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

The medicine is dispensed with a doctor's prescription only

Xtandi 40 mg.
Soft capsules.

Composition:
Each Xtandi 40 mg soft capsule contains: enzalutamide 40 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

- Has spread to other parts of the body and responds to a hormone therapy or surgical treatment 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, breast-feeding and fertility').

Special warnings regarding use of the medicine

- Seizures:

Seizures were reported in 5 in every 1,000 patients taking Xtandi, and in fewer than 3 in every 1,000 patients 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 chance of having seizures (the list of medicines is provided below, see section 'Drug Interactions').

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

- Posterior reversible encephalopathy syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome is a rare and reversible condition involving the brain. There have been rare reports of this syndrome in patients treated with Xtandi. If you have a seizure, worsening headache, confusion, blindness or other vision problems, 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.

- Talk to your doctor before taking Xtandi
  - If you are taking medicines to prevent blood clots (e.g., warfarin, acenocoumarol, clopidogrel).
  - If you use chemotherapy like docetaxel.
  - If you have liver function problems.
  - If you have kidney function problems.
  - If you have one of the following conditions: heart or blood vessel conditions, including heart rhythm problems (arrhythmia), or if you 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 have been reported in association with Xtandi treatment. Seek medical attention immediately if you notice any of these symptoms.

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.

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:

- Medicines that increase the risk for seizures, such as:
  - Certain medicines used to treat asthma or respiratory tract 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)
- Medicines which may influence the efficacy of Xtandi, or which Xtandi may influence their efficacy, such as:
  - Medicines to lower cholesterol (e.g., gemfibrozil, atorvastatin, simvastatin)
  - Medicines to treat pain (e.g., fentanyl, tramadol)
  - Medicines to treat cancer (e.g., cabazitaxel)
  - Medicines to treat epilepsy (e.g., carbamazepine, clonazepam, phenytoin, primidone, valproic acid)

- Medicines to treat certain psychiatric disorders such as severe anxiety or schizophrenia (e.g., diazepam, midazolam, haloperidol)
- Medicines to treat sleep disorders (e.g., zolpidem)
- Medicines to treat heart problems or to lower blood pressure (e.g., bisoprolol, digoxin, diltiazem, felodipine, nicardipine, nifedipine, propranolol, verapamil)
- Medicines to treat serious diseases related to inflammations (e.g., dexamethasone, prednisolone)
- Medicines to treat HIV (e.g., indinavir, ritonavir)
- Medicines to treat bacterial infections (e.g., clarithromycin, doxycycline)
- Medicines to treat thyroid disorders (e.g., levothyroxine)
- Medicines to treat gout (e.g., colchicine)
- Medicines to treat stomach disorders (e.g., omeprazole)
- Medicines to prevent heart conditions or strokes (e.g., dabigatran etexilate)
- Medicines to 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 additional 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, breast-feeding and fertility:
- **Xtandi is not intended for use in women.** The medicine may cause harm to the unborn child or potential loss of pregnancy if it is taken by women who are pregnant. The medicine must not be taken by women who are pregnant, women who are planning to become pregnant, or women who are breast-feeding.
- The 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 with the medicine and for three months after completing treatment with the 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.

Important information about some of the ingredients of the medicine: The medicine contains 57.8 mg sorbitol (a type of sugar) per soft capsule.

3. HOW SHOULD YOU USE THE MEDICINE?

Always use according to your doctor's instructions.
Check with your doctor or pharmacist if you are uncertain.
The dosage and treatment regimen will be determined by your doctor only. The usual dosage is generally 160 mg (four soft capsules), taken at the same time once a day.

Do not exceed the recommended dose.

Directions for use:
- Swallow the soft capsule whole with water.
- Do not chew, dissolve or open the soft capsule 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 damaged or opened Xtandi capsules without wearing protection like gloves.

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

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 take more soft capsules than prescribed, stop taking Xtandi and contact your doctor. You may be at increased risk of seizures or of other side effects.
If you forgot to take this medicine at the scheduled time, take a dose as soon as you remember.
If you forgot to take Xtandi over an entire day, take the next dose at the regular time.
If you forgot to take Xtandi for more than one day, inform your doctor immediately.
Do not take two doses together to make up for a forgotten dose!

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 the medicine without an instruction from your doctor.

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 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: were reported in 5 in every 1,000 patients taking Xtandi, and in fewer than 3 in every 1,000 patients receiving placebo. The risk of seizures is higher if you take a dosage higher than the recommended dosage, if you take certain other medicines or if you have risk factors for seizures.
If you have seizures: refer to your doctor as soon as possible. Your doctor may decide that you should stop taking Xtandi.

Posterior Reversible Encephalopathy Syndrome (PRES):
Posterior Reversible Encephalopathy Syndrome is a rare and reversible condition involving the brain. There have been rare reports of the syndrome in patients treated with Xtandi. If you have a seizure, worsening headache, confusion, blindness or other vision problems, contact your doctor as soon as possible.

Additional side effects:
- Very common side effects (may affect more than 1 in 10 patients):
  - hot flushes.
  - tiredness.
  - high blood pressure.
  - fall.
  - broken bones.
- Common side effects (may affect 1-10 in 100 patients):
  - headaches.
  - feeling anxious.
  - dry skin.
  - itching.

- difficulty remembering.
- blockage of the arteries in the heart (ischemic heart disease).
- breast enlargement in men (gynecomastia).
- 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.

- Uncommon side effects (may affect 1-10 in 1000 patients):
  - hallucinations.
  - difficulty thinking clearly.
  - low white blood cell count.
- Not known side effects (frequency cannot be estimated from the available data):
  - muscle pain, muscle spasms, muscular weakness, back pains.
  - changes in ECG (QT prolongation).
  - 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).
  - 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.

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

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.

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 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 a temperature not exceeding 25°C, in the original package.

Do not take any soft capsule that is leaking, damaged, or shows signs of tampering.

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:
caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320), and butylhydroxytoluene (E321)
The ingredients of the soft capsule shell are:
gelatin, sorbitol sorbitan solution, glycerol, titanium dioxide (E171), and purified water.
Each soft capsule contains 57.8 mg of sorbitol.

The ingredients of the ink are:
iron oxide black (E172), polyvinyl acetate phthalate

What the medicine looks like and the contents of the package:
Xtandi 40 mg soft capsules are white to off-white, oblong soft capsules, with “ENZ” written on one side.
The carton contains 112 soft capsules in 4 blister wallets of 28 soft capsules 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., Hogemaat 2, 7942 JG Meppel, the Netherlands

Approved in 11.2015

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Registration number of the medicine in the National Drug Registry of the Ministry of Health:
154-81-34201