ZEPAD SOLUTION FOR INJECTION, PEN AUTOINJECTOR 5mg/0.5mL

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Zepad Solution for Injection, Pre-filled Pen Autoinjector 5mg/0.5mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

3. PHARMACEUTICAL FORM

Clear & Colorless to light yellow solution filled in a USP Type I colorless & graduated glass syringe preassembled in a white color autoinjector having transparent dose window and dark blue color cap consisting of dark blue color needle shield remover.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Zepad is indicated as an adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with type 2 diabetes mellitus.

4.2. Posology and method of administration

- The recommended starting dosage of Zepad is 2.5 mg injected subcutaneously once weekly. The 2.5mg 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 2.5mg increments after at least 4 weeks on the current dose. The maximum dosage of Zepad is:
  - 15 mg injected subcutaneously once weekly in adults.
  - 10 mg injected subcutaneously once weekly in pediatric patients.
- If a dose is missed, instruct patients to administer Zepad 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).

Important Administration Instructions

- Prior to initiation, train patients and their caregiver(s) on proper injection technique for the prescribed Zepad Presentation. After training, a patient may self-inject Zepad if the healthcare provider determines that it can be properly administered, except for the following:
- Zepad is not recommended for self-administration by pediatric patients.
- Zepad is not recommended for self-administration by those who are visually impaired.
- Administer Zepad once weekly, any time of day, with or without meals.
- Inject Zepad subcutaneously in the abdomen, thigh, or another person should inject in the back of the upper arm.

- Rotate injection sites with each dose.
- Inspect Zepad visually before use. It should appear clear and colorless to slightly yellow. Do not use Zepad if particulate matter or discoloration is seen.
- When using Zepad with insulin, administer as separate injections and never mix. It is acceptable to inject Zepad and insulin in the same body region, but the injections should not be adjacent to each other.

4.3. Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
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.

4.4. Special warnings and special precautions for use

Risk of Thyroid C-Cell Tumors
In both sexes of rats, tirzepatide caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) in a 2-year study at clinically relevant plasma 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 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. Such monitoring may increase the risk of unnecessary procedures, due to the low test specificity for serum calcitonin and a high background incidence of thyroid disease. Significantly elevated serum calcitonin values may indicate MTC and patients with MTC usually have calcitonin values >50 ng/L. If serum calcitonin is measured and found to be elevated, the patient should be further evaluated. Patients with thyroid nodules noted on physical examination or neck imaging should also be further evaluated.

Acute pancreatitis
Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis, has been observed in patients treated with GLP-1 receptor agonists, or Tirzepatide. After initiation of Tirzepatide, observe patients carefully for signs and symptoms of acute pancreatitis, which may include persistent or severe abdominal pain (sometimes radiating to the back) and which may or may not be accompanied by nausea or 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
Serious hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported in patients treated with Tirzepatide. 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 any of the excipients in Tirzepatide. Anaphylaxis and angioedema have been reported with GLP-1 receptor agonists. Use caution in patients with a history of angioedema or anaphylaxis with a GLP-1 receptor agonist because it is unknown whether such patients will be predisposed to these reactions with Tirzepatide.

Acute Kidney Injury Due to Volume Depletion
There have been postmarketing reports of acute kidney injury, in some cases requiring hemodialysis, in patients treated with GLP-1 receptor agonists, or Tirzepatide. The majority of the reported events occurred in patients who experienced gastrointestinal adverse reactions leading to dehydration such as nausea, vomiting, or diarrhea. Monitor renal function in patients reporting adverse reactions to Tirzepatide that could lead to volume depletion, especially during dosage initiation and escalation of Tirzepatide.

Severe Gastrointestinal Adverse Reactions
Use of Tirzepatide has been associated with gastrointestinal adverse reactions, sometimes In the pool of placebo-controlled trials in adults, severe gastrointestinal adverse reactions occurred more frequently among patients receiving Tirzepatide (5mg 1.3%, 10mg 0.4%, 15mg 1.2%) than placebo (0.9%). Severe gastrointestinal adverse reactions have also been reported postmarketing with GLP-1 receptor agonists. Tirzepatide is not recommended in patients with severe gastroparesis.

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. Tirzepatide has not been studied in patients with non-proliferative diabetic retinopathy requiring acute therapy, proliferative diabetic retinopathy, or diabetic macular edema. 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.
In Tirzepatide placebo-controlled clinical trials in adults, acute gallbladder disease (cholelithiasis, biliary colic, and cholecystectomy) was reported by 0.6% of Tirzepatide treated patients and 0% of placebo-treated patients. If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

Pulmonary Aspiration During General Anesthesia or Deep Sedation
Tirzepatide delays gastric emptying. There have been rare postmarketing reports of pulmonary aspiration in patients receiving GLP-1 receptor agonists undergoing elective surgeries or procedures requiring general anesthesia or deep sedation who had residual gastric contents despite reported adherence to preoperative fasting recommendations.
Available data are insufficient to inform recommendations to mitigate the risk of pulmonary aspiration during general anesthesia or deep sedation in patients taking Tirzepatide, including whether modifying preoperative fasting recommendations or temporarily discontinuing Tirzepatide could reduce the incidence of retained gastric contents. Instruct patients to inform healthcare providers prior to any planned surgeries or procedures if they are taking Tirzepatide.

4.5. Interaction with other medicinal products and other forms of 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.

4.6. Fertility, pregnancy and lactation

Pregnancy
Risk Summary
Available data with Tirzepatide use in pregnant women are insufficient to evaluate for a drug-related risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with poorly controlled diabetes in pregnancy. Based on animal reproduction studies, there may be risks to the fetus from exposure to tirzepatide during pregnancy. Tirzepatide should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In pregnant rats administered tirzepatide during organogenesis, fetal growth reductions and fetal abnormalities occurred at clinical exposure in maternal rats based on AUC. In rabbits administered tirzepatide during organogenesis, fetal growth reductions were observed at clinically relevant exposures based on AUC. These adverse embryo/fetal effects in animals coincided with pharmacological effects on maternal weight and food consumption.

The estimated background risk of major birth defects is 6–10% in women with pre-gestational diabetes with an HbA1c >7% and has been reported to be as high as 20–25% in women with an HbA1c >10%. The estimated background risk of miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively.

Clinical Considerations
Disease-Associated Maternal and/or Embryo/Fetal Risk
Poorly controlled diabetes in pregnancy increases the maternal risk for diabetic ketoacidosis, pre-eclampsia, spontaneous abortions, preterm delivery, and delivery complications. Poorly controlled diabetes increases the fetal risk for major birth defects, stillbirth, and macrosomia-related morbidity.

Animal Data
In pregnant rats given twice weekly subcutaneous doses of 0.02, 0.1, and 0.5 mg/kg tirzepatide (0.03-, 0.07-, and 0.5-fold the MRHD of 15 mg once weekly based on AUC) during organogenesis, increased incidences of external, visceral, and skeletal malformations, increased incidences of visceral and skeletal developmental variations, and decreased fetal weights coincided with pharmacologically-mediated reductions in maternal body weights and food consumption at 0.5 mg/kg. In pregnant rabbits given once weekly subcutaneous doses of 0.01, 0.03, or 0.1 mg/kg tirzepatide (0.01-, 0.06-, and 0.2-fold the MRHD) during organogenesis, pharmacologically-mediated effects on the gastrointestinal system resulting in maternal mortality or abortion

in a few rabbits occurred at all dose levels. Reduced fetal weights associated with decreased maternal food consumption and body weights were observed at 0.1 mg/kg. In a pre- and post-natal study in rats administered subcutaneous doses of 0.02, 0.10, or 0.25 mg/kg tirzepatide twice weekly from implantation through lactation, F1 pups from F0 maternal rats given 0.25 mg/kg tirzepatide had statistically significant lower mean body weight when compared to controls from post-natal day 7 through post-natal day 126 for males and post-natal day 56 for females.

Lactation

Risk Summary

In a single-dose clinical lactation study, the concentration of tirzepatide in breast milk was found to be either undetectable or low compared to the maternal administered dose. There are no available data on the effects of tirzepatide on the breastfed infant or 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.

Data

Following subcutaneous administration of a single 5 mg dose to 11 healthy lactating adult females, the concentration of tirzepatide in breast milk was found to be undetectable (limit of detection in breast milk 4 ng/mL) in 164/171 samples assayed. The cumulative amount of tirzepatide detected in the remaining 7 breast milk samples over the 28-day sampling window was equivalent to less than 0.02% of the maternal administered dose, with the last measurable concentrations occurring 5 days post-dose. The AUC of tirzepatide in breast milk could not be calculated, due to insufficient quantifiable concentrations.

4.7. 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.

4.8. Undesirable effects

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.

<u>Reporting of suspected adverse reactions</u>

'Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, Pharmacovigilance Electronic Reporting System

(PvERS) https://pv.pharmacyboardkenya.org'

4.9. Overdose

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).

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, blood glucose lowering drugs, excl. insulins,
ATC code: A10BX16.

Mechanism of action
Tirzepatide is a GIP receptor and GLP-1 receptor agonist. It contains 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.

5.2. Pharmacokinetic properties

The pharmacokinetics of tirzepatide is similar between healthy subjects and patients with type 2 diabetes mellitus. Steadystate 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.

Pediatric Patients
A population pharmacokinetic analysis was conducted for tirzepatide 5mg and 10mg using data from 93 pediatric patients 10 years of age and older with type 2 diabetes mellitus. The tirzepatide exposure in pediatric patients was within the range observed in adult patients.

Patients with Renal Impairment
Renal impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5mg dose was evaluated in patients with different degrees of renal impairment (mild, moderate, severe, ESRD) compared with subjects with normal renal function.

Patients with Hepatic Impairment
Hepatic impairment does not impact the pharmacokinetics of tirzepatide. The pharmacokinetics of tirzepatide after a single 5mg dose was evaluated in patients with different degrees of hepatic impairment (mild, moderate, severe) compared with subjects with normal hepatic function.

5.3. Preclinical safety data

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. In fertility and early embryonic development studies, male and female rats were administered twice weekly subcutaneous doses of 0.5, 1.5, or 3 mg/kg (0.3-, 1-, and 2-fold and 0.3-, 0.9-, and 2-fold, respectively, the MRHD of 15mg once weekly based on AUC). 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.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

- Disodium Hydrogen Phosphate Heptahydrate
- Sodium Chloride
- Hydrochloric Acid
- Sodium Hydroxide
- Water for Injection

6.2. Incompatibilities

None

6.3. Shelf-life

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

6.4. Special precautions for storage

- Store in a refrigerator at 2°C - 8°C.
- Protect from light.
- If needed, each single-dose pen can be stored unrefrigerated at temperatures not to exceed 30°C for up to 21 days.
- Do not freeze. Always check your pen to ensure it is not frozen before using it. Do not use pen, if you drop the pen on hard surface.
- Store Zepad (Tirzepatide) in the original carton to protect from light.

6.5. Nature and contents of container

Zepad Solution for Injection 5mg/0.5mL is available in a pack of 1 pre-filled pen autoinjector, packed in a printed unit carton with the package insert.

6.6. Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER AND MANUFACTURING SITE ADDRESS

Getz Pharma (Private) Limited
Plot No. 29-30, Sector 27, Korangi Industrial Area Karachi 74900,
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8. MARKETING AUTHORIZATION NUMBER

CTD13276

9. DATE OF FIRST AUTHORIZATION / RENEWAL OF THE AUTHORIZATION

6th March, 2026

10. DATE OF REVISION OF THE TEXT

6th March, 2026