention.
  - Moderate weight loss, defined as a 5–10% reduction from baseline weight, is associated with clinically meaningful improvements in obesity-related metabolic risk factors. Even weight loss of 5% has been shown to improve pancreatic beta cell function and the sensitivity of liver and skeletal muscle to insulin.

Indication for obesity medications:

- Overweight (BMI 27-29.9 kg/m^2) or obese (BMI ≥ 30 kg/m^2) patients unable to achieve or sustain a weight loss of 7-10% with lifestyle changes alone
- See Medications for Weight Loss for pharmacologic treatment options

Indications for medications to prevent progression to T2D:

- No medications have been approved for the treatment of prediabetes
- Pharmacotherapy can be considered for patients who remain glucose-intolerant following lifestyle changes and/or use of weight loss medications

Preferred medications:

Drug/class	Efficacy data	Considerations
Metformin	• 31% decrease in progression to T2D vs placebo	• Inferior to lifestyle-modification • More effective with A1c 6.1-6.4%, BMI ≥30 kg/m^2, those aged <60 years, and in women with prior GDM • Further decrease in progression to T2D was seen when metformin was combined with linagliptin
GLP-1 RA	Liraglutide 3mg/day • 66% decrease in progression to T2D vs placebo Semaglutide 2.4mg/week • Significantly more patients with prediabetes at baseline converted to normoglycemia by the end of the study period vs placebo • Fewer patients progressed to prediabetes vs placebo • Trials not powered to assess prevention of T2D	• GLP-1 RAs studied at weight loss indication dosages • Effects are a combination of improved glycemic control in combination with weight loss • Cost may be a barrier

Pioglitazone	• 72% decrease in progression to T2D vs placebo	• Also associated with a decrease in diastolic blood pressure and increase in HDL cholesterol • Also associated with increased weight gain and edema

Prediabetes Pharmacotherapy Treatment Algorithm

1. Consider metformin as first-line pharmacotherapy.
2. If metformin is not tolerated, contraindicated, or ineffective, consider GLP-1 RA.
3. If GLP-1 RA is not tolerated or cost is a barrier, consider pioglitazone.

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