Journal Academy Formulary (JACF)

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Drug Review: Tirzepatide

Registrations: Tirzepatide has been registered in the following countries United States of America (USA), United Kingdom (U.K.), Canada, Saudi Arabia (S.A.).
Trade name (USA): MOUNJARO
Registration number (S.A.); Not Available.
Insurance Drug Formulary (S.A.); Not covered (28.1.2023).
General Information:
Registered Company: Lilly USA.
Regulatory Status: R.X.
Mechanism of Action:
Tirzepatide is a Glucose-dependent Insulinotropic Polypeptide (GIP) receptor and Glucagon-Like Peptide-1 (GLP-1) receptor agonist. It is a 39-amino acid-modified peptide containing a C20 fatty diacid component that facilitates albumin binding and increases the half-life. Tirzepatide preferentially binds to and activates GIP and GLP-1 receptors, hence targeting endogenous GIP and GLP. Tirzepatide increases the first and second phases of insulin secretion and decreases glucagon levels in a glucose-dependent manner. Tirzepatide reduces fasting and postprandial glucose levels, food consumption, and body weight in people with type 2 diabetes.
Indication: Type 2 diabetes mellitus.
Route of Administration: Sub-Q.
Dosage Forms:
Subcutaneous Solution: 2.5 MG/0.5 ML, 5 M.G./0.5 ML, 7.5 MG/0.5 ML, 10 M.G./0.5 ML, 12.5 MG/0.5 ML, 15 M.G./0.5 ML.
Dosing/Administration:

Subcutaneous
- Inject sub Q into the thigh, abdomen, or upper arm; rotate injection sites.
- Administer at any time of day, with or without meals.
- Administer separately from insulin (do not mix the products); may inject both medications in the same body region but not adjacent to each other.
- The day of the weekly administration can be changed as long as the time between the two doses is at least three days (72 hr).
- Administer a missed dose as soon as possible within four days (96 hr) of missed dose; if more than four days have passed, skip the dose and administer the next dose on a regularly scheduled day and resume the regular once-weekly dosing schedule.

Dose: Initial, 2.5 mg sub Q once weekly for four weeks, then increase to 5 mg sub Q once weekly; if additional glycemic control is needed, increase the dosage in 2.5-mg increments after at least four weeks on the current dose; MAX, 15 mg sub Q once weekly.
Dose in Renal/Hepatic failure: No adjustment necessary.
Geriatric Dose: No dosage adjustment is needed.
Adjustment required in Specific population: Concomitant use with insulin secretagogues or insulin: Consider reducing the dose of the concomitantly administered insulin secretagogue or insulin to reduce the risk of Hypoglycemia.
Indicated for pediatrics: Safety and effectiveness not established in pediatric patients.

Pharmacokinetic:
Pharmacokinetic
Absorption
- Tmax, sub Q: 8 to 72 hr.
- Bioavailability, sub Q: 80%.

Distribution
- Protein binding: 99% (plasma albumin).
- Vd, sub Q: 10.3 L.

Metabolism
- Metabolism: Proteolytic cleavage of the peptide backbone, beta-oxidation of the C20 fatty diacid moiety, amide hydrolysis.

Excretion
- Renal excretion: Primary route for tirzepatide metabolites.
- Fecal excretion: Primary route for tirzepatide metabolites.
- Total body clearance: 0.061 L/hr.

Elimination Half-Life: 5 days.

Safety:
Common Adverse Reactions (%):
The most commonly reported adverse effects are in the gastrointestinal tract, such as nausea or diarrhea.
Severe/rare adverse Reactions (%):
Endocrine metabolic: C-cell hyperplasia of thyroid, Hypoglycemia (9.9% to 19%).
Gastrointestinal: Disorder of gallbladder, Acute (0.6%), Pancreatitis.
Immunologic: Anaphylaxis, Hypersensitivity reaction (3.2%).
Ophthalmic: Retinopathy due to diabetes mellitus.

Drug Interactions:
- Interact with:
- Aspirin.
- Benadryl (diphenhydramine).
- Cialis (tadalafil).
- CoQ10 (ubiquinone).
- Jardiance (empagliflozin).
- Lasix (furosemide).
- Linzess (linaclotide).
- Ozempic (semaglutide).

Contraindications / Precautions:
Contraindications
Family history of Medullary Thyroid Carcinoma (MTC).
History of MEN 2 (Multiple Endocrine Neoplasia syndrome types 2).
Known severe hypersensitivity to tirzepatide or any component of the product.
Precautions
- Endocrine and metabolic: Increased risk of Hypoglycemia when concomitantly used with insulin and insulin secretagogues (e.g., sulfonylureas); dose adjustment may be necessary.
- Gastrointestinal: Acute Pancreatitis, including fatal and nonfatal hemorrhagic or necrotizing Pancreatitis, has been reported with glucagon-like peptide-1 (GLP-1) receptor agonists; monitoring is recommended, discontinue use if suspected, and initiate appropriate

management.

Immunologic:

- Use caution in patients with prior anaphylaxis and angioedema history with another glucagon-like peptide 1 (GLP-1) receptor agonist.

Monitoring Requirements:

- Achieving glycemic control, including meeting the HbA1c goal, indicates efficacy.
- HbA1c: Twice annually in patients who are meeting goals of management; every three months in patients whose therapy has changed and who are not meeting glycemic goals; much frequently as clinically warranted.
- Elevated serum calcitonin levels: The patient should be further evaluated; monitoring of serum calcitonin is of uncertain value.
- Thyroid nodules: If noted on physical exam or neck imaging patient should be further evaluated; thyroid ultrasound is of uncertain value.
- Renal function: When starting or escalating doses and in patients reporting severe adverse gastrointestinal reactions, especially in patients with renal impairment.
- Monitor oral medications with a narrow therapeutic index and those dependent on threshold concentrations for efficacy.
- Signs and symptoms of Pancreatitis, including severe or persistent abdominal pain, sometimes radiating to the back with or without vomiting.
- Progression of diabetic retinopathy: in patients with the disease history.
- Renal function: When starting or escalating doses and in patients reporting severe adverse.

Sound-Alikes/ Look-Alikes: Not available.

High Alert: Not available.

Boxed warnings or alerts issue:

Subcutaneous (Solution)

- Risk of Thyroid C-Cell Tumors.
- At clinically relevant exposures, tirzepatide induces dose- and treatment-dependent thyroid C-cell cancers in both male and female mice; the relevance of tirzepatide-induced rodent thyroid C-cell tumors to humans is unknown.
- Tirzepatide is contraindicated in people having a personal or familial history of medullary thyroid cancer or MEN 2.

Regular monitoring of blood calcitonin or thyroid ultrasonography for early diagnosis of MTC in patients treated with tirzepatide is of dubious benefit. Toxicity if antidote required: Not available.

Storage if there is a unique condition.

subcutaneous route.

1) Solution.

a) Store in the original carton under refrigerated conditions between 2°C and 8°C (36°F and 46°F). Protect from light. Do not freeze; do not use if frozen.

b) If needed, the single-dose pen can be stored unrefrigerated at temperatures not exceeding 30°C (86°F) for up to 21 days.

Patient counseling

1. Inform the patient to report thyroid tumor symptoms.
2. Warn the patient to report pancreatitis or gallbladder disease symptoms.
3. Inform the patient to report persistent or severe gastrointestinal symptoms.
4. Instruct patient to report eyesight changes.
5. Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive technique or add a contraception barrier method for four weeks after initiation and four weeks after each dose increase.
6. Nausea, diarrhea, decreased appetite, vomiting, constipation, dyspepsia, and abdominal discomfort are possible adverse reactions.
7. Advise the patient to take preventative measures against dehydration.
8. Teach the patient the correct injection technique and placement.
9. Instruct the patient to administer any missed dosage within four days. If more than four days have gone since the missed dose, the following dose should be administered on the usually scheduled day, and the once-weekly dosing pattern should resume.

Cost Analysis:

Drugs	Drug classes	Approval Indication	Dose	Cost (American Dollar)	Insurance drug formulary(SCHI)
Tirzepatide	Antidiabetic | Endocrine-Metabolic Agent	Type 2 diabetes mellitus	Subcutaneous Solution: 2.5 MG/0.5 ML, 5 M.G./0.5 ML, 7.5 MG/0.5 ML, 10 M.G./0.5 ML, 12.5 MG/0.5 ML, 15 M.G./0.5 ML.	Around $13,000 annually, or around $1,100 a month.	Not Covered
Semaglutide	Antidiabetic | Endocrine-Metabolic Agent	Type 2 diabetes mellitus Obesity Nonalcoholic steatohepatitis	Initial, 0.25 mg sub Q once weekly for four weeks, then increase to 0.5 mg once weekly; might increase to MAX 1 mg once weekly.	Around $907.22.	Covered
Dulaglutide	Antidiabetic | Endocrine-Metabolic Agent	• Disorder of the cardiovascular system; Prophylaxis - Type 2 diabetes mellitus • Type 2 diabetes mellitu	Initial, 0.75 mg subQ once weekly; may increase to 1.5 mg subQ once weekly for additional glycemic control; may increase to 3 mg once weekly after at least Four weeks on the 1.5-mg dose; may increase to MAX 4.5 mg once weekly after at least four weeks on the 3-mg dose.	(0.75 mg/0.5 mL) is around $990 for a supply of 2 milliliters.	Covered

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