Ireland and Northern Ireland Abbreviated Prescribing Information: XTANDI™ 40 mg film-coated tablets (enzalutamide).

For full prescribing information, refer to the Summary of Product Characteristics (SPC).

Presentation: 40 mg film-coated tablets each containing 40 mg of 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.

Posology and administration: Treatment with enzalutamide should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer. The recommended dose is 160 mg enzalutamide (four 40 mg film-coated tablets) as a single oral daily dose. The tablets should be swallowed whole with water, and can be taken with or without food. Medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients with CRPC or mHSPC who are not surgically castrated. If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld for one week or until symptoms improve to ≤ Grade 2, then resumed at the same or a reduced dose (120 mg or 80 mg) if warranted.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. Women who are or may become pregnant.

Special warnings and precautions for use: Risk of seizure: Use of enzalutamide has been associated with seizure. The decision to continue treatment in patients who develop seizures 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. 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. 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. Excipients: This medicine contains less than 1 mmol sodium (less than 23 mg) per film-coated tablet, that is to say essentially 'sodium-free'.

Interactions: Potential for other medicinal products to affect enzalutamide exposures: CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Strong inhibitors (e.g. gemfibrozil) of CYP2C8 are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily. No dose adjustment is necessary when XTANDI is co-administered with inducers of CYP2C8. CYP3A4 plays a minor role in the metabolism of enzalutamide. No dose adjustment is necessary when XTANDI is co-administered with inhibitors or inducers of CYP3A4. Potential for enzalutamide to affect exposures to other medicinal products: Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19, and uridine 5'-diphospho-glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). Some transporters may also be induced, e.g. multidrug resistance-associated protein 2 (MRP2) and the organic anion transporting polypeptide 1B1 (OATP1B1). *In vivo* studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking medicinal products that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of enzalutamide treatment, and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days), effects on enzymes may persist for one month or longer after stopping enzalutamide. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping enzalutamide treatment. *In vitro* data indicate that enzalutamide may be an inhibitor of the efflux transporter P-gp. A mild inhibitory effect of enzalutamide, at steady-state, on P-gp was observed in a study in patients with prostate cancer that received a single oral dose of the probe P-gp substrate digoxin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC and C_{max} of digoxin increased by 33% and 17%, respectively. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with XTANDI and may require dose adjustment to maintain optimal plasma concentrations. At steady state, enzalutamide did not cause a clinically meaningful change in exposure to the probe breast cancer resistance protein (BCRP) substrate rosuvastatin in patients with prostate cancer that received a single oral dose of rosuvastatin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC of rosuvastatin decreased by 14% while Cmax increased by 6%. No dose adjustment is necessary when a BCRP substrate is co administered with XTANDI. Based on *in vitro* data, inhibition of MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3) and organic cation transporter 1 (OCT1) (systemically) cannot be excluded. Theoretically, induction of these transporters is also possible, and the net effect is presently unknown. Since androgen deprivation treatment may prolong the QT interval, the concomitant use of XTANDI with medicinal products known to prolong the QT interval or medicinal products able to induce Torsade de pointes should be carefully evaluated.

Fertility, pregnancy and lactation: There are no human data on the use of XTANDI in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant. It is not known whether enzalutamide or its metabolites are present in semen. A condom is required during and for 3 months after treatment with enzalutamide if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential a condom and another form of birth control must be used during and for 3 months after treatment. Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are, or who may become, pregnant. It is not known if enzalutamide is present in human milk. Enzalutamide and/or its metabolites are secreted in rat milk. Animal studies showed that enzalutamide affected the reproductive system in male rats and dogs.

Effects on ability to drive and use machines: XTANDI may have a moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported. Patients should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines.

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.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). Adverse reactions are presented according to Medical Dictionary for Regulatory Activities (MedDRA) system organ classification and within each frequency grouping they 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 Psychiatric disorders: Common: anxiety; Uncommon: visual hallucination. 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*: nausea, vomiting, diarrhoea. 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: Very 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 Standardised MedDRA Queries (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 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.

‡ Includes all preferred terms with the word 'fracture' in bones.

\# Adverse reactions for enzalutamide as monotherapy.

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. Prescribers should consult the full SPC in relation to other adverse reactions.

Overdose: There is no antidote for enzalutamide. In the event of an overdose, treatment with enzalutamide should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.
Cost (excluding VAT): XTANDI 40 mg film-coated tablets x 112: Ireland: POA. Northern Ireland: £2,734.67.
Legal classification: Ireland: POM/S1A. Northern Ireland: POM.
Marketing Authorisation number: XTANDI 40 mg film-coated tablets: EU/1/13/846/002
Marketing Authorisation Holder: Astellas Pharma Europe B.V., Sylviusweg 62, 2333 BE Leiden, The Netherlands.
Date of preparation of Prescribing Information: April 2024
Job number: MAT-UKE-XTD-2024-00001
Further information is available on request from:
Ireland: Astellas Pharma Co. Ltd., Tel.: +353 1 467 1555.
Northern Ireland: Astellas Pharma Ltd, Medical Information 0800 783 5018.
For full prescribing information, refer to the SPCs, which may be found at www.medicines.ie (Ireland) and https://www.emcmedicines.com/en-GB/northernireland/ (Northern Ireland).

Adverse events should be reported. For Ireland, Healthcare professionals are asked to report any suspected adverse reactions via: HPRA Pharmacovigilance, Website: www.hpra.ie or Astellas Pharma Co. Ltd. Tel: +353 1 467 1555, E-mail: irishdrugsafety@astellas.com.

Adverse events should be reported. For Northern Ireland, reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd on 0800 783 5018.