Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Trajenta Duo® **2.5 mg/500 mg** **Film-coated tablets**	**Trajenta Duo®** **2.5 mg/850 mg** **Film-coated tablets**	**Trajenta Duo®** **2.5 mg/1000 mg** **Film-coated tablets**
Each film-coated tablet of **Trajenta Duo 2.5 mg/500 mg** contains: 2.5 mg linagliptin 500 mg metformin hydrochloride	Each film-coated tablet of **Trajenta Duo 2.5 mg/850 mg** contains: 2.5 mg linagliptin 850 mg metformin hydrochloride	Each film-coated tablet of **Trajenta Duo 2.5 mg/1000 mg** contains: 2.5 mg linagliptin 1000 mg metformin hydrochloride

Inactive ingredients and allergens in this medicine: see section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist. This medicine has been prescribed to treat your illness. Do not pass it on to others. It may harm them, even if it seems to you that their illness is similar to yours.

1. What is this medicine intended for?

Trajenta Duo is intended, in addition to diet and physical exercise, to control blood sugar levels in adults with type 2 diabetes for whom combined treatment with two active ingredients, linagliptin and metformin hydrochloride is appropriate.

Limitations of use: Do not use Trajenta Duo to treat type 1 diabetes or diabetic ketoacidosis, because Trajenta Duo is not effective with these conditions.
Trajenta Duo has not been studied in patients who have previously had pancreatitis (inflammation of the pancreas). It is not known whether patients who have previously had pancreatitis are at an increased risk of developing pancreatitis during treatment with Trajenta Duo.

Therapeutic groups:
Linagliptin: DPP-4 (dipeptidyl peptidase-4) inhibitor.
Metformin: biguanides.

2. Before using this medicine

Do not use this medicine if:

- You are sensitive (allergic) to the active ingredients or to any of the other ingredients in this medicine (for a list of inactive ingredients, please see section 6). Symptoms of severe allergy to Trajenta Duo may include skin rash, itching, peeling of the skin, hives (red raised patches on the skin), swelling of the face, lips, tongue, and throat, which may cause difficulty breathing or swallowing. If you experience any of these symptoms, stop taking this medicine and contact your doctor or go to the nearest hospital emergency room as soon as possible.
- You have either type 1 diabetes (your body does not produce insulin), or acute or chronic metabolic ketoacidosis including diabetic ketoacidosis (increased ketone levels in your blood and/or urine). Trajenta Duo is not suitable for treating these conditions.
- You have severely reduced kidney function (your doctor will tell you how badly your kidney function is affected).

Special warnings about using this medicine:

1. Lactic acidosis:

Metformin hydrochloride, one of the ingredients of Trajenta Duo, can cause a rare but serious side effect called lactic acidosis, which manifests in build-up of lactic acid in the blood and may be fatal. Lactic acidosis is a medical emergency requiring treatment in hospital. If you feel symptoms of lactic acidosis, stop taking Trajenta Duo and see your doctor immediately (see more information in section 4: 'Side effects').

Stop taking Trajenta Duo and consult your doctor immediately or go to the emergency room if you develop any of the following symptoms of lactic acidosis: feeling of weakness or tiredness, unusual muscle pain, difficulty breathing, unusual sleepiness or sleeping longer than usual, unexplained stomach or intestinal problems accompanied by nausea and vomiting, or diarrhea, feeling cold, especially in the hands and feet, dizziness, irregular or slow heartbeat.

Most of the people who developed lactic acidosis while taking metformin hydrochloride had other problems which, combined with metformin hydrochloride, led to lactic acidosis. You have a higher chance of developing lactic acidosis if you:

- have severe kidney problems.
- have liver problems.
- drink a lot of alcohol very often or in short period of time (see the section 'Using this medicine and alcohol consumption').
- get dehydrated (lose a large amount of body fluids). This can happen if you do not drink enough fluids or if you have fever, vomiting, or diarrhea. Dehydration can also happen when you sweat a lot with normal activity or with exercise.
- have certain x-ray tests with injectable dyes or contrast agents.
- have surgery or other procedures for which you need to restrict the amount of food and liquid you eat and drink.
- have congestive heart failure.
- have a heart attack, severe infection, or stroke.
- are 65 years of age or older.

Tell your doctor if you have any of the problems listed above. Tell your doctor that you are taking Trajenta Duo before you have surgery or x-ray tests
Your doctor may decide to stop your Trajenta Duo treatment for a while if you have surgery or certain x-ray tests.

2. **Pancreatitis** (see more information in section 4 'Side effects') may occur in patients treated with Trajenta Duo; it may be severe and even life threatening. Certain medical problems may increase the risk of pancreatitis.
   Before you start taking Trajenta Duo, consult your doctor if you currently have or have ever had any of the following conditions:
   - pancreatitis.
   - stones in your gall bladder.
   - a history of alcoholism.
   - high levels of triglycerides in your blood.

   Stop taking Trajenta Duo and consult a doctor immediately if you have severe abdominal pain that will not go away. You may feel pain going from your abdomen through to your back and it may appear with or without vomiting. These may be symptoms of pancreatitis.
   If you have ever had pancreatitis, it is unknown whether your chance of having pancreatitis is higher while you are taking Trajenta Duo.

3. **Heart failure:** Before you start taking Trajenta Duo, tell your doctor if you currently have or have ever had heart failure or problems with your kidneys. Consult your doctor immediately if you experience any of the following symptoms:
   - increasing shortness of breath or trouble breathing, especially when you lie down.
   - swelling or fluid retention, especially in the feet, ankles or legs.
   - an unusually fast increase in weight.
   - unusual tiredness.

   All these may be symptoms of heart failure. Heart failure means that your heart does not pump blood well enough.

Before using Trajenta Duo, tell your doctor if:
- You have, or have ever had pancreatitis.
- You have kidney problems.
- You have impaired liver or heart function (including heart failure) or any other medical problem.
- You are 65 years of age or older.
- You drink alcohol very often, or drink a lot of alcohol in a short period of time (binge drinking).
- You are going to get an injection of dye or contrast agent for an x-ray procedure. You may need to stop taking Trajenta Duo for a short time. Talk to your doctor about when you should stop Trajenta Duo and when you should start taking it again.
- You have type 1 diabetes. Trajenta Duo is not intended for use in patients with type 1 diabetes.
- You have low levels of vitamin B_{12} in your blood.
- You are pregnant or plan to become pregnant, are breastfeeding or planning to breastfeed (see the section 'Pregnancy, breastfeeding, and fertility').
- You are breastfeeding or planning to breastfeed. Trajenta Duo may pass into your breast milk and may cause harm to your baby. Consult your doctor about the best way to feed your baby if you are taking Trajenta Duo.
- You are a premenopausal woman who does not have periods regularly or at all. Trajenta Duo may cause release of an egg from an ovary in a woman (ovulation). This may increase your chance of getting pregnant. Tell your doctor immediately if you become pregnant while taking Trajenta Duo.

Children and adolescents
The safety and efficacy of this medicine have not been tested in children and adolescents under 18 years old.

Tests and follow-up
- During the course of treatment, your blood sugar levels must be tested according to the doctor's instructions.
- Taking metformin hydrochloride (one of the ingredients of Trajenta Duo) may cause a decrease in vitamin B_{12} levels in the blood, therefore your doctor may ask you to perform blood tests to check your vitamin B_{12} levels.

Other medicines and Trajenta Duo
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
- **Insulin or other blood sugar lowering medicines:** especially sulfonylurea or insulin medicines. Combining these medicines with Trajenta Duo increases the risk of a drop in blood sugar level (hypoglycemia). Please see section 2, above, under 'Do not use this medicine if', and section 4 'Side effects'.
- Diuretics.
- Rifampicin (an antibiotic for treating tuberculosis): This combination may reduce the efficacy of Trajenta Duo.
- Ranolazine, vandetanib, dolutegravir, and cimetidine: The combination may increase the levels of metformin (one of the ingredients in Trajenta Duo) in your blood which increases the risk of lactic acidosis. Topiramate (a medicine used to treat epileptic seizures), zonisamide, acetazolamide, or dichlorphenamide: The combination may increase the risk of lactic acidosis (see also section 2 under 'Special warnings about using this medicine').

Using this medicine and food
Take this medicine with a meal. Taking this medicine with food can reduce digestive tract problems.

Using this medicine and alcohol consumption
Do not consume alcohol often or in large amounts in a short time period. Consuming alcohol increases your risk of experiencing side effects.

Pregnancy, breastfeeding, and fertility
If you are pregnant or planning to become pregnant, or if you are breastfeeding, consult your doctor before taking this medicine.
- There is no information about the effect of this medicine on your unborn baby. If you are pregnant, talk to your doctor about the best way to control your sugar levels during pregnancy.
- There is no information about this medicine passing into breastmilk. Consult your doctor about the best way to feed your baby while using this medicine.

3. How to use this medicine?

Always use this medicine according to your doctor's instructions. Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine. Only your doctor will determine your dose and how you should take this medicine.

The recommended dose is usually one tablet twice a day with meals. If your kidney function is impaired, your doctor may prescribe you a lower dose.
Taking this medicine with a meal can help lower the risk of abdominal pain. **Do not exceed the recommended dose**.
Swallow the medicine with water. There is no information about crushing/splitting/chewing the tablets.

If you are taking Trajenta Duo with other medicines for lowering blood sugar, you are at a higher risk of getting low blood sugar levels (hypoglycemia). Your doctor may decide to change your dose of these medicines.

If you have accidentally taken a higher dose: If you have taken an overdose, or if a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine at the scheduled time, take it with food as soon as you remember. If it is time to take the next dose, skip the forgotten dose and go back to your regular schedule. Do not take two doses together. Adhere to the treatment as recommended by your doctor.

Even if your health improves, do not stop taking this medicine without consulting your doctor or pharmacist. **If you stop taking this medicine,** your blood sugar levels may go up.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them. If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>

Like with all medicines, using Trajenta Duo may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them. See further important information in section 2 under 'Special warnings about using this medicine'.

Low blood sugar levels (hypoglycemia):
Signs and symptoms of low blood sugar level may include the following: headache, hunger, fast heart beat, sweating, irritability, drowsiness, weakness, dizziness, confusion, tremor and nervousness. If you take Trajenta Duo with other medicines that can cause low blood sugar levels, such as sulfonylurea or insulin, your risk of getting low blood sugar levels is higher. If you notice any of these signs, check your blood sugar levels, treat them if they are low, and contact your doctor.

Allergic reactions (hypersensitivity):
Severe allergic reactions have occurred in people taking Trajenta Duo. The symptoms may include:

- swelling of the face, lips, throat and other areas on your skin.
- difficulty breathing or swallowing.
- hives (raised red patches on the skin).
- rash, itch, peeling of the skin.

If symptoms of a severe allergic reaction develop, stop taking the treatment and contact your doctor or go to the nearest hospital emergency room right away.

Low vitamin B_{12} (vitamin B_{12} deficiency):
Using metformin for long periods of time may cause a decrease in vitamin B_{12} levels in the blood, especially if you have had low vitamin B_{12} levels before. Your doctor may ask you to perform blood tests to check your vitamin B_{12} levels.

Joint pain:
Some people who take medicines called DPP-4 inhibitors, one of the ingredients in Trajenta Duo, may develop joint pain that can be severe and disabling (arthralgia). Consult your doctor if you have severe joint pain.

Skin reactions:
Some patients who take medicines called DPP-4 inhibitors, one of the ingredients in Trajenta Duo, may develop a skin reaction called bullous pemphigoid which may require treatment in hospital. Consult a doctor immediately if you develop blisters or sores on the upper layer of your skin (erosions). Your doctor may advise you to stop taking Trajenta Duo.

Pancreatitis:
Pancreatitis can appear in patients who are taking Trajenta Duo and it may be severe and even life-threatening (see also section 2 under 'Special warnings about using this medicine').
Stop taking this medicine and consult a doctor immediately if you have severe abdominal pain that will not go away. The pain may radiate to the back and may appear with or without vomiting. These may be symptoms of pancreatitis.

Lactic acidosis:
Stop using this medicine and consult a doctor immediately if you develop any symptoms of **lactic acidosis** (see also section 2 under 'Special warnings about using this medicine'): feeling cold, especially in your hands and feet, dizziness, irregular or slow heart beat, feeling weak or tired, unusual muscle pain, difficulty breathing, feeling unusually sleepy or sleeping longer than usual, unexplained stomach or intestinal problems accompanied by nausea and vomiting, or diarrhea.

Very common side effects (appear in 1-10 in 10 users):
low blood sugar level (hypoglycemia).

Common side effects (appear in 1-10 in 100 users):
stuffy or runny nose, sore throat and diarrhea.
Side effects that were observed when taking one of the ingredients of Trajenta Duo (linagliptin/metformin): cough, constipation, increase in uric acid, increase in enzymes that break down fat (lipase), increase in amylase and reduced levels of vitamin B_{12}.

Uncommon side effects (appear in 1-10 in 1,000 users):
decreased appetite, hypersensitivity, nausea, vomiting, damage to the liver, rash.

Rare side effects (appear in 1-10 in 10,000 users):
blister and/or wound shaped skin reactions (bullous pemphigoid), mouth sores.

Side effects of unknown frequency (the frequency of these effects has not been established yet):
itch, pancreatitis, muscle pain, swelling, weakness, digestion pain, abdominal discomfort, and headache.

Spontaneous post-marketing reports mention side effects that were observed when taking either one of the ingredients of Trajenta Duo (linagliptin/metformin):

- rash
- acute pancreatitis that was even fatal
- hypersensitivity
- severe and disabling joint pain
- mouth sores, inflammation of the mouth
- blister and/or wound shaped skin reactions (bullous pemphigoid)
- damage to the liver
- breakdown of skeletal muscle (rhabdomyolysis)

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il

5. How to store the medicine?

- Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.
- Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:

- Store below 25˚C.

6. Additional information

- In addition to the active ingredients, this medicine also contains the following inactive ingredients:
  arginine, maize starch, copovidone, silica colloidal anhydrous, magnesium stearate, hypromellose, propylene glycol, titanium dioxide, talc.
  Trajenta Duo 2.5 mg/500 mg and Trajenta Duo 2.5 mg/850 mg also contain yellow iron oxide.
  Trajenta Duo 2.5 mg/850 mg and Trajenta Duo 2.5 mg/1000 mg also contain red iron oxide.

- What the medicine looks like and contents of the pack:
  Trajenta Duo 2.5 mg/500 mg is a light yellow, convex, oval tablet imprinted with D2/500 on one side and the Boehringer Ingelheim logo on the other.
  Trajenta Duo 2.5 mg/850 mg is a light orange, convex, oval tablet imprinted with D2/850 on one side and the Boehringer Ingelheim logo on the other.
  Trajenta Duo 2.5 mg/1000 mg is a light pink, convex, oval tablet imprinted with D2/1000 on one side and the Boehringer Ingelheim logo on the other.
  The packages contain blister trays of 7 or 10 tablets. Each package contains 14 or 60 film-coated tablets.
  Not all pack sizes may be marketed.

- **Registration holder's name and address:**

Boehringer Ingelheim Israel Ltd., 89 Medinat Heyehudim St., P.O.B. 4124, Herzeliya Pituach 4676672.

- **Manufacturer's name and address:** Boehringer Ingelheim Pharma, Binger Strasse 173, Ingelheim am Rheine, Germany
  or Boehringer Ingelheim Ellas A. E., Koropi, Greece
  or Dragenopharm Apotheker Püschl GmbH, Tittmoning, Germany

This leaflet was revised in May 2020.

Registration number of the medicine in the Ministry of Health's National Drug Registry:
Trajenta Duo 2.5 mg/500 mg: 150-17-33739
Trajenta Duo 2.5 mg/850 mg: 150-18-33740
Trajenta Duo 2.5 mg/1000 mg: 150-19-33741