ONCE A WEEK

ZEPMARK™
(TIRZEPATIDE)

INSTRUCTIONS MANUAL

زیپ مارک ہدایات نامہ

PRE-FILLED PEN AUTO-INJECTOR

پری فلڈ پین آٹو انجیکٹر

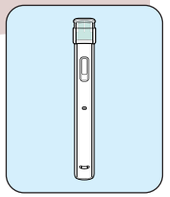
Wash your hands with soap and Water

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 is 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 کہ دوا کی معیاد باقی ہو۔

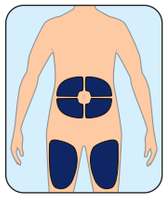
۲ اس بات کو یقینی بنائیں کہ پین خراب نہ ہو اور بند ہو۔

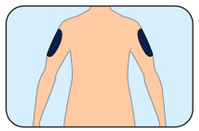
۳ اس بات کو یقینی بنائیں کہ دوا:
- منجمد نہ ہو
- بے رنگ یا ہلکی پیلی ہو
- میں گدلا پن نہ ہو
- میں کوئی ذرات موجود نہ ہوں۔

Step 2 Choose your injection site

دوسرا مرحلہ: انجکشن لگانے کی جگہ کا انتخاب کریں

1. ZEPMARK 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 زیپ مارک کو پیٹ کے اردگرد یا رانوں پر یا کسی اور کی مدد سے بازو کے پچھلے اوپری حصے پر زیر جلد لگایا جا سکتا ہے۔

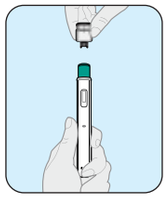
۲ انجکشن لگانے کی جگہ ہر ہفتے تبدیل کرتے رہیں۔

۳ آپ جسم کے ایک ہی حصے پر انجکشن لگا سکتے ہیں مگر ہر 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۔

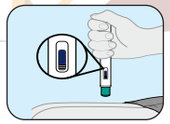
۲ سوئی پین کے اندر موجود ہے، اس لیئے اسے دیکھنے یا چھونے سے گریز کریں۔

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

Step 4 Inject your dose

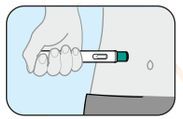
چوتھا مرحلہ: انجکشن لگانے کا طریقہ

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 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 آ جائے 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).

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)

ONCE A WEEK

ZEPMARK™

(TIRZEPATIDE)

زیپ مارک

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
Solution for Injection.
Pre-Filled Pen Auto-Injector

DESCRIPTION:

ZEPMARK (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:

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

ZEPMARK Solution for Injection 2.5 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 2.5 mg in 0.5 ml solution

Product Specs.: Innovator

ZEPMARK Solution for Injection 5 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 5 mg in 0.5 ml solution

Product Specs.: Innovator

ZEPMARK Solution for Injection 7.5 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 7.5 mg in 0.5 ml solution

Product Specs.: Innovator

ZEPMARK Solution for Injection 10 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 10 mg in 0.5 ml solution

Product Specs.: Innovator

ZEPMARK Solution for Injection 12.5 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 12.5 mg in 0.5 mL solution

Product Specs.: Innovator

ZEPMARK Solution for Injection 15 mg/0.5 ml:
Each single dose pre-filled pen contains:
Tirzepatide 15 mg in 0.5 ml solution

Product Specs.: Innovator

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 bi-phasic 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 faeces. Intact Tirzepatide is not observed in urine or faeces.

THERAPEUTIC INDICATIONS:

Type 2 Diabetes Mellitus:
ZEPMARK (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, or in addition to other medicinal products for the treatment of diabetes.

Weight Management:
ZEPMARK (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):
ZEPMARK (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:

Treatment period	Dose
Weeks 1–4	2.5 mg once weekly
From Week 5	5 mg once weekly
Further escalation	Increase by 2.5 mg increments after at least 4 weeks on the current dose
Maximum dose	15 mg once weekly

Recommended Maintenance and Maximum Dosage:

- Type 2 Diabetes Mellitus & Weight Management: The recommended maintenance dosage of ZEPMARK (Tirzepatide) is 5mg, 10mg or 15mg injected subcutaneously once weekly.
- Obstructive Sleep Apnea (OSA): The recommended maintenance dosage of ZEPMARK (Tirzepatide) is 10mg or 15mg injected subcutaneously once weekly.
- Maximum Recommended Dosage: The maximum dosage of ZEPMARK (Tirzepatide) for all indications is 15mg injected subcutaneously once weekly.

Important Instructions for Administration:

- Prior to initiation, train patients and caregivers on proper injection technique.
- When ZEPMARK (Tirzepatide) is added to existing metformin and/or SGLT2i therapy, the current dose of metformin and/or SGLT2i can be continued.
- When ZEPMARK (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 ZEPMARK (Tirzepatide) once weekly any time of day, with or without meals.
- Inject ZEPMARK (Tirzepatide) subcutaneously in the abdomen, thigh, or upper arm. Rotate injection sites with each dose.
- Inspect ZEPMARK (Tirzepatide) visually before use. It should appear clear and colorless to slightly yellow. Do not use ZEPMARK (Tirzepatide) if particulate matter or discoloration is seen.
- When using ZEPMARK (Tirzepatide) with insulin, administer as separate injections and never mix. It is acceptable to inject ZEPMARK (Tirzepatide) and insulin in the same body region, but the injections should not be adjacent to each other.

Missed Dose:
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:

- 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 ZEPMARK (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 ZEPMARK (Tirzepatide) in patients with severe hepatic impairment is limited. Caution should be exercised when treating these patients with ZEPMARK (Tirzepatide).

• Pediatric Population: The safety and efficacy of ZEPMARK (Tirzepatide) in children aged less than 18 years have not yet been established.

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 distension, 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 Mass Pharma Pvt Ltd Section, please contact at masspharma.com or +92-42-35926927.

CONTRAINDICATIONS:

Tirzepatide is contraindicated in patients with:

- Known serious hypersensitivity to Tirzepatide or 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 & WARNINGS:

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. 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.

- ***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. 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. Inform patients using these concomitant medications of the risk of hypoglycemia and educate them on the signs and symptoms.
- ***Hypersensitivity Reactions:*** If hypersensitivity reactions occur, discontinue use of Tirzepatide; treat promptly per standard of care, and monitor until signs and symptoms resolve.
- ***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.
- ***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:*** 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.
- ***Acute Gallbladder Disease:*** Acute events of gallbladder disease such as cholelithiasis or cholecystitis have been reported. 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 anesthesia or deep sedation due to delayed gastric emptying.
- ***Suicidal Behavior and Ideation:*** 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.
- ***Effects on Ability to Drive and Use Machines:*** Tirzepatide has no or negligible influence on the ability to drive or use machines. Where Tirzepatide is used in combination with a sulphonylurea or insulin, patients should take precautions to avoid hypoglycaemia while driving.
- ***Pregnancy & Nursing Mothers:*** Tirzepatide is not recommended during pregnancy and in women of childbearing potential not using contraception. Discontinue at least 1 month before a planned pregnancy. It is unknown whether Tirzepatide is excreted in human milk; a decision must be made whether to discontinue breast-feeding or refrain from Tirzepatide therapy.

DRUG INTERACTIONS:

- ***Concomitant Use with Insulin Secretagogues or Insulin:*** When initiating Tirzepatide, consider reducing the dose of concomitantly administered insulin secretagogues 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. Exercise caution and monitor patients on oral medications dependent on threshold concentrations for efficacy or narrow therapeutic index (e.g., warfarin, digoxin).
- ***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 and for 4 weeks after each dose escalation with Tirzepatide.

OVERDOSAGE:

In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment of these symptoms may be necessary, taking into account the half-life of Tirzepatide (approximately 5 days).

INSTRUCTIONS:

– Store in a refrigerator at 2°C - 8°C.
– Protect from light.
– Do not freeze. If needed ZEPMARK pen can be stored at room temperature upto 30°C for a total of 21 days.
– Keep out of the reach of children.
– To be sold on prescription of a registered medical practitioner only.

PRESENTATION:

ZEPMARK (Tirzepatide) Solution for Injection 2.5 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.
ZEPMARK (Tirzepatide) Solution for Injection 5 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.
ZEPMARK (Tirzepatide) Solution for Injection 7.5 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.
ZEPMARK (Tirzepatide) Solution for Injection 10 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.
ZEPMARK (Tirzepatide) Solution for Injection 12.5 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.
ZEPMARK (Tirzepatide) Solution for Injection 15 mg/0.5 ml is available in pack of 1 Pre-filled pen autoinjector.

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

استعمال کرنے سے پہلے اندرونی معلومات کا دھیان سے مطالعہ کریں۔
یہ معلوماتی پرچہ وقت فوقتاً اپ ڈیٹ کیا جاتا رہے گا۔

ہدایات: دوا کو ریفریجریٹر میں ۲-۸ ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔
روشنی سے بچائیں۔
منجمد ہونے سے بچائیں۔ اگر ضرورت ہو، زیپ مارک پین کو کمرے کے
درجہ حرارت پر ۳۰ ڈگری سینٹی گریڈ تک ۲۱ دن کیلئے رکھا جا سکتا ہے۔
بچوں کی پہنچ سے دور رکھیں۔
صرف مستند ڈاکٹر کے نسخہ پر فروخت کریں۔

Manufactured by:
Weather Folds Pharmaceuticals
Plot No. 69/2, Phase II, Industrial Estate, Hattar, KPK, Pakistan.

Manufactured for:
Welmark Pharmaceuticals
Plot No. 122, Block B, Phase V, Industrial Estate, Hattar, Pakistan.

FOR FURTHER INFORMATIONS PLEASE CONTACT:

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