Abbreviated prescribing information of Xtandi

Abbreviated prescribing information of Xtandi® soft capsules

Version: 007

Composition:

Enzalutamide

Indications:

- as monotherapy or in combination with androgen deprivation therapy for the treatment of adult men with high-risk biochemical recurrent (BCR) non-metastatic hormone-sensitive prostate cancer (nmHSPC) who are unsuitable for salvage-radiotherapy.
- in combination with androgen deprivation therapy for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC).
- for the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC).
- for the treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.
- for the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

Dosage:

160 mg (four 40 mg cap) as a single oral daily dose.

Administration:

Swallow whole with a sufficient amount of water, can be taken with or without food.

Contraindications:

Hypersensitivity to the active substance or to any of the excipients.

Women who are or may become pregnant.

Special warnings and precautions for use:

Risk of seizure

Use of enzalutamide has been associated with seizure (see section Undesirable effects). The decision to continue treatment in patients who develop seizure should be taken case by case.

Posterior reversible encephalopathy syndrome

There have been rare reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving Xtandi. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of Xtandi in patients who develop PRES is recommended.

Second Primary Malignancies

Cases of second primary malignancies have been reported in patients treated with enzalutamide in clinical studies. In phase 3 clinical studies, the most frequently reported events in enzalutamide treated patients, and greater than placebo, were bladder cancer (0.3%), adenocarcinoma of the colon (0.2%), transitional cell carcinoma (0.2%) and malignant melanoma (0.2%).

Patients should be advised to promptly seek the attention of their physician if they notice signs of gastrointestinal bleeding, macroscopic haematuria, or other symptoms such as dysuria or urinary urgency develop during treatment with enzalutamide.

Concomitant use with other medicinal products

Enzalutamide is a potent enzyme inducer and may lead to loss of efficacy of many commonly used medicinal products. A review of concomitant medicinal products should therefore be conducted when initiating enzalutamide treatment. Concomitant use of enzalutamide with medicinal products that are sensitive substrates of many metabolising enzymes or transporters should generally be avoided if their therapeutic effect is of large importance to the patient, and if dose adjustments cannot easily be performed based on monitoring of efficacy or plasma concentrations.

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If Xtandi is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin or acenocoumarol), additional International Normalised Ratio (INR) monitoring should be conducted.

Renal impairment

Caution is required in patients with severe renal impairment as enzalutamide has not been studied in this patient population.

Severe hepatic impairment

An increased half-life of enzalutamide has been observed in patients with severe hepatic impairment, possibly related to increased tissue distribution. The clinical relevance of this observation remains unknown. A prolonged time to reach steady state concentrations is however anticipated, and the time to maximum pharmacological effect as well as time for onset and decline of enzyme induction may be increased.

Recent cardiovascular disease

The phase 3 studies excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association Class (NYHA) III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi is prescribed in these patients.

Androgen deprivation therapy may prolong the QT interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval physicians should assess the benefit risk ratio including the potential for *Torsade de pointes* prior to initiating Xtandi.

Use with chemotherapy

The safety and efficacy of concomitant use of Xtandi with cytotoxic chemotherapy has not been established. Co-administration of enzalutamide has no clinically relevant effect on the pharmacokinetics of intravenous docetaxel; however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.

Severe skin reactions

Severe cutaneous adverse reactions (SCARs), including Stevens-Johnson syndrome, which can be life threatening or fatal, has been reported with enzalutamide treatment.

At the time of prescription, patients should be advised of the signs and symptoms and monitored closely for skin reactions.

If signs and symptoms suggestive of this reaction appear, enzalutamide should be withdrawn immediately and an alternative treatment considered (as appropriate).

Hypersensitivity reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed with enzalutamide. Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide.

Xtandi as monotherapy in patients with high-risk BCR nmHSPC

Results of the EMBARK study suggest that Xtandi as monotherapy and in combination with androgen deprivation therapy are not equivalent treatment options in patients with high-risk BCR nmHSPC (see sections 4.8 and 5.1). Xtandi in combination with androgen deprivation therapy is considered the preferred treatment option except for cases in which the addition of androgen deprivation therapy may result in unacceptable toxicity or risk.

Dysphagia related to product formulation

There have been reports of patients experiencing difficulty swallowing Xtandi, including reports of choking. The swallowing difficulties and choking events were mostly reported with the capsule formulation, which could be related to a larger product size. Patients should be advised to swallow the capsules whole with a sufficient amount of water.

Excipients

Xtandi contains 57.8 mg sorbitol (E420) per soft capsule.

Undesirable effects:

Summary of the safety profile

The most common adverse reactions are asthenia/fatigue, hot flush, hypertension, fractures, and fall. Other important adverse reactions include ischemic heart disease and seizure.

Seizure occurred in 0.6% of enzalutamide-treated patients, 0.1% of placebo-treated patients, and 0.3% in bicalutamide-treated patients.

Rare cases of posterior reversible encephalopathy syndrome have been reported in enzalutamide-treated patients.

Stevens-Johnson syndrome has been reported with enzalutamide treatment.

List of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Adverse reactions identified in controlled clinical trials and post-marketing:
Blood and lymphatic system disorders: Uncommon: leucopenia, neutropenia. *Not known*:* thrombocytopenia.
Immune system disorders: Not known:* face oedema, tongue oedema, lip oedema, pharyngeal oedema.
Metabolism and nutrition disorders: Not known:* decreased appetite

Psychiatric disorders: Common: anxiety. *Uncommon:* visual hallucinations.
Nervous system disorders: Common: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome, cognitive disorder. *Uncommon* seizure[¥]. *Not known*:* posterior reversible encephalopathy syndrome.
Cardiac disorders: Common: ischemic heart disease[†]. *Not known*:* QT-prolongation.
Vascular disorders: Very common: hot flush, hypertension.
Gastrointestinal disorders: Not known:* dysphagia[∞], nausea, vomiting, diarrhea.
Hepatobiliary disorders: Uncommon: hepatic enzymes increased.
Skin and subcutaneous tissue disorders: Common: dry skin, pruritus. *Not known*:* erythema multiforme, Stevens-Johnson syndrome, rash.
Musculoskeletal and connective tissue disorders : Common: fractures[‡]. *Not known*:* myalgia, muscle spasms, muscular weakness, back pain.
Reproductive system and breast disorder: Common: gynaecomastia, nipple pain[#], breast tenderness[#].
General disorders and administration site conditions: Very Common: asthenia, fatigue
Injury, poisoning and procedural complications: Very common: fall.

* Spontaneous reports from post-marketing experience.
¥ As evaluated by narrow SMQs of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death.
† As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomised placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery.
‡ Includes all preferred terms with the word 'fracture' in bones.
# Adverse reactions for enzalutamide as monotherapy.
∞ There have been reports of dysphagia, including reports of choking. Both events have mostly been reported with the capsule formulation, which could be related to a larger product size.

Description of selected adverse reactions:

Seizure

In controlled clinical studies, 31 patients (0.6%) experienced a seizure out of 5110 patients treated with a daily dose of 160 mg enzalutamide, whereas four patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

In the 9785-CL-0403 (UPWARD) single-arm trial to assess incidence of seizure in patients with predisposing factors for seizure (whereof 1.6% had a history of seizures), 8 of 366 (2.2%) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.

The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA gated chloride channel.

Ischemic Heart Disease

In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 3.5% of patients treated with enzalutamide plus ADT compared to 2 % of patients treated with placebo plus ADT. Fourteen (0.4%) patients treated with enzalutamide plus ADT and 3 (0.1%) patients treated with placebo plus ADT had an ischemic heart disease event that led to death.

In the EMBARK study, ischemic heart disease occurred in 5.4% of patients treated with enzalutamide plus leuprolide and 9% of patients treated with enzalutamide as monotherapy. No patients treated with enzalutamide plus leuprolide and one (0.3%) patient treated with enzalutamide as monotherapy had an ischemic heart disease event that led to death.

Gynaecomastia

In the EMBARK study, gynaecomastia (all grades) was observed in 29 of 353 patients (8.2%) who were treated with enzalutamide plus leuprolide and 159 of 354 patients (44.9%) who were treated with enzalutamide as monotherapy. Grade 3 or higher gynaecomastia was not observed in any patients who were treated with enzalutamide plus leuprolide, and was observed in 3 patients (0.8%) who were treated with enzalutamide as monotherapy.

Nipple pain

In the EMBARK study, nipple pain (all grades) was observed in 11 of 353 patients (3.1%) who were treated with enzalutamide plus leuprolide and 54 of 354 patients (15.3%) who were treated with enzalutamide as monotherapy. Grade 3 or higher nipple pain was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Breast tenderness

In the EMBARK study, breast tenderness (all grades) was observed in 5 of 353 patients (1.4%) who were treated with enzalutamide plus leuprolide and 51 of 354 patients (14.4%) who were treated with enzalutamide as monotherapy. Grade 3 or higher breast tenderness was not observed in any patients who were treated with enzalutamide plus leuprolide or with enzalutamide as monotherapy.

Full prescribing information is available upon request.