Xtandi™ enzalutamide

Xtandi significantly extended overall survival in both patients with non metastatic CRPC[2] and metastatic CRPC[1].

Mets? No Mets? Start Xtandi™

Regardless of metastatic status, Xtandi offers your patients with CRPC the confidence of proven efficacy when PSA is rising* during LHRH therapy[1]

Abbreviated Prescribing Information XtandiTM soft capsules, containing enzalutamide. INDICATIONS: For the treatment of adult men with high-risk non-metastatic castrationresistant prostate cancer (CRPC). Treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated. Treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy. POSOLOGY AND METHOD OF ADMINISTRATION: Recommended dose is 160 mg (four 40 mg capsules) as a single daily dose. Medical castration with an LHRH analogue should be continued during treatment of patients not surgically castrated. Xtandi can be taken with/without food and should be taken at approximately the same time daily. If a patient misses a dose, take the prescribed dose as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the usual daily dose. If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for 1 week or until symptoms improve to ≤ Grade 2, then resumed at the same/a reduced dose (120 mg or 80 mg) if warranted. Concomitant use with strong CYP2C8 inhibitors Should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the enzalutamide dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor. Hepatic impairment An increased drug half-life has been observed in patients with severe hepatic impairment. Renal impairment Caution is advised in patients with severe renal impairment or endstage renal impairment. Paediatric population No relevant use of enzalutamide. Method of administration Xtandi is for oral use. The capsules should be swallowed whole with water. Do not cut, crush or chew. CONTRAINDICATIONS: Hypersensitivity to the active substance or to any of the excipients. Women who are or may become pregnant. SPECIAL WARNINGS AND PRECAUTIONS: Risk of seizure Use of enzalutamide has been associated with events of seizure. Permanently discontinue enzalutamide in patients who develop a seizure during treatment. 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. Hypersensitivity Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue, lip, or pharyngeal oedema, have been observed 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 drug half-life 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%, patients with diagnosed or suspected congenital long QT syndrome, QTcF > 470 ms, bradycardia or uncontrolled hypertension. This should be taken into account if Xtandi is prescribed in these patients. 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. Excipients Xtandi contains sorbitol (E420). Patients with rare hereditary problems of fructose intolerance should not take this medicinal product. UNDESIRABLE EFFECTS: Summary of the safety profileThe most common adverse reactions are asthenia/fatigue, hot flush, fractures and hypertension. Other important adverse reactions include fall, cognitive disorder and neutropenia. Seizure occurred in 0.4% 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 (see section 4.4). Tabulated summary 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.

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	Very common	Common	Uncommon	Not known[1]
Blood and lymphatic system disorders			leucopenia neutropenia	
General disorders	asthenia, fatigue			
Psychiatric disorders		anxiety	visual hallucinations	
Nervous system disorders		headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome	cognitive disorder, seizure[7]	posterior reversible encephalopathy syndrome
Reproductive system and breast disorder		gynaecomastia		
Vascular disorders	hot flush, hypertension			
Skin and subcutaneous tissue disorders		dry skin, pruritus		rash
Musculoskeletal and connective tissue disorders	fractures[6]			myalgia, muscle spasms, muscular weakness, back pain
Injury, poisoning and procedural complications		falls		
Gastrointestinal disorders				nausea, vomiting, diarrhea
Cardiac disorders		ischemic heart disease[2]		
Immune system disorders				face edema[3], tongue edema[4] lip edema[4], pharyngeal edema

1. Adverse reactions of an unknown frequency have been identified during post approval use of enzalutamide. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure. 2. 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 randomized 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. 3. Includes events of face edema and swelling face. 4. Includes events of swollen tongue and tongue edema. 5. Includes events of lip swelling and lip edema. 6. Includes all preferred terms with the word 'fracture' in bones. 7. 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. **Description of selected adverse reactions Seizure** In controlled clinical studies,13 patients (0.4%) experienced a seizure out of 3179 patients treated with a daily dose of 160 mg enzalutamide, whereas one patient (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. In the patients who experienced a seizure when treated with enzalutamide, there was one case of seizure where the patient experienced complications resulting in death. 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 seizures (whereof 1.7% 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 2.5% of patients treated with enzalutamide plus ADT compared to 1.3 % patients treated with placebo plus ADT. **Full prescribing information is available on request**. Reference: Xtandi™ Package Insert, Singapore. Updated January 2019. Report any adverse events to Astellas Pharma Singapore Pte. Ltd. at pv@sg.astellas.com. Alternatively, you may submit AE reports directly to HSA via the HSA website at www.hsa.gov.sg/ae_online or download the AE reporting forms at the same website and submit the completed forms via the following modes: Email: HSA_productsafety@hsa.gov.sg Fax: 6478 9069

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References: 1. Xtandi Package Insert Singapore. Update Jan 2019. 2. Sternberg CN et al. Enzalutamide and Survival in Nonmetastatic, Castration-Resistant. Prostate cancer. N Engl J Med 2020;382(23):2198-2206.

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*PSA level >2ng/mL with at least 2 consecutive rises despite castrate testosterone levels (<50ng/dL)

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