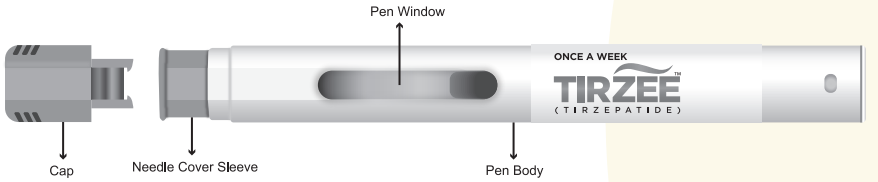
TIRZEE™ (TIRZEPATIDE)

PRE-FILLED PEN AUTOINJECTOR

INSTRUCTION MANUAL



ٹرزی ہدایت نامہ

پری فلڈ پین آٹو انجیکٹر

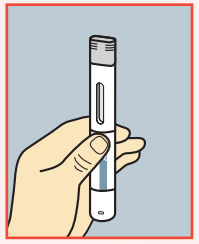
Wash your hands with soap and water.

اپنے ہاتھ صابن اور پانی سے دھوئیں۔

Step 1 Check the pen

پہلا مرحلہ: پین کی جانچ کریں

1. Check the pen label to make sure you have the right medicine and dose, and that it has not expired.
2. Make sure the pen is not damaged and is locked.
3. Make sure the medicine:
   - is not frozen
   - is colorless to slightly yellow
   - is not cloudy
   - does not have particles



۱. صحیح دوا اور خوراک کی تصدیق کیلئے پین کا لیبل چیک کریں اور یہ بھی کے دوا کی معیاد باقی ہو۔

۲. اس بات کو یقینی بنائیں کہ پین خراب نہ ہو اور بند ہو۔

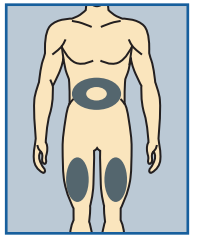
۳. اس بات کو یقینی بنائیں کہ دوا:

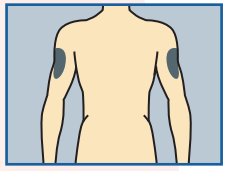
- منجمد نہ ہو۔
- بے رنگ یا ہلکی پیلی ہو۔
- میں گدلا پن نہ ہو۔
- میں کوئی ذرات موجود نہ ہوں۔

Step 2 Choose your injection site

دوسرا مرحلہ: انجکشن لگانے کی جگہ کا انتخاب کریں

1. TIRZEE can be injected under the skin (subcutaneously) of your stomach area (abdomen) or thighs, and with the help of someone else, in the back of the upper arm.
2. Change (rotate) your injection site each week.
3. You may use the same area of your body but be sure to choose a different injection site in that area.





۱. ٹرزی کو پیٹ کے اردگرد یا رانوں پر یا کسی اور کی مدد سے بازو کے پچھلے اوپری حصے پر زیرِ جلد لگایا جا سکتا ہے۔

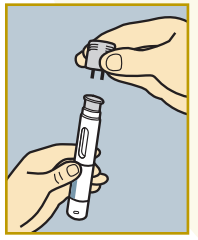
۲. انجکشن لگانے کی جگہ ہر ہفتے تبدیل کرتے رہیں۔

۳. آپ جسم کے ایک ہی حصے پر انجکشن لگا سکتے ہیں مگر ہر بار انجکشن کی جگہ تبدیل کریں۔

Step 3 Remove the pen cap

تیسرا مرحلہ: پین کے کیپ کو ہٹائیں

1. Pull the pen cap straight off your pen.
2. The needle is hidden, so you do not have to see or handle it.
3. Be careful not to push down on the needle cover to avoid needle stick injuries.



۱. پین کے کیپ کو پین سے سیدھا ہٹائیں۔

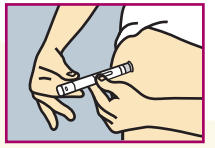
۲. سوئی پین کے اندر موجود ہے، اس لیئے اسے دیکھنے یا چھونے سے گریز کریں۔

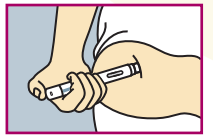
۳. سوئی کی چوٹ سے بچنے کیلئے احتیاط کریں کہ سوئی کے کور کو نیچے نہ کیا جائے۔

Step 4 Inject your dose

چوتھا مرحلہ: انجکشن لگانے کا طریقہ

1. Push the pen (needle cover sleeve) firmly against your skin and keep applying pressure.
2. Listen for click sound during the injection and hold for approximately 10-15 seconds.
3. You will know your injection is complete when the plunger rod entirely covers the pen window.
4. After using the injection, reattach the pen cap.
5. Dispose of the used pen.





۱. پین کی سوئی کے حفاظتی کور کو اپنی جلد کے مخالف مضبوطی سے دبائیں اور دباؤ کو مسلسل برقرار رکھیں۔

۲. انجکشن لگانے کے دوران کلک کی آواز سنیں اور تقریباً ۱۰-۱۵ سیکنڈ تک انتظار کریں۔

۳. جب پین کی ونڈو پر پلنجر راڈ مکمل نظر آجائے تو یہ اس بات کی نشاندہی ہے کہ آپ کا انجکشن مکمل لگ گیا ہے۔

۴. انجکشن لگانے کے بعد پین کے کیپ کو واپس پین پر لگا دیں۔

۵. استعمال شدہ پین کو ضائع کر دیں۔

Important Instructions for Use

- Change (rotate) your injection site within the area you choose for each dose to reduce your risk of getting lipodystrophy (pits in skin or thickened skin) and localized cutaneous amyloidosis (skin with lumps) at the injection sites.
- Do not inject where the skin has pits, is thickened, or has lumps.
- Do not inject where the skin is tender, bruised, scaly or hard, or into scars or damaged skin.
- If you see blood after you take the needle out of your skin, press the injection site lightly. Do not rub the area.
- Do not freeze (if frozen, do not use the pen).

Getz pharma

استعمال کے لئے اہم ہدایات

- اپنی انجکشن کی جگہ کو ہر بار تبدیل کریں تا کہ انجکشن کی جگہوں پر جلد میں گڑھے، گانٹھیں یا جلد موٹی ہونے کے خطرے کو کم کیا جا سکے۔
- جلد میں جہاں گڑھے، گانٹھیں یا جلد موٹی ہو وہاں انجکشن نہ لگائیں۔
- جہاں جلد نرم ہو، چوٹ لگی ہو، کھردری یا سخت ہو، داغ ہوں یا جلد خراب ہو وہاں انجکشن نہ لگائیں۔
- اگر جلد سے سوئی نکالنے کے بعد خون نظر آئے تو انجکشن کی جگہ کو ہلکے سے دبائیں، جگہ کو نہ رگڑیں۔
- دوا کو منجمد ہونے سے بچائیں (اگر دوا منجمد ہو جائے تو استعمال نہ کریں)۔

TIRZEE™ ٹرزی

(TIRZEPATIDE)

2.5mg/0.5mL, 5mg/0.5mL, 7.5mg/0.5mL & 10mg/0.5mL

Solution for Injection
Pre-filled Pen Autoinjector

DESCRIPTION

TIRZEE (Tirzepatide) injection, for subcutaneous use, contains Tirzepatide, a once weekly 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. Its molecular formula is $C_{225}H_{348}N_{48}O_{68}$.

QUALITATIVE AND QUANTITATIVE COMPOSITION

TIRZEE (Tirzepatide) Solution for Injection is available for subcutaneous administration as:

TIRZEE Solution for Injection 2.5mg/0.5mL
Each 0.5mL PFS contains:
Tirzepatide…2.5mg
(Pre-filled syringe with disposable autoinjector)

TIRZEE Solution for Injection 5mg/0.5mL
Each 0.5mL PFS contains:
Tirzepatide…5mg
(Pre-filled syringe with disposable autoinjector)

TIRZEE Solution for Injection 7.5mg/0.5mL
Each 0.5mL PFS contains:
Tirzepatide…7.5mg
(Pre-filled syringe with disposable autoinjector)

TIRZEE Solution for Injection 10mg/0.5mL
Each 0.5mL PFS contains:
Tirzepatide…10mg
(Pre-filled syringe with disposable autoinjector)

CLINICAL PHARMACOLOGY

Mechanism of Action

Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It is an amino-acid sequence including 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, Tirzepatide enhances first-and second-phase insulin secretion, and reduces glucagon levels, both in a glucose-dependent manner. In addition, both GIP and GLP-1 receptors are expressed in the areas of the brain important to appetite regulation.

Pharmacokinetics

Absorption

Following subcutaneous administration, the time to maximum plasma concentration of Tirzepatide ranges from 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 apparent steady-state volume of distribution of Tirzepatide following subcutaneous administration in patients with type 2 diabetes mellitus is approximately 10.3L and 9.7L in patients with obesity. Tirzepatide is highly bound to plasma albumin (99%).

Metabolism

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

Elimination

The apparent population mean clearance of Tirzepatide is 0.061L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing. The primary excretion routes of Tirzepatide metabolites are via urine and feces. Intact Tirzepatide is not observed in urine or feces.

THERAPEUTIC INDICATIONS

Type 2 Diabetes Mellitus

TIRZEE (Tirzepatide) 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.

Weight Management

TIRZEE (Tirzepatide) 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.

Obstructive Sleep Apnea (OSA)

TIRZEE (Tirzepatide) is indicated in combination with a reduced-calorie diet and increased physical activity to treat moderate to severe Obstructive Sleep Apnea (OSA) in adults with obesity.

DOSAGE & ADMINISTRATION

- The starting dose of TIRZEE (Tirzepatide) is 2.5mg once weekly. After 4 weeks, the dose should be increased to 5mg once weekly. If needed, dose increases can be made in 2.5mg increments after a minimum of 4 weeks on the current dose.
- Consider treatment response and tolerability when selecting the maintenance dosage. If patients do not tolerate a maintenance dosage, consider a lower maintenance dosage.
- The maximum dose is 15mg once weekly.

Recommended Maintenance and Maximum Dosage

Recommended Maintenance Dosage

Type 2 Diabetes Mellitus & Weight Management

The recommended maintenance dosage of TIRZEE (Tirzepatide) is 5mg, 10mg, or 15mg injected subcutaneously once weekly.

Obstructive Sleep Apnea (OSA)

The recommended maintenance dosage of TIRZEE (Tirzepatide) is 10mg or 15mg injected subcutaneously once weekly.

Maximum Recommended Dosage

The maximum dosage of TIRZEE (Tirzepatide) for all indications is 15mg injected subcutaneously once weekly.

Important Administration Instructions

- Prior to initiation, train patients and caregivers on proper injection technique.
- When TIRZEE (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 TIRZEE (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.
- Administer TIRZEE (Tirzepatide) once weekly, any time of day, with or without meals.
- Inject TIRZEE (Tirzepatide) subcutaneously in the abdomen, thigh, or upper arm.
- Rotate injection sites with each dose.
- Inspect TIRZEE (Tirzepatide) visually before use. It should appear clear and colorless to slightly yellow. Do not use TIRZEE (Tirzepatide) if particulate matter or discoloration is seen.
- When using TIRZEE (Tirzepatide) with insulin, administer as separate injections and never mix. It is acceptable to inject TIRZEE (Tirzepatide) and insulin in the same body region, but the injections should not be adjacent to each other.

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 Population

Patients with Renal Impairment

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

Patients with Hepatic Impairment

No dose adjustment is required for patients with hepatic impairment. Experience with the use of TIRZEE (Tirzepatide) in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with TIRZEE (Tirzepatide).

Pediatric Population

The safety and efficacy of TIRZEE (Tirzepatide) in children aged less than 18 years have not yet been established.

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

ADVERSE REACTIONS

Very common:

Hypoglycemia when used with sulphonylurea or insulin, nausea, diarrhoea, vomiting, abdominal pain and constipation.

Common:

Hypersensitivity reactions, hypoglycaemia when used with metformin and SGLT2i, decreased appetite, dizziness, hypotension, dyspepsia, abdominal distention, eructation, flatulence, gastroesophageal reflux disease, hair loss, fatigue, injection site reactions, heart rate increased, lipase increased, amylase increased and blood calcitonin increased.

Uncommon:

Hypoglycaemia when used with metformin, weight decreased, dysgeusia, dysaesthesia, cholelithiasis, cholecystitis, acute pancreatitis, delayed gastric emptying and injection site pain.

Rare:

Anaphylactic reaction and angioedema.

"To report SUSPECTED ADVERSE REACTIONS to Getz Pharma's Pharmacovigilance Section, please contact at dsafety@getzpharma.com or +92-21-38636363"

CONTRAINDICATIONS

Tirzepatide is contraindicated in patients with:

- Known serious hypersensitivity to Tirzepatide to any of the excipients of product.
- A personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

PRECAUTIONS

WARNING: RISK OF THYROID C-CELL TUMORS

- In both male and female rats, Tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures. It is unknown whether Tirzepatide 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.
- Tirzepatide 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 for MTC with the use of Tirzepatide 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 Tirzepatide.

Risk of Thyroid C-Cell Tumors

It is unknown whether Tirzepatide 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. Tirzepatide 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.

Pancreatitis

Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists. After initiation of Tirzepatide, observe patients carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back and which may or may not be accompanied by vomiting). If pancreatitis is suspected, discontinue Tirzepatide and initiate appropriate management.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin

Patients receiving Tirzepatide in combination with an insulin secretagogue (e.g., sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia.
The risk of hypoglycemia may be lowered by a reduction in the dose of sulfonylurea (or other concomitantly administered insulin secretagogue) or insulin. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms of hypoglycemia.

Hypersensitivity Reactions

If hypersensitivity reactions occur, discontinue use of Tirzepatide; treat promptly per standard of care, and monitor until signs and symptoms resolve. Do not use in patients with a previous serious hypersensitivity reaction to Tirzepatide or to any of the excipients used in Tirzepatide Injection.

Acute Kidney Injury

Tirzepatide has been associated with gastrointestinal adverse reactions, which include nausea, vomiting, and diarrhea. These events may lead to dehydration, which if severe could cause acute kidney injury.
Monitor renal function when initiating or escalating doses of Tirzepatide in patients with renal impairment reporting severe gastrointestinal adverse reactions.

Severe Gastrointestinal Adverse Reactions

Use of Tirzepatide has been associated with gastrointestinal adverse reactions, sometimes severe. Tirzepatide is not recommended in patients with severe gastrointestinal disease.

Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy

Rapid improvement in glucose control has been associated with a temporary worsening of diabetic retinopathy. Patients with a history of diabetic retinopathy should be monitored for progression of diabetic retinopathy.

Acute Gallbladder Disease

Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported in GLP-1 receptor agonist trials and postmarketing. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

Pulmonary Aspiration During General Anesthesia 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 should be considered prior to performing procedures with general anaesthesia or deep sedation.

Suicidal Behavior and Ideation

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

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.

Pregnancy

There are no or a limited amount of data from the use of Tirzepatide in pregnant women. 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.

Nursing Mothers

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.

DRUG INTERACTIONS

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

When initiating Tirzepatide, consider reducing the dose of concomitantly administered insulin secretagogues (e.g., sulfonylureas) or insulin to reduce the risk of hypoglycemia.

Oral Medications

Tirzepatide 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 Tirzepatide.

Monitor patients on oral medications dependent on threshold concentrations for efficacy and those with a narrow therapeutic index (e.g., warfarin, digoxin) when concomitantly administered with Tirzepatide.
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 and for 4 weeks after each dose escalation with Tirzepatide. Hormonal contraceptives that are not administered orally should not be affected.

OVERDOSAGE

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).

STORAGE

Store in a refrigerator at 2°C - 8°C.
Protect from light.
If needed, each single-dose pen can be stored unrefrigerated at temperature not to exceed 30°C for up to 21 days.
Do not freeze.
Store TIRZEE (Tirzepatide) in the original carton to protect from light.

The expiration date refers to the product correctly stored at the required conditions.

HOW SUPPLIED

TIRZEE (Tirzepatide) Solution for Injection 2.5mg/0.5mL is available in pack of 1 Pre-filled pen autoinjector.
TIRZEE (Tirzepatide) Solution for Injection 5mg/0.5mL is available in pack of 1 Pre-filled pen autoinjector.
TIRZEE (Tirzepatide) Solution for Injection 7.5mg/0.5mL is available in pack of 1 Pre-filled pen autoinjector.
TIRZEE (Tirzepatide) Solution for Injection 10mg/0.5mL is available in pack of 1 Pre-filled pen autoinjector.

Keep out of reach of children.

To be sold on prescription of a registered medical practitioner only.

Please read the contents carefully before use.
This package insert is continually updated from time to time.

Manufactured by:
Getz pharma (PVT) LIMITED
www.getzpharma.com
29-30/27, K.I.A., Karachi, Pakistan
PAK-200021831