

**PATIENT PACKAGE INSERT IN ACCORDANCE WITH THE
PHARMACISTS' REGULATIONS (PREPARATIONS) - 1986**

The medicine is dispensed with a doctor's prescription only

Xigduo® XR 5 mg/500 mg

Extended-release tablets

Composition:

Each tablet contains:

Dapagliflozin 5 mg

Metformin hydrochloride 500 mg

Xigduo® XR 5 mg/1000 mg

Extended-release tablets

Composition:

Each tablet contains:

Dapagliflozin 5 mg

Metformin hydrochloride 1000 mg

Xigduo® XR 10 mg/500 mg

Extended-release tablets

Composition:

Each tablet contains:

Dapagliflozin 10 mg

Metformin hydrochloride 500 mg

Xigduo® XR 10 mg/1000 mg

Extended-release tablets

Composition:

Each tablet contains:

Dapagliflozin 10 mg

Metformin hydrochloride 1000 mg

For inactive ingredients, please see section 6 – “Further Information”.

Read this leaflet carefully in its entirety before using the medicine.

Keep this leaflet, as you may need to read it later.

This leaflet contains concise information about the medicine. If you have further questions, refer to the doctor or pharmacist.

This medicine has been prescribed for the treatment of your ailment. Do not pass it on to others. It may harm them even if it seems to you that their ailment is similar.

- Xigduo XR may cause serious side effects, including lactic acidosis - please see section 2 “Special warnings regarding use of Xigduo XR”.
- Xigduo XR is not intended for type 1 diabetes patients.
- Xigduo XR is not intended for patients with diabetic ketoacidosis (increased ketones in blood or urine).
- Xigduo XR is not intended for children and adolescents under 18 years of age.

1. WHAT IS THE MEDICINE INTENDED FOR?

Xigduo XR is given to treat type 2 diabetes in adults (18 years of age and over), in combination with diet and exercise. Xigduo XR is intended to improve control of blood sugar levels, when treatment with dapagliflozin or metformin alone have not brought to controlled blood sugar levels.

Therapeutic group:

Dapagliflozin – inhibitor of the SGLT2 sugar carrier in the kidney, which inhibits reuptake of glucose and causes increased glucose excretion in the urine.

Metformin hydrochloride – from the biguanide group.

2. BEFORE USING THE MEDICINE

X Do not use Xigduo XR if:

- you are sensitive to the active ingredients dapagliflozin, metformin, or to any of the ingredients of the medicine (see section 6 below, “Further Information”). Signs of a serious allergic reaction to Xigduo XR may include:
 - skin rash,
 - raised red patches on the skin (hives),
 - swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing.

If you notice any of these signs, stop taking Xigduo XR immediately, and refer to a doctor or proceed to the nearest hospital emergency room.

- you have severe kidney problems or are on dialysis.
- you have metabolic acidosis or diabetic ketoacidosis (high levels of ketones in the urine or blood).
- you have uncontrolled diabetes, with, for example severe hyperglycaemia (high blood glucose levels), nausea, vomiting, diarrhoea, rapid weight loss, lactic acidosis or ketoacidosis. Ketoacidosis is a condition in which ketone bodies accumulate in the blood and which can lead to a diabetic pre-coma. Symptoms include stomach pain, fast and deep breathing, sleepiness or your breath developing an unusual fruity smell.

⚠ Special warnings regarding use of Xigduo XR

Lactic acidosis: Metformin, the active ingredient in Xigduo XR, may cause a very rare, but very severe side effect called lactic acidosis. Lactic acidosis is characterized by high levels of lactic acid in the blood, which can cause death. Lactic acidosis requires emergency medical treatment in a hospital.

Stop taking Xigduo XR and refer to the doctor immediately if you have any of the following signs, which could be a sign of lactic acidosis:

- sensation of feeling cold in palms of hands and soles of feet
- dizziness or lightheadedness
- slow or irregular heartbeat
- feeling of extreme weakness and tiredness
- unusual muscle pain
- difficulty breathing
- unusual sleepiness or sleeping longer than usual
- stomach pain, nausea, or vomiting

Most people who have had lactic acidosis with metformin (active ingredient in Xigduo XR) have other things that, combined with the metformin use, led to the lactic acidosis. Tell your doctor if you have any of the following, because you have a higher chance of developing lactic acidosis with Xigduo XR:

- suffer from severe kidney problems or your kidney is affected by a contrast agent injected into you for an X-ray test.
- suffer from liver problems.
- drink alcohol very often or drink a lot of alcohol in a short period of time.
- are dehydrated (losing a large amount of fluids). This can happen if you are sick with a fever, vomiting, or diarrhea. Dehydration can also happen if you sweat a lot when exercising and do not drink enough fluids.
- are undergoing surgery.
- have a heart attack, severe infection, or stroke.

The best way to keep from having a problem with lactic acidosis from metformin is to tell your doctor if you have any of the problems in the list above. Your doctor may decide to stop treatment for a while.

Before or during treatment with Xigduo XR, tell the doctor, pharmacist or nurse if:

- you have type 1 diabetes or have or have had diabetic ketoacidosis.
- you are also taking insulin and there is sudden reductions in your insulin dose.
- you have kidney problems, the doctor will check your kidney function.

- you have liver problems.
- you have a history of urinary tract infections or problems urinating.
- you have heart problems, including heart failure.
- you are eating less or if there is a change in your diet.
- you have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas.
- you drink alcohol very often, or drink a lot of alcohol in a short period of time.
- you are going to get an injection of dye or contrast agent for an X-ray test. In such a case, you may need to stop using Xigduo XR for a short time. Refer to the doctor for instructions as to when you should stop taking Xigduo XR and when you should resume and continue treatment with Xigduo XR again.
- you are going to have surgery and will not be able to eat or drink a lot. Stop taking Xigduo XR for a short time. Refer to the doctor for instructions about when you should stop taking Xigduo XR and when you should resume and continue treatment with Xigduo XR again.
- you often suffer from urinary tract infections. When using this medicine, there is an increased risk of urinary tract infection (the doctor may temporarily stop the treatment with the medicine if a severe urinary tract infection develops).

Tests and follow-up

Kidney function

Kidney function tests should be performed before starting treatment with Xigduo XR and during treatment.

Your doctor may do certain blood tests before you start Xigduo XR and during your treatment. Your doctor will check your diabetes with regular blood tests, including your blood sugar levels and your A1C.

Sugar (glucose) in the urine

Due to the mechanism of action of dapagliflozin, a urine glucose test will be positive for glucose.

Drug interactions

⚠ If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell the doctor or pharmacist. In particular, inform if you are taking medicines:

- diuretics
- to treat or prevent tuberculosis (e.g., rifampin)
- to treat seizures (e.g., phenytoin)
- to treat heart problems (e.g., digoxin)
- to treat asthma (beta-2 agonist bronchodilators)
- to treat digestion problems (e.g., cimetidine)
- corticosteroids to treat inflammations in diseases such as asthma and arthritis
- to lower blood sugar level, such as insulin or sulfonylurea. The doctor may instruct you to lower the dosage of these medicines to prevent too large a reduction in blood sugar (hypoglycemia).

⚠ Use of the medicine and food

The medicine should be taken with a meal to prevent disturbances in the digestive system. See section 3 – “How should you use the medicine?”

⚠ Use of the medicine and alcohol consumption

Do not drink alcohol often and do not drink a lot of alcohol in a short period of time during the course of treatment with Xigduo XR. This may increase the risk of getting serious side effects.

⚠ Pregnancy and breastfeeding:

If you are pregnant, planning to become pregnant, think you are pregnant, consult the doctor before using the medicine. Xigduo XR can cause damage to the fetus. Speak to the doctor about the best way to control your blood sugar level.

If you are breastfeeding, or plan to breastfeed, consult the doctor before using the medicine. It is not known whether Xigduo XR passes into breast milk. Speak to the doctor about the best way to feed your baby when you are taking Xigduo XR.

⚠ Driving and using machinery

This medicine has no or a negligible effect on the ability to drive or use machines. Taking this medicine with other medicines that lower blood sugar level, such as sulfonylureas or insulin, may lead to a blood sugar level that is too low (hypoglycemia), which can lead to signs such as weakness, dizziness, increased sweating, rapid heartbeat, vision changes or difficulty concentrating, and may affect the ability to drive and use machines. Do not drive or operate machinery or equipment if you feel these symptoms.

⚠ Use in children:

This medicine is not intended for children and adolescents under 18 years of age. There is no information regarding the safety and efficacy of use of Xigduo XR in children and adolescents under 18 years of age.

⚠ Xigduo XR contains lactose:

The tablets contain lactose, which is a type of sugar. If you have been told by the doctor that you have intolerance to certain sugars, consult the doctor before taking this medicine (lactose content – see section 6 “Further Information”).

3. HOW SHOULD YOU USE THE MEDICINE?

- Always use according to the doctor’s instructions. Check with the doctor or pharmacist if you are not sure.
- The dosage and treatment regimen will be determined by the doctor only.
- The usual dosage is one tablet per day with a meal, to reduce digestive disturbances. Speak with the doctor about the best time for you during the day to take the medicine.
- Swallow the tablet whole. Do not halve, crush or chew the tablet.
- A soft mass that looks like the Xigduo XR tablet may sometimes be passed in stool.
- When your body is in a state of stress, such as fever, trauma (e.g., a car accident), infection or surgery, the required dosage of the diabetes medicines may change. If you are in one of these states, tell the doctor immediately and follow his instructions.

- **Diet and exercise**

Continue watching your diet and exercising while taking Xigduo XR.

- **If you forgot to take the medicine** – take the medicine as soon as you remember. If this happens close to the time you are supposed to take the next dose, skip the missed dose and take the next dose at the regular time. **Do not take** two Xigduo XR doses at the same time unless the doctor tells you to do so.
- **If you accidentally took too high a dosage of Xigduo XR**, call the doctor or urgently proceed to the nearest hospital emergency room.

Adhere to the treatment as recommended by the doctor.

Even if there is an improvement in your health, do not stop the treatment with the medicine without consulting the doctor. Your blood sugar level can increase without the medicine.

If you have further questions regarding use of the medicine, consult a doctor or pharmacist.

Do not take medicines in the dark! Check the label and dose each time you take a medicine. Wear glasses if you need them.

4. SIDE EFFECTS

As with any medicine, use of Xigduo XR may cause side effects in some users. If the side effects do not pass, or if they are bothersome or worsen, consult the doctor. Do not be alarmed by the list of side effects. You may not suffer from any of them.

Side effects that require special attention: refer to the doctor immediately if the following effects appear:

- Metformin, the active ingredient in Xigduo XR, may cause a rare (may affect 1 in 10,000 patients) but serious side effect called lactic acidosis. See above section **Special warnings regarding use of Xigduo XR – lactic acidosis**. If this effect happens you must stop taking the medicine and contact a doctor or the nearest hospital immediately, as lactic acidosis may lead to coma.

Additional side effects:

- Dehydration - extensive loss of fluids and salts from the body. Dehydration may cause you to feel dizzy, faint, lightheaded or weak, especially when you stand up (orthostatic hypotension).
- You may be at a higher risk of dehydration if you:
 - have low blood pressure
 - take medicines to lower blood pressure, including diuretics
 - are 65 years of age or older
 - are on a low salt diet
 - have kidney problems
- Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis.

- **Ketoacidosis (increased ketone level in the blood or urine)**

Ketoacidosis has occurred in patients, during treatment with dapagliflozin, which is one of the active ingredients in Xigduo XR. Ketoacidosis has happened in people with diabetes who were sick or who had surgery during treatment with XIGDUO XR. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death.

Ketoacidosis can also occur even if blood sugar levels are less than 250 mg/dL.

Stop taking Xigduo XR and refer to the doctor immediately if you have any of the following signs:

- nausea
- tiredness
- vomiting
- difficulty breathing
- pains in the abdominal area

If you have any of these signs while taking Xigduo XR, if possible, check the ketone levels in your urine, even if your sugar levels are below 250 mg/dL.

- **Kidney problems.**

Sudden kidney injury has happened to people taking Xigduo XR. Contact the doctor right away if you:

- reduce the amount of food or liquid you drink, if you are sick and cannot eat or
- you start to lose liquids from your body, for example, from vomiting, diarrhea, or being in the sun too long.

- **Serious urinary tract infection:**

Serious urinary tract infections that may lead to hospitalization has occurred in people who are taking dapagliflozin, one of the active ingredients of Xigduo XR. Tell the doctor if you have signs or symptoms of a urinary tract infection such as: a burning feeling when passing urine, frequent urination, a need to urinate right away, pains in the lower part of the stomach, or blood in the urine. Sometimes fever, back pains, nausea and vomiting also occur.

- **Infections of the genitals area (Fournier's gangrene/necrotising fasciitis of the perineum)**, a serious soft tissue infection of the genitals or the area between the genitals and the anus, seen very rarely.

- Seek medical attention immediately if you develop any of the following symptoms: redness, tenderness or swelling in the area between and around the anus and genitals and have fever above 38°C or general unwell feeling.
- These symptoms may worsen rapidly, its important to seek medical attention immediately.

- **Low blood sugar level (hypoglycemia)**

If you take Xigduo XR with other medicines that can cause a reduction in blood sugar level, such as sulfonylureas or insulin, you have a higher risk of low blood sugar level. The dosage of sulfonylurea or insulin may need to be lowered while using Xigduo XR. Signs and symptoms of low blood sugar level can include:

- headache,
- weakness,
- confusion,
- shaking or,
- irritability,
- dizziness,
- drowsiness,

- restlessness,
 - sweating,
 - hunger,
 - fast heartbeat.
- Reduction/deficiency in vitamin B12:
Using metformin for long periods of time may cause a decrease in the level of vitamin B12 in your blood, especially if you have had a vitamin B12 deficiency before. The doctor may perform blood tests to check vitamin B12 level.
 - Vaginal yeast infection
Signs of a vaginal yeast infection include:
 - vaginal odor,
 - white or yellowish discharge (may be with lumps),
 - vaginal itching
 - Yeast infection of the skin of the penis (balanitis). Men who are not circumcised can develop swelling of the penis. Other signs of infection include:
 - redness, itching, or swelling of the penis
 - rash on the penis
 - foul-smelling discharge
 - pain in the skin around the penis
- Please refer to the doctor if you noticed signs of a vaginal or penis yeast infection. The doctor may suggest treatment with an antifungal medicine. Contact the attending doctor again if you are taking this medicine and your condition does not improve.

The most common side effects when taking Xigduo XR:

- yeast infection of the vagina or penis
- stuffy or runny nose and sore throat
- diarrhea
- urinary tract infection
- headache

If a side effect occurs, if any of the side effects worsen, or if you suffer from a side effect not mentioned in the leaflet, consult the doctor.

Reporting side effects

Side effects can be reported to the Ministry of Health by clicking on the link "Report Side Effects of Drug Treatment" found on the Ministry of Health homepage www.health.gov.il that directs you to the online form for reporting side effects, or by entering the link:

<https://sideeffects.health.gov.il/>

5. HOW SHOULD THE MEDICINE BE STORED?

- Avoid poisoning! This medicine, and any other medicine, should be kept in a safe place out of the reach and sight of children and/or infants to avoid poisoning. Do not induce vomiting without an explicit instruction from the doctor.
- Do not use the medicine after the expiry date (exp. date) that appears on the package. The expiry date refers to the last day of that month.
- Store at room temperature, below 30°C.

6. FURTHER INFORMATION

- In addition to the active ingredient, the medicine also contains:
 - In the tablet -
microcrystalline cellulose PH302, lactose anhydrous, crospovidone, silicon dioxide, magnesium stearate, carboxymethylcellulose sodium, and hypromellose 2208

Xigduo XR 5 mg/500 mg and Xigduo XR 10 mg/500 mg also contain hypromellose 2910 and microcrystalline cellulose PH102
 - In the tablet coating -
polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc

Xigduo XR 5 mg/500 mg also contains FD&C Yellow No. 6/Sunset Yellow FCF Aluminum Lake

Xigduo XR 5 mg/1000 mg, Xigduo XR 10 mg/500 mg, Xigduo XR 10 mg/1000 mg also contain iron oxides
 - Lactose content
Xigduo XR 5 mg/500 mg – each tablet contains 48 mg lactose
Xigduo XR 5 mg/1000 mg – each tablet contains 48 mg lactose

Xigduo XR 10 mg/500 mg – each tablet contains 48 mg lactose

Xigduo XR 10 mg/1000 mg – each tablet contains 48 mg lactose

- **What does the medicine look like?**

Xigduo XR 5 mg/500 mg – an orange, biconvex, capsule-shaped tablet, with “1070” and “5/500” debossed on one side and the other side is plain.

Xigduo XR 5 mg/1000 mg – a pink to dark pink, biconvex, oval-shaped tablet, with “1071” and “5/1000” debossed on one side and the other side is plain.

Xigduo XR 10 mg/500 mg – a pink, biconvex, capsule-shaped tablet, with “1072” and “10/500” debossed on one side and the other side is plain.

Xigduo XR 10 mg/1000 mg – a yellow to dark yellow, biconvex, oval-shaped tablet, with “1073” and “10/1000” debossed on one side and the other side is plain.

License Holder: AstraZeneca (Israel) Ltd., P.O.B. 1455 Hod Hasharon 4524075

Manufacturer: AstraZeneca Pharmaceuticals LP, 4601 Highway 62 East, Mount Vernon, Indiana, USA.

Registration number of the medicine in the National Drug Registry of the Ministry of Health:

Xigduo XR 5 mg/500 mg - 1556634419

Xigduo XR 5 mg/1000 mg - 1556734424

Xigduo XR 10 mg/500 mg - 1556834425

Xigduo XR 10 mg/1000 mg - 1556934428

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