

TRIXIBET® EXTENDED RELEASE F. C. TABLET

TRIXIBET® ER EMPAGLIFLOZIN/LINAGLIPTIN/METFORMIN HCl

TRIXIBET® ER (EMPAGLIFLOZIN, LINAGLIPTIN, and METFORMIN HYDROCHLORIDE EXTENDED-RELEASE) F. C. TABLET FOR ORAL USE Read this patient information carefully before you start taking Trixibet® ER because it answers some common questions about Trixibet® ER. This medication is prescribed for your current condition, therefore do not use it in similar cases and do not recommend it to others. To report any SUSPECTED ADVERSE REACTIONS, contact Noavaran Daroui Kimia Co. at +982166435789 or send email to medical@kimia-pharma.com. **Read this patient information carefully before you start taking Trixibet® ER because it contains important information for you. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.**

Composition

- Trixibet® ER tablets are available as follows:
- 5 mg Empagliflozin/2.5 mg Linagliptin/1000 mg Metformin HCl extended-release.
 - 10 mg Empagliflozin/5 mg Linagliptin/1000 mg Metformin HCl extended-release.
 - 12.5 mg Empagliflozin/2.5 mg Linagliptin/1000 mg Metformin HCl extended-release.
 - 25 mg Empagliflozin/5 mg Linagliptin/1000 mg Metformin HCl extended-release.

Mechanism of action

- **Empagliflozin:** Empagliflozin is an inhibitor of SGLT2.
- **Linagliptin:** Linagliptin is an inhibitor of DPP-4.
- **Metformin HCl:** Metformin is an antihyperglycemic agent.

Pharmacokinetic

Absorption

Administration of Trixibet® ER with food resulted in no change in overall exposure of empagliflozin or linagliptin. For metformin extended-release, high-fat meals increased systemic exposure by approximately 70% relative to fasting, while C_{max} is not affected. Meals prolonged T_{max} by approximately 3 hours.

Distribution

Empagliflozin: The apparent steady-state volume of distribution was estimated to be 73.8 L.

Linagliptin: The mean apparent volume of distribution at steady-state is approximately 1110 L.

Metformin HCl: The apparent volume of distribution of metformin following single oral doses of immediate-release metformin HCl tablets 850 mg averaged 654±358 L. Metformin is negligibly bound to plasma proteins.

Metabolism

Empagliflozin: No major metabolites of empagliflozin were detected in human plasma. The primary route of metabolism of empagliflozin in humans is glucuronidation.

Linagliptin: The majority (about 90%) of linagliptin is excreted unchanged, and metabolism represents a minor elimination pathway.

Metformin HCl: Metformin does not undergo hepatic metabolism nor biliary excretion.

Elimination

Empagliflozin: The apparent terminal elimination half-life of empagliflozin was estimated to be 12.4 h and apparent oral clearance was 10.6 L/h.

Linagliptin: Linagliptin has a terminal half-life of about 200 hours at steady-state, though the accumulation half-life is about 11 hours. Renal clearance at steady-state was approximately 70 mL/min.

Metformin HCl: Metformin has a plasma elimination half-life of approximately 6.2 hours.

Excretion

Empagliflozin: Following administration of an oral [¹⁴C]-empagliflozin, approximately 95.6% of the drug-related radioactivity was eliminated in feces (41.2%) or urine (54.4%).

Linagliptin: Following administration of an oral [¹⁴C]-linagliptin, approximately 85% of the administered radioactivity was eliminated via the enterohepatic system (80%) or urine (5%) within 4 days of dosing.

Metformin HCl: Following oral administration, approximately 90% of the absorbed drug is excreted via the renal route within the first 24 hours.

Indication

Trixibet® ER is a combination of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and metformin hydrochloride (HCl), a biguanide, indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Empagliflozin is indicated to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

Limitations of Use:

- Not recommended in patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.
- Has not been studied in patients with a history of pancreatitis.

It is not known if Trixibet® ER is safe and effective in children.

Dosage and administration

- Assess renal function before initiating and as clinically indicated.
- Individualize the starting dose of Trixibet® ER based on the patient's current regimen and renal function.
- Initiation of Trixibet® ER is not recommended in patients with an eGFR less than 45 mL/min/1.73 m², due to the metformin component.
- The maximum recommended dose of Trixibet® ER is 25 mg empagliflozin, 5 mg linagliptin and 2000 mg metformin HCl.
- Take Trixibet® ER once daily with a meal in the morning. Swallow tablets whole. Do not split, crush, dissolve, or chew.

Side effects / adverse reactions

It should be noted that these side effects do not occur in all patients. These are not all the possible side effects of Trixibet® ER. For more information, ask your healthcare provider or pharmacist.

Trixibet® ER may cause serious side effects including:

- **Lactic Acidosis.** Metformin hydrochloride, one of the medicines in Trixibet® ER, can cause a rare but serious condition called lactic acidosis (a build-up of lactic acid in the blood) that may be life-threatening. Stop taking Trixibet® ER and tell your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms of lactic acidosis:
 - o feel cold, especially in your arms and legs
 - o have unusual (not normal) muscle pain
 - o have unusual sleepiness or sleep longer than usual
 - o have unexplained stomach or intestinal problems with nausea and vomiting, or diarrhea
 - o have trouble breathing
 - o feel very weak and tired
 - o feel dizzy or lightheaded
 - o have a slow or irregular heartbeat
 - **Inflammation of the pancreas (Pancreatitis)** which may be severe and life-threatening. Certain medical problems make you more likely to get pancreatitis. Stop taking Trixibet® ER and tell your healthcare provider right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen to your back and may happen with or without vomiting.
 - **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis has happened in people who have type 1 diabetes or type 2 diabetes, during treatment with empagliflozin, one of the medicines in Trixibet® ER. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with Trixibet® ER. Ketoacidosis is a serious and life-threatening condition, which needs to be treated in a hospital. **Ketoacidosis can happen with Trixibet® ER even if your blood sugar is less than 250 mg/dL. Stop taking Trixibet® ER and tell your healthcare provider right away or go to the nearest hospital emergency room if you get any of the following symptoms:**
 - o nausea
 - o tiredness
 - o vomiting
 - o trouble breathing
 - o stomach-area (abdominal) painIf you get any of these symptoms during treatment with Trixibet® ER, if possible, check for ketones in your urine, even if your blood sugar is less than 250 mg/dL.
 - **Dehydration.** Trixibet® ER can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). There have been reports of sudden worsening of kidney function in people who are taking Trixibet® ER. Tell your healthcare provider about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.
 - **Serious urinary tract infections.** Serious urinary tract infections that may lead to hospitalization have happened in people who are taking empagliflozin, one of the medicines in Trixibet® ER. Tell your healthcare provider if you have any signs or symptoms of a urinary tract infection such as a burning feeling when passing urine, a need to urinate often, the need to urinate right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Sometimes people also may have a back pain, nausea or vomiting.
 - **Low blood sugar (hypoglycemia).** If you take Trixibet® ER with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take Trixibet® ER. Signs and symptoms of low blood sugar may include:
 - o headache
 - o confusion
 - o drowsiness
 - o sweating
 - o hunger
 - o dizziness
 - o irritability
 - o weakness
 - o shaking or feeling jittery
 - o fast heartbeat
 - **A rare but serious bacterial infection that causes damage to the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take empagliflozin, one of the medicines in Trixibet® ER. Necrotizing fasciitis of the perineum may lead to hospitalization and may be life-threatening. Tell your healthcare provider right away if you have a fever or you are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals:
 - o pain or tenderness
 - o redness of skin (erythema)
 - o swelling
 - **Vaginal yeast infection.** Empagliflozin, one of the medicines in Trixibet® ER, increases the risk for vaginal yeast infections. Symptoms of a vaginal yeast infection include:
 - o vaginal odor
 - o vaginal itching
 - o white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese)
 - **Yeast infection of the penis (balanitis).**
 - o Swelling of an uncircumcised penis
 - o redness, itching, or swelling of the penis
 - o rash of the penis
 - o foul smelling discharge from the penis
 - o pain in the skin around the penis
- Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis.** Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.
- **Allergic (hypersensitivity) reactions.** Serious allergic reactions have happened in patients who are taking Trixibet® ER. Stop taking Trixibet® ER and tell your healthcare provider right away or go to the nearest hospital emergency room if you notice any of the following changes:
 - o difficulty with swallowing or breathing
 - o raised, red areas on your skin (hives)
 - o swelling of your face, lips, tongue, throat, and other areas on your skin
 - o skin rash, itching, flaking, or peeling

- **Low vitamin B12 (vitamin B12 deficiency).** Using metformin for long periods of time may cause a decrease in the amount of vitamin B12 can cause low blood counts. Vitamin B12 deficiency can also cause other symptoms related to the brain and nerves. They include:
 - o tingling or numbness in the hands or feet
 - o trouble walking
 - o memory problems or trouble thinking clearly
 - o mood changesYour healthcare provider may do blood tests to check your vitamin B12 levels. Your healthcare provider treats vitamin B12 deficiency by giving people vitamin B12. It comes as a shot or pills. You can talk to your healthcare provider about which form is better for your situation.
- **Joint pain.** Some people who take linagliptin, one of the medicines in Trixibet® ER, may develop joint pain that can be severe. Tell your healthcare provider right away if you have any severe joint pain.
- **Skin reaction.** Some people who take linagliptin, one of the medicines in Trixibet® ER, may develop a skin reaction called bullous pemphigoid that can require treatment in a hospital. Tell your healthcare provider right away if you develop blisters or the breakdown of the outer layer of your skin (erosion). Your healthcare provider may tell you to stop taking Trixibet® ER.
- **Heart failure.** Tell your healthcare provider right away if you have any of the following symptoms of heart failure:
 - o increasing shortness of breath or trouble breathing, especially when you lie down
 - o swelling or fluid retention, especially in the feet, ankles or legs
 - o an unusually fast increase in weight
 - o unusual tiredness

Call your healthcare provider right away if you have aforementioned symptoms.

The most common side effects of Trixibet® ER include:

- upper respiratory tract infection
- stuffy or runny nose and sore throat
- urinary tract infection
- inflammation of the stomach and intestine (gastroenteritis)
- constipation
- headache
- diarrhea

Tell your healthcare provider if you have any side effect that bothers you or does not go away.

Drug interactions

Since the drug interactions with Trixibet® ER are not limited to the following medicines tell your doctor or pharmacist if you are taking, have recently taken, or might take any other medicines. This includes herbal medicines and other medicines you bought without a prescription.

Tell your healthcare provider before taking Trixibet® ER if you are taking any of the following medicines. The following medicines may reduce how well Trixibet® ER works:

- **Carbonic Anhydrase Inhibitors** (e.g., topiramate, zonisamide, acetazolamide or dichlorphenamide)
- **Drugs that Reduce Metformin Clearance** (e.g., ranolazine, vandetanib, dolutegravir, and cimetidine)
- **Alcohol**
- **Diuretics** – a medicine to lower blood pressure or treat edema
- **Insulin or insulin Secretagogues** (e.g., sulfonylurea)
- **Drugs Affecting Glycemic Control** (e.g., thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid)
- **Lithium** – an antipsychotic drug
- **Rifampin** – an antibiotic

Trixibet® ER and test:

- **Interference with 1,5-anhydroglucitol (1,5-AG) Assay**
- **Positive Urine Glucose Test**

Warnings

Before taking Trixibet® ER, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems.
- have heart problems, including congestive heart failure.
- have a history of infection of the vagina or penis.
- are 65 years of age or older.
- have a history of urinary tract infections or problems with urination.
- are going to have surgery. Your healthcare provider may stop your Trixibet® ER before you have surgery. Treatment with Trixibet® ER in patients who are hospitalized for major surgery or acute serious illnesses may be restarted once the patient's condition has stabilized. Talk to your healthcare provider if you are having surgery about when to stop taking Trixibet® ER and when to start it again.
- are getting dehydrated (losing a large amount of body fluids due to fever, vomiting, or diarrhea, and excessive sweating).
- have or have had problems with your pancreas, including stones in your gallbladder, pancreatitis, or surgery on your pancreas.
- have high blood triglyceride levels.
- are on low sodium (salt) diet.
- are eating less, there is a change in your diet, have surgery or other procedure for which you need to restrict the amount of food and liquid you eat and drink.
- drink alcohol very often or drink a lot of alcohol in the short term ("binge" drinking) or have ever had a history of alcoholism.
- are going to get an injection of dye or contrast agents for an x-ray procedure. Trixibet® ER may need to be stopped for a short time. Talk to your healthcare provider about when you should stop Trixibet® ER and when you should start Trixibet® ER again.
- have type 1 diabetes. Trixibet® ER should not be used to treat people with type 1 diabetes.
- are pregnant or plan to become pregnant. Trixibet® ER may harm your unborn baby.
- are a person who has not gone through menopause (premenopausal) who does not have periods regularly or at all.

Do not take Trixibet® ER if you:

- have severe kidney problems, end stage renal disease, or are on dialysis.
- have a condition called metabolic acidosis or diabetic ketoacidosis (increased ketones in the blood or urine).
- are allergic to empagliflozin, linagliptin, metformin, or any of the ingredients in Trixibet® ER. Symptoms of a serious allergic reaction to Trixibet® ER may include:
 - o skin rash, itching, flaking or peeling
 - o raised red patches on your skin (hives)
 - o difficulty with swallowing or breathing
 - o swelling of your face, lips, tongue and throat that may cause difficulty in breathing or swallowingIf you have any of these symptoms, stop taking Trixibet® ER and tell your healthcare provider right away or go to the nearest hospital emergency room.

Tell your healthcare provider about all the medicines you take or treatments you receive, including prescription and over-the-counter medicines, vitamins, and herbal supplements. You should not start or stop any medicine before you talk with the healthcare provider that prescribed Trixibet® ER. Trixibet® ER and other medicines may affect each other causing serious side effects.

Missed dose

If you miss a dose of Trixibet® ER take it as soon as you remember on the same day. Take your next dose of Trixibet® ER at your regular time on the next day. Do not take extra doses of Trixibet® ER to make up for a missed dose.

Overdose

If you take too much Trixibet® ER, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation

Trixibet® ER can cause harm to your unborn baby.

- If you become pregnant while taking Trixibet® ER, tell your healthcare provider as soon as possible. Talk with your healthcare provider about the best way to control your blood sugar while you are pregnant.
- Trixibet® ER can cause the release of an egg from an ovary in a person (ovulation). This can increase your chance of getting pregnant. Tell your healthcare provider right away if you become pregnant while taking Trixibet® ER.
- Trixibet® ER may pass into your breast milk and may harm your baby. Talk with your healthcare provider about the best way to feed your baby if you are taking Trixibet® ER. Do not breastfeed while taking Trixibet® ER.

Patient information

- Take Trixibet® ER exactly as your healthcare provider tells you to take it.
- Take Trixibet® ER by mouth 1 time each day with a meal in the morning. Taking Trixibet® ER with a meal may lower your chance of having an upset stomach.
- Swallow Trixibet® ER tablets whole. Do not break, cut, crush, dissolve, or chew Trixibet® ER. If you cannot swallow Trixibet® ER tablets whole, tell your healthcare provider.
- You may see something that looks like the Trixibet® ER tablet in your stool (bowel movement). This is not harmful and should not affect the way Trixibet® ER works to control your diabetes.
- Your healthcare provider may tell you to take Trixibet® ER along with other diabetes medicines. Low blood sugar can happen more often when Trixibet® ER is taken with certain other diabetes medicines.
- Your healthcare provider will do blood tests to check how well your kidneys are working before and during your treatment with Trixibet® ER.
- When taking Trixibet® ER, you may have sugar in your urine, which will show up on a urine test.
- Avoid drinking alcohol very often or drinking a lot of alcohol in a short period of time ("binge" drinking). It can increase your chances of getting serious side effects.
- Trixibet® ER contains lactose. If you have been told by your healthcare provider that you have an intolerance to some sugars, contact your healthcare provider before taking this medicinal product.

Storage

- Keep away from light and moisture. Store below 30°C.
- Keep out of the reach of children.
- Keep the desiccant in the bottle. Do not eat or throw away desiccant pack.
- Keep in the original container.
- Safely throw away medicine that is out of date or that you no longer need. Ask your pharmacist how to safely throw away Trixibet® ER tablets.

Packaging

Bottle of 30 F. C. Tablets.

Issued: October 2023

License Holder: Noavaran Daroui Kimia Co., Tehran, Iran.

Telefax: +982166437014

www.kimia-pharma.com

References

https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208716s01s011tbl.pdf
https://www.ema.europa.eu/en/documents/product-information/verzenios-epar-product-information_en.pdf
BNF 84 (British National Formulary) September 2022–March 2023