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

The medicine is dispensed with a doctor's prescription only

Xtandi 40 mg
Xtandi 80 mg
Film coated tablets

Composition:
Each Xtandi 40 mg film coated tablet contains: enzalutamide 40 mg.
Each Xtandi 80 mg film coated tablet contains: enzalutamide 80 mg.

Inactive ingredients and allergens - see 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, consult your 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.
The medicine is intended for adult men only.
The medicine is not intended for use by women.

1. WHAT IS THE MEDICINE INTENDED FOR?

The medicine is intended to treat men with prostate cancer:
- That no longer responds to a hormone therapy or surgical treatment to lower testosterone

Or
- That has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone

Or
- Who had prior prostate removal or radiation and have rapidly rising PSA, but cancer has not spread to other parts of the body and responds to a hormone therapy to lower testosterone

Therapeutic group: hormone antagonists and related agents, anti-androgens.

2. BEFORE USING THE MEDICINE

Do not use the medicine if:
- you are sensitive (allergic) to the active ingredient or to any of the other ingredients included in the medicine (see section 6 'Further information').
- you are pregnant or may become pregnant (see 'Pregnancy, breastfeeding and fertility').

Special warnings regarding use of the medicine:
Seizures
Seizures were reported in 6 in every 1,000 people taking Xtandi, and in fewer than 3 in every 1,000 people receiving placebo (see 'Drug interactions' below and section 4 'Side effects').
If you are taking medicines that may cause seizures or that can increase the susceptibility for having seizures (see 'Drug interactions' below).

If you have a seizure during treatment:
See your doctor as soon as possible. Your doctor may decide that you should stop taking Xtandi.

Posterior reversible encephalopathy syndrome (PRES)
There have been rare reports of PRES, a rare, reversible condition involving the brain, in patients treated with Xtandi. If you have a seizure, worsening headache, confusion, blindness or other vision problems, please contact your doctor as soon as possible (see also section 4 'Side effects').

Risk of new cancers (second primary malignancies)
There have been reports of new (second) cancers including cancer of the bladder and colon in patients treated with Xtandi.
See your doctor as soon as possible if you notice signs of gastrointestinal bleeding, blood in the urine, or frequently feel an urgent need to urinate when taking Xtandi.

Difficulty swallowing related to product formulation
There have been reports of patients experiencing difficulty swallowing this medicine, including reports of choking. The swallowing difficulties or choking events were more commonly observed in patients receiving capsules, which could be related to a larger product size. Swallow the tablets whole with a sufficient amount of water.

Talk to your doctor before taking Xtandi if:
- you have ever developed a severe skin rash or skin peeling, blistering and/or mouth sores after taking Xtandi or other medicines.
- you are taking medicines to prevent blood clots (e.g., warfarin, acenocoumarol, clopidogrel).
- you use chemotherapy like docetaxel.
- you have problems with your liver.
- you have problems with your kidneys.
- you have one of the following: Any heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or are being treated with medicines for these conditions. The risk of heart rhythm problems may be increased when using Xtandi.

If you are allergic to enzalutamide, this may result in a rash or swelling of the face, tongue, lip or throat. If you are allergic to enzalutamide or any of the other ingredients of this medicine, do not take Xtandi.

Serious skin rash or skin peeling, blistering and/or mouth sores, including Stevens-Johnson syndrome, have been reported in association with Xtandi treatment. Stop using Xtandi and seek medical attention immediately if you notice any of the symptoms related to these serious skin reactions described in section 4 'Side effects'.

If any of the above applies to you or you are not sure, talk to your doctor before taking this medicine.

Children and adolescents:
The drug is not intended for children and adolescents under 18 years of age.
There is no data on the safety and efficacy of this medicine in children and adolescents under 18 years of age.

Drug interactions:
If you are taking, or have recently taken, other medicines, including non-prescription medicines and nutritional supplements, tell your doctor or pharmacist. You need to know the names of the medicines you take. Keep a list of them with you to show to your doctor when you are prescribed a new medicine. You should not start or stop taking any medicine before you talk with the doctor that prescribed Xtandi.

In particular, inform the doctor or pharmacist if you are taking the following medicines:
When taken at the same time as Xtandi, these medicines may increase the risk of a seizure:

- Certain medicines used to treat asthma and other respiratory diseases (e.g. aminophylline, theophylline).
- Medicines used to treat certain psychiatric disorders such as depression and schizophrenia (e.g. clozapine, olanzapine, risperidone, ziprasidone, bupropion, lithium, chlorpromazine, mesoridazine, thioridazine, amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine).
- Certain medicines for the treatment of pain (e.g. pethidine).

These medicines may influence the effect of Xtandi, or Xtandi may influence the effect of these medicines. This includes certain medicines used to:

- Lower cholesterol (e.g. gemfibrozil, atorvastatin, simvastatin).
- Treat pain (e.g. fentanyl, tramadol).
- Treat cancer (e.g. cabazitaxel).
- Treat epilepsy (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid).
- Treat certain psychiatric disorders such as severe anxiety or schizophrenia (e.g. diazepam, midazolam, haloperidol).
- Treat sleep disorders (e.g. zolpidem).
- Treat heart conditions or to lower blood pressure (e.g. bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil).
- Treat serious diseases related to inflammations (e.g. dexamethasone, prednisolone).
- Treat HIV infection (e.g. indinavir, ritonavir).
- Treat bacterial infections (e.g. clarithromycin, doxycycline).
- Treat thyroid disorders (e.g. levothyroxine).
- Treat gout (e.g. colchicine).
- Treat stomach disorders (e.g. omeprazole).
- Prevent heart conditions or strokes (e.g. dabigatran etexilate).
- Prevent organ rejection (e.g. tacrolimus).

Xtandi might interfere with some medicines used to treat heart rhythm problems (e.g. quinidine, procainamide, amiodarone and sotalol) or might increase the risk of heart rhythm problems when used with some other medicines [e.g. methadone (used for pain relief and part of drug addiction detoxification), moxifloxacin (an antibiotic), antipsychotics (used for serious mental illnesses)].

Tell your doctor if you are taking any of the medicines listed above. The dose of Xtandi or any other medicines that you are taking may need to be changed.

Use of the medicine and food:
The medicine can be taken with or without food.

Pregnancy, breastfeeding and fertility:

- **Xtandi is not for use in women**. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. It must not be taken by women who are pregnant, may become pregnant, or who are breast-feeding.
- This medicine could possibly have an effect on male fertility.

- If you are having sex with a woman who can become pregnant, use a condom and another effective birth control method, during treatment and for 3 months after treatment with this medicine. If you are having sex with a pregnant woman, use a condom to protect the unborn child.
- Female caregivers see section 3 ‘How should you use the medicine?' for handling and use.

Driving and using machines:
Xtandi may have moderate influence on the ability to drive and use machines. Seizures have been reported in patients taking Xtandi. If you are at higher risk of seizures, talk to your doctor.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use 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.
The dosage and treatment regimen will be determined by your doctor only. The usual dose is 160 mg (four 40 mg film coated tablets or two 80 mg film coated tablets), taken at the same time once a day.

Do not exceed the recommended dose.

Directions for use:
- Swallow the tablets whole with a sufficient amount of water.
- Do not cut, crush or chew the tablets before swallowing.
- Xtandi can be taken with or without food.
- Xtandi should not be handled by persons other than the patient or his caregivers. Women who are or may become pregnant should not handle broken or damaged Xtandi tablets without wearing protection like gloves.

Your doctor may also prescribe other medicines while you are taking Xtandi.

If you accidentally take a higher dose than you should
If you take more tablets than prescribed, stop taking Xtandi and contact your doctor. You may have an increased risk of seizure or other side effects.

If a child accidentally swallowed the medicine, immediately refer to a doctor or proceed to a hospital emergency room and bring the package of the medicine with you.

If you forgot to take this medicine at the scheduled time
- If you forget to take Xtandi at the usual time, take your usual dose as soon as you remember.
- If you forget to take Xtandi for the whole day, take your usual dose the following day.
- If you forget to take Xtandi for more than one day, talk to your doctor immediately.
- **Do not take a double dose** to make up for the dose you forgot.

Adhere to the treatment as recommended by your doctor.

Even if there is an improvement in your health, do not stop treatment with the medicine without consulting your doctor.

If you stop taking the medicine
Do not stop taking this medicine unless your doctor tells you to.

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

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

4. SIDE EFFECTS

As with any medicine, use of Xtandi 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.

Seizures
Seizures were reported in 6 in every 1,000 people taking Xtandi, and in fewer than 3 in every 1,000 people taking placebo.

Seizures are more likely if you take more than the recommended dose of this medicine, if you take certain other medicines, or if you are at higher than usual risk of seizure.

If you have a seizure, see your doctor as soon as possible. Your doctor may decide that you should stop taking Xtandi.

Posterior Reversible Encephalopathy Syndrome (PRES)
There have been rare reports of PRES (may affect up to 1 in 1,000 people), a rare, reversible condition involving the brain, in patients treated with Xtandi. If you have a seizure, worsening headache, confusion, blindness or other vision problems, please contact your doctor as soon as possible.

Other possible side effects include:
- **Very common** side effects (may affect more than 1 in 10 people):
  - tiredness
  - fall
  - broken bones
  - hot flushes
  - high blood pressure
- **Common** side effects (may affect 1-10 in 100 people):
  - headaches
  - feeling anxious
  - dry skin
  - itching
  - difficulty remembering
  - blockage of the arteries in the heart (ischemic heart disease)
  - breast enlargement in men (gynecomastia)
  - nipple pain
  - breast tenderness
  - symptoms of restless legs syndrome (an uncontrollable urge to move a part of the body, usually the leg)
  - reduced concentration
  - forgetfulness
  - change in sense of taste
  - difficulty thinking clearly
- **Uncommon** side effects (may affect 1-10 in 1000 people):
  - hallucinations
  - low white blood cell count
  - increased liver enzyme levels in blood test (a sign of liver problems)
- **Not known** side effects (frequency cannot be estimated from the available data):
  - muscle pains, muscle spasms, muscular weakness, back pain
  - changes in ECG (QT prolongation)

- difficulty swallowing this medicine including choking
- upset stomach including feeling sick (nausea)
- a skin reaction that causes red spots or patches on the skin that may look like a target or “bulls-eye” with a dark red centre surrounded by paler red rings (erythema multiforme), or another serious skin reaction presenting reddish non-elevated, target-like or circular patches on the trunk, often with central blisters, skin peeling, ulcers of mouth, throat, nose, genitals and eyes that can be preceded by fever and flu-like symptoms (Stevens-Johnson syndrome)
- rash
- being sick (vomiting)
- swelling of the face, lips, tongue and/or throat
- reduction in blood platelets (which increases risk of bleeding or bruising)
- diarrhoea
- decreased appetite

If you get any side effects, if any of the side effects worsen, or if you are suffering from a side effect not mentioned in the leaflet, consult your doctor.

Reporting of side effects
Side effects may be reported to the Ministry of Health by clicking on the link “report side effects due to medicinal treatment” found on the Ministry of Health website homepage (www.health.gov.il), which will direct you to the online form for reporting side effects, or by clicking on the following 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 in order to avoid poisoning.
Do not induce vomiting without an explicit instruction from your doctor.

Do not use this medicine after the expiry date which is stated on package.
The expiry date refers to the last day of that month.

No special storage conditions. It is recommended to store the medicine in room temperature.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. FURTHER INFORMATION

In addition to the active ingredient, the medicine also contains:
• Tablet core: Hypromellose acetate succinate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica, magnesium stearate.
• OPADRY Yellow 03F42210 (Tablet coating): Hypromellose, talc, macrogol 8000, titanium dioxide (E171), yellow iron oxide (E172).

What the medicine looks like and the contents of the package:
Xtandi 40 mg film coated tablets are yellow round film coated tablets, debossed with E 40.

Each carton contains 112 tablets in 4 blister wallets of 28 tablets each.

Xtandi 80 mg film coated tablets are yellow oval film coated tablets, debossed with E 80.

Each carton contains 56 tablets in 4 blister wallets of 14 tablets each.

License holder and address:
Astellas Pharma International B.V., 21 Ha'melacha Street, Rosh Ha'ayin, 4809157, Israel.

Manufacturer and address:
Astellas Pharma Europe B.V.
Sylviusweg 62, 2333 BE Leiden, The Netherlands

Registration number of the medicine in the National Drug Registry of the Ministry of Health:
Xtandi 40 mg, film coated tablets: 169-82-36204

Xtandi 80 mg, film coated tablets: 169-83-36205

Approved in 06.2022
Revised in 03.2025 according to MOH guidelines.