Strike now with XTANDI™ (enzalutamide) in men with mHSPC

XTANDI (enzalutamide) is indicated for the treatment of adult men with:
mHSPC in combination with ADT; high-risk[3] nmCRPC; mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated; mCRPC whose disease has progressed on or after docetaxel therapy.[3]

The phase III ARCHES study* established the value of adding XTANDI to ADT for treating men with mHSPC:[1,2]

61% **reduction** in the risk of radiographic progression or death vs ADT alone[1]

34% **reduction** in the risk of death vs ADT alone†[2]

Quality of life was **maintained** on treatment and **comparable** to the control arm[1]

Proportion of exposure-adjusted AEs of any Grade and Grade ≥3 AEs, and AEs leading to treatment discontinuation, were **comparable** to the control arm[1,2]

Xtandi™ enzalutamide

*ARCHES was a multinational, double-blind, randomised, placebo-controlled phase III study comparing the efficacy and safety profile of XTANDI + ADT vs placebo + ADT in 1,150 men with mHSPC. The primary endpoint was rPFS and OS was a key secondary endpoint.[1,2]
†These data are from the ARCHES final analysis (data cutoff date of 28 May 2021). Following the primary analysis, the study was unblinded to allow patients on placebo + ADT to cross over to XTANDI + ADT in an open-label extension study.[2]
‡High risk is defined as patients with rising PSA despite castration-associated testosterone levels, with ≥3 rising PSA levels ≥1 week apart, a baseline PSA level ≥2 ng/ml and a PSA doubling time of ≤10 months.[4]

ADT=androgen deprivation therapy; AE=adverse event; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; nmCRPC=non-metastatic castration-resistant prostate cancer; OS=overall survival; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival.

XTANDI™ (Abbreviated Prescribing Information)
Presentation: Soft Capsules containing 40 mg of enzalutamide. **Indications:** Treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT) (see section 5.1). Treatment of adult men with high-risk non-metastatic castration-resistant 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. **Dosage:** 160 mg (four 40 mg capsules) as a single daily dose. **Method of Administration:** Xtandi is for oral use. The soft capsules should not be chewed, dissolved or opened but should be swallowed whole with water, and can be taken with or without food. **Contraindication:** Hypersensitivity to the active substance or to any of the excipients. Women who are or may become pregnant. **Special Precautions:** Risk of seizure: Use of enzalutamide has been associated with seizure (see section 4.8). 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 (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 bladder transitional cell carcinoma (0.1%). 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 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) U 45%, 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 (see section 4.5); however, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded. 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 (see section 4.8). Severe cutaneous adverse reactions (SCARs) have been reported with enzalutamide. At the time of prescription patients should be advised of the signs and symptoms and monitored closely for skin reactions. 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 0.5% of enzalutamide-treated patients, 0.2% 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 (U 1/10); common (U 1/100 to < 1/10); uncommon (U 1/1,000 to < 1/100); rare (U 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (Spontaneous reports from post-marketing experience, cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness: Blood and lymphatic system disorders: *uncommon*: leucopenia, neutropenia; Immune system disorders: *not known*[1]: face oedema, tongue oedema, lip oedema, pharyngeal oedema. Psychiatric disorders: *common*: anxiety; *uncommon*: visual hallucinations. Nervous system disorders: *common*: headache, memory impairment, amnesia, disturbance in attention, dysgeusia, restless legs syndrome; *uncommon*: cognitive disorder, seizure; *not known*: posterior reversible encephalopathy syndrome. Cardiac disorders: *common*: ischemic heart disease. Vascular disorders: *very common*: hot flush, hypertension. Gastrointestinal disorders: *not known*: nausea, vomiting, diarrhea. Skin and subcutaneous tissue disorders: *common*: dry skin, pruritus; *not known*: erythema multiforme, rash. Musculoskeletal and connective tissue disorders: *very common*: fractures (Includes all fractures with the exception of pathological fractures); *not known (Spontaneous reports from post-marketing experience)*: myalgia, muscle spasms, muscular weakness, back pain. Reproductive system and breast disorder: *common*: gynaecomastia. General disorders and administration site conditions: *very common*: asthenia, fatigue. Injury, poisoning and procedural complications: *very common*: falls. *Description of selected adverse reactions*: Seizure: In controlled clinical studies, 24 patients (0.5%) experienced a seizure out of 4403 patients treated with a daily dose of 160 mg enzalutamide, whereas four patients (0.2%) 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 randomised placebo-controlled clinical studies, ischemic heart disease occurred in 3.9% of patients treated with enzalutamide plus ADT compared to 1.5% patients treated with placebo plus ADT. Fifteen (0.4%) patients treated with enzalutamide and 2 (0.1%) patients treated with placebo had an ischemic heart disease event that led to death. **Packs:** 112 soft capsules of 40 mg. **API date:** 04042023. **Please refer to the full prescribing information before prescribing XTANDI™.**

References:
1. Armstrong AJ *et al. J Clin Oncol* 2019;**37**(32):2974–2986.
2. Armstrong AJ *et al. J Clin Oncol* 2022;**40**(15):1616–1622.
3. XTANDI (Enzalutamide) Malaysia Full Prescribing Information revised 24082022.
4. Hussain M *et al. N Engl J Med* 2018;**378**(26):2465–2474.

Report any adverse events to Astellas Pharma Malaysia Sdn.Bhd. at pv.my@astellas.com

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Astellas Pharma Malaysia Sdn Bhd
Suite 1805, Level 18, CenterPoint North Tower, Mid Valley City, Lingkaran Syed Putra, 59200 Kuala Lumpur.
Tel: +603-22026999 Fax: +603-2202 6988, +603-2202 6977
www.astellas.com

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