Zeptide

(Tirzepatide)

2.5 mg | 5mg | 7.5 mg | 10 mg | 12.5mg | 15 mg

Solution for Injection for Subcutaneous Use

Prefilled Syringe For Single Dose Only

4000003492

زیپٹائڈ

(ٹرزیپیٹائڈ) سلوشن فار انجیکشن زیر جلد استعمال کیلئے

Composition:

Zeptide 2.5mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....2.5mg

Zeptide 5mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....5mg

Zeptide 7.5mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....7.5mg

Zeptide 10mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....10mg

Zeptide 12.5mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....12.5mg

Zeptide 15mg Injection
Each Prefilled Syringe of 0.5 mL contains:
Tirzepatide.....15mg

Product Specifications: Innovator

WARNING: RISK OF THYROID C-CELL TUMORS

Tirzepatide causes thyroid C-cell tumors in rats. 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.

DESCRIPTION

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. The molecular weight is 4813.53 Da and the empirical formula is $C_{225}H_{348}N_{48}O_{68}$.

Mechanism of Action:

Tirzepatide is a long-acting GLP and GLP-1 receptor agonist. It is a 39-amino-acid sequence with a C20 fatty diacid moiety that enables albumin binding and prolongs half-life. Both receptors are present on the pancreatic α and β endocrine cells, brain, heart, vasculature, immune cells (leukocytes), gut and kidney. GIP receptors are also present on adipocytes. Tirzepatide is 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. Tirzepatide is a biased agonist at the GLP-1 receptor with preferential signaling towards the activation of adenylyl cyclase as opposed to the recruitment of β - arrestin.

CLINICAL PARTICULARS

Therapeutic indications:

Zeptide (Tirzepatide) is indicated:

Type 2 Diabetes Mellitus:

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 not tolerated or contraindicated
- in addition to other medicinal products for the treatment of type 2 diabetes.

Chronic Weight Management:

Tirzepatide is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic 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).

Obstructive Sleep Apnoea (OSA):

Tirzepatide is indicated for the treatment of moderate to severe obstructive sleep apnoea in adults with obesity.

Posology and method of administration

Important Administration Instructions

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

Recommended Dosage

- The recommended starting dosage of tirzepatide is 2.5 mg injected subcutaneously once weekly. Follow the dosage escalation below to reduce the risk of gastrointestinal adverse reactions. The 2.5 mg dosage is for treatment initiation and is not intended for glycemic control.
- After 4 weeks, increase the dosage to 5 mg injected subcutaneously once weekly.
- If additional glycemic control is needed, increase the dosage in 2.5 mg increments after at least 4 weeks on the current dose.
- The maximum dosage of tirzepatide is 15 mg injected subcutaneously once weekly.
- If a dose is missed, instruct patients to administer tirzepatide 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).

Special populations

Elderly: No overall differences in safety or efficacy were detected between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal impairment: No dosage adjustment of TIRZEPATIDE 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. Monitor renal function when initiating or escalating doses of tirzepatide in patients with renal impairment reporting severe adverse gastrointestinal reactions.

Hepatic impairment: No dosage adjustment of TIRZEPATIDE 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.

Contraindication:

Tirzepatide is contraindicated in patients with:

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

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been reported with tirzepatide.

Warnings and precautions

Acute Pancreatitis: Has been observed in patients treated with GLP-1 receptor agonists, or Tirzepatide. Discontinue if pancreatitis is suspected.

Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin: Concomitant use with an insulin secretagogue or insulin may increase the risk of hypoglycemia, including severe hypoglycemia. Reducing dose of insulin secretagogue or insulin may be necessary.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis and angioedema) have been reported. Discontinue Tirzepatide if suspected and promptly seek medical advice.

Acute Kidney Injury Due to Volume Depletion: Monitor renal function in patients reporting adverse reactions that could lead to volume depletion.

Severe Gastrointestinal Adverse Reactions: Use may be associated with gastrointestinal adverse reactions, sometimes severe. Tirzepatide is not recommended in patients with severe gastroparesis.

Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy: 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.

Acute Gallbladder Disease: Has occurred in clinical trials. If cholelithiasis is suspected, gallbladder studies and clinical follow up are indicated.

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.

Use in specific populations

Pregnancy: Based on animal studies, may cause fetal harm.

Females of Reproductive Potential: Use of TIRZEPATIDE may reduce the efficacy of oral hormonal contraceptives due to delayed gastric emptying. This delay is the 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 and for 4 weeks after each dose escalation with TIRZEPATIDE.

Breast-feeding There are no data on the presence of tirzepatide 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 TIRZEPATIDE and any potential adverse effects on the breastfed infant from TIRZEPATIDE or from the underlying

maternal condition.
Fertility: 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.

Drug & Other 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) 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.
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 males (≥0.5 mg/kg) and
females (≥0.15 mg/kg), and a statistically significant increase in thyroid C-cell adenomas and carcinomas combined was observed in males and females 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.

Adverse Reactions

Risk of Thyroid C-cell Tumors.
Acute Pancreatitis.
Hypoglycemia with Concomitant Use of Insulin Secretagogues or Insulin
Hypersensitivity Reactions
Acute Kidney Injury Due to Volume Depletion
Severe Gastrointestinal Adverse Reactions
Diabetic Retinopathy Complications in Patients with a History of Diabetic Retinopathy.
Acute Gallbladder Disease
Pulmonary Aspiration During General Anesthesia or Deep Sedation
Immunogenicity: There was no identified clinically significant effect of anti-tirzepatide antibodies on pharmacokinetics or effectiveness of TIRZEPATIDE. More TIRZEPATIDE-treated patients who developed anti-tirzepatide antibodies experienced hypersensitivity
reactions or injection site reactions than those who did not develop these antibodies GLP-1 neutralising effect at end-of-trial.
Post-Marketing Experience:
Hypersensitivity: anaphylaxis, angioedema.
Gastrointestinal: acute pancreatitis, hemorrhagic and necrotizing pancreatitis (sometimes resulting in death), ileus.
Pulmonary: Pulmonary aspiration has occurred in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation
Renal: acute renal failure or worsening of chronic renal failure, sometimes requiring hemodialysis
Skin and Subcutaneous Tissue: alopecia

Overdosage:

Appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.

CLINICAL PHARMACOLOGY

Pharmacodynamics

Tirzepatide lowers fasting and postprandial glucose concentration, decreases food intake, and reduces body weight in patients with type 2 diabetes mellitus.
First and Second-Phase Insulin Secretion: Tirzepatide enhances the first- and second-phase insulin secretion.
Insulin Sensitivity: Tirzepatide increases insulin sensitivity, as demonstrated in a hyperinsulinemic euglycemic clamp study after 28 weeks of treatment.
Glucagon Secretion: Tirzepatide reduces fasting and postprandial glucagon concentrations. Tirzepatide 15 mg reduced fasting glucagon concentration by 28% and glucagon AUC after a mixed meal by 43%, compared with no change for placebo after 28 weeks of treatment.
Gastric Emptying: Tirzepatide delays gastric emptying. The delay is largest after the first dose and this effect diminishes over time. Tirzepatide slows post-meal glucose absorption, reducing postprandial glucose.

Pharmacokinetics

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. 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 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 10.3 L. Tirzepatide is highly bound to plasma albumin (99%).
Elimination: The apparent population mean clearance of tirzepatide is 0.061 L/h with an elimination half-life of approximately 5 days, enabling once-weekly dosing.
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, gender, race, ethnicity, or body weight do not have a clinically relevant effect on the PK of Tirzepatide

HOW SUPPLIED

Each pack contains one PFS of Zeptide placed in a PVC Tray along with a leaflet enclosed in a Unit Carton.

Zeptide Solution for Injection in a single dose PFS (Prefilled Syringes)

Each PFS of 2.5mg contains:
Zeptide(2.5mg)/0.5ml (Pack of 1's)

Each PFS of 5mg contains:
Zeptide(5mg)/0.5ml (Pack of 1's)

Each PFS of 7.5mg contains:
Zeptide(7.5mg)/0.5ml (Pack of 1's)

Each PFS of 10mg contains:
Zeptide(10mg)/0.5ml (Pack of 1's)

Each PFS of 12.5mg contains:
Zeptide(12.5mg)/0.5ml (Pack of 1's)

Each PFS of 15mg contains:
Zeptide(15mg)/0.5ml (Pack of 1's)

STORAGE

Refrigerate at 2°C to 8°C. Do not Freeze.

INSTRUCTIONS

Keep out of reach of children. Protect from heat and light.
To be sold on Prescription of a registered medical practitioner only.Do not shake the prefilled syringe.

Manufactured by:
BF BIOSCIENCES
FEROZSONS LABORATORIES LIMITED
BF Biosciences Limited
(A subsidiary of Ferozsons Laboratories Limited)
5 km, Sunder-Raiwind Road, Raiwind, Lahore, Pakistan.
Mfg. Lic. No. 000655