

**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 and allergenic ingredients, please see section 2 - "Important information regarding some of the medicine ingredients" and section 6 - "Further Information".

Read this leaflet carefully in its entirety before using the medicine. 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 both dapagliflozin and metformin is appropriate.

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

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:
 - 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, diarrhea, 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 symptoms, which could be a sign of lactic acidosis:

- sensation of feeling cold in the hands or 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 new or worsening symptoms of congestive heart failure such as shortness of breath or increased fluid or swelling of the legs.
- have a heart attack, severe infection or stroke.
- are 65 years of age or older.

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.

- **Diabetic Ketoacidosis (increased ketones in your blood or urine) in people with type 1 diabetes and other ketoacidosis.** Xigduo XR can cause ketoacidosis that can be life-threatening and may lead to death. Ketoacidosis is a serious condition which needs to be treated in a hospital. People with type 1 diabetes have a high risk of getting ketoacidosis. People with type 2 diabetes or pancreas problems also have an increased risk of getting ketoacidosis. Ketoacidosis can also happen in people who are sick, cannot eat or drink as usual, skip meals, are on a diet high in fat and low in carbohydrates (ketogenic diet), take less than the usual amount of insulin or miss insulin doses, drink too much alcohol, have a loss of too much fluid from the body (volume depletion), or who have surgery. Ketoacidosis can happen even if your blood sugar is less than 250 mg/dL. Your healthcare provider may ask you to periodically check ketones in your urine or blood.

Stop taking Xigduo XR and call your doctor or get medical help right away if you get any of the following. If possible, check for ketones in your urine or blood, even if your blood sugar is less than 250 mg/dL.

- nausea
 - vomiting
 - stomach area (abdominal) pain
 - tiredness
 - trouble breathing
 - ketones in your urine or blood
-
- **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 have a decrease in your insulin dose.
 - You have a serious infection.
 - you have a history of infection of the vagina or penis.
 - you have kidney problems.
 - you have liver problems.
 - you have a history of urinary tract infections or problems urinating.
 - You are on a low sodium (salt) diet. Your doctor may ask you to change your diet.
 - you have heart problems, including congestive heart failure.
 - You are 65 years of age or older.
 - You are going to have surgery. Your doctor may stop Xigduo XR before you have surgery. Talk to your doctor if you are having surgery about when to stop taking Xigduo XR and when to start it again.
 - you are eating less or if there is a change in your diet.
 - You are dehydrated.
 - 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.

- have low levels of vitamin B12 in your blood.
- you are a person who has not gone through menopause (premenopausal) who does not have periods regularly or at all. Xigduo XR can cause the release of an egg from an ovary in a person (ovulation). This can increase your chance of getting pregnant. Tell your doctor right away if you become pregnant while taking Xigduo XR.
- 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).

Children and adolescents

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.

Tests and follow-up

Your doctor may do certain blood tests before you start Xigduo XR and during your treatment as needed. Your doctor may change your dose of Xigduo XR based on the results of your blood tests. Your doctor may check your diabetes with regular blood tests, including your blood sugar levels and your A1C.

Kidney function

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

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.

Xigduo XR may affect the way other medicines work and other medicines may affect the way Xigduo XR works.

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. You should not breastfeed if you take 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 start feeling these symptoms.

Important information regarding some of the medicine ingredients

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 about dosage or manner of treatment.
- The dosage and treatment regimen will be determined by the doctor only.
- The usual dosage is generally: 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.
- **Do not exceed the recommended dose.**
- 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.
- Your doctor may tell you to take Xigduo XR along with other diabetes medicines. Low blood sugar can happen more often when Xigduo XR is taken with certain other diabetes medicines. See Chapter 4: "Side Effects".

- **Diet and exercise**
Continue watching your diet and exercising while taking Xigduo XR.

If you forgot to take the medicine

If you forgot to take the medicine at the scheduled time, 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. Talk with your doctor if you have questions about a missed dose.

If you have accidentally taken a higher dose

If you have accidentally taken a higher dose of Xigduo XR or if a child has accidentally swallowed the medicine, refer immediately to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

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. If you stop taking the medicine, your blood sugar level can increase.

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

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

4. SIDE EFFECTS

As with any medicine, use of Xigduo XR may cause side effects in some users. 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 users) 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). There have been reports of sudden kidney injury in people with type 2 diabetes mellitus who are taking dapagliflozin, a medicine in Xigduo XR.

You may be at a higher risk of dehydration if you:

- o take medicines to lower blood pressure, including diuretics
- o are on a low salt diet
- o have kidney problems
- o are 65 years of age or older

Talk to your doctor about what you can do to prevent dehydration including how much fluid you should drink on a daily basis. Call your doctor right away if you reduce the amount of food or liquid you drink, for example, if you 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 patients who are taking dapagliflozin, one of the medicines in 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, pain in the lower part of the stomach (pelvis), or blood in the urine. Sometimes fever, back pain, nausea or vomiting also occur.

- **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:

- o headache,
- o drowsiness,
- o weakness,
- o confusion,
- o dizziness, sweating,
- o hunger,
- o fast heartbeat.
- o irritability,

- o shaking or feeling jittery,

- **Infections of the genitals area (Fournier's gangrene/necrotising fasciitis of the perineum)**

a rare but serious bacterial infection that causes damage to the soft tissue under the skin in the area between and around the genitals or the area between the genitals and the anus, seen in women and men who take dapagliflozin, one of the medicines in Xigduo XR.

This infection may lead to hospitalization, may require multiple surgeries and may lead to death.

- o Seek medical attention immediately if you have a fever or you are feeling very weak, tired or general unwell feeling and if you develop any of the following symptoms: pain, tenderness, swelling or redness in the genital area and the anus.

- **Serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking Xigduo XR and refer immediately to a doctor or to the nearest hospital emergency room. See in chapter 2: when **Xigduo XR should not be used**. Your doctor may prescribe you a medicine for your allergic reaction and prescribe a different medicine for your diabetes.

- **Low level of vitamin B12 (vitamin B12 deficiency):**

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**

Women who take Xigduo XR may get vaginal yeast infections. Signs of a vaginal yeast infection include:

- o vaginal odor,
- o white or yellowish vaginal discharge (may be with lumps or look like cottage cheese),
- o vaginal itching

- **Yeast infection of the skin of the penis (balanitis).**

Swelling of an uncircumcised penis may develop and makes it difficult to pull back the skin around the tip of the penis. Other symptoms of a yeast infection of the penis include:

- redness, itching, or swelling of the penis
- foul-smelling discharge
- rash of the penis
- 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.

Very common side effects - side effects occurring in more than 1 of 10 users

- yeast infection of the vagina
- 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. In any case of doubt, consult the pharmacist who dispensed the medicine to you.
- Store below 30°C.

6. FURTHER INFORMATION

- In addition to the active ingredients, 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 and the content of the pack?**

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.

The package contains 7, 14, 28, 30 or 56 tablets in blisters.

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.

The package contains 7, 14, 28, 30 or 56 tablets in blisters.

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.

The package contains 7, 14, 28, 30 or 56 tablets in blisters.

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.

The package contains 7, 14, 28, 30 or 56 tablets in blisters.

Not all pack sizes may be marketed.

License Holder: AstraZeneca (Israel) Ltd., 1 Atirei Yeda St., Kfar Saba 4464301

Manufacturer: AstraZeneca Pharmaceuticals LP, 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 - 155-66-34419-01

Xigduo XR 5 mg/1000 mg - 155-67-34424-01

Xigduo XR 10 mg/500 mg - 155-68-34425-01

Xigduo XR 10 mg/1000 mg - 155-69-34428-01

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