XTANDI™ (ENZALUTAMIDE)

# *Public Risk Management Plan (RMP) Summary*

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of XTANDI is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of XTANDI in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Astellas Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of XTANDI.

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Astellas Pharma AG
Richtiring 28, CH-8304 Wallisellen
Tel. +41 (0)44 832 40 00
office.ch@astellas.com, www.astellas.ch

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

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**Summary of risk management plan for XTANDI (Enzalutamide)**

This is a summary of the RMP for XTANDI®. The RMP details important risks of XTANDI, how these risks can be minimized, and how more information will be obtained about XTANDI's risks and uncertainties (missing information).

XTANDI's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how XTANDI should be used.

This summary of the RMP for XTANDI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of XTANDI's RMP.

## I. THE MEDICINE AND WHAT IT IS USED FOR

XTANDI is authorized for the treatment of adult men with high risk nmCRPC, the treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, and the treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy (see the SmPC for the full indication). XTANDI is also authorized for expanded indication for the treatment of adult men with mHSPC. It is proposed that indication be expanded for the treatment of adult men with high-risk BCR nmHSPC who are unsuitable for salvage- radiotherapy. Thus, the overall target indication is the treatment of patients with mHSPC, nmHSPC, mCRPC and nmCRPC. It contains enzalutamide as the active substance, and it is given orally as tablets or capsules (four 40 mg oral capsules once daily or four 40 mg oral film-coated tablets once daily or two 80 mg oral film-coated tablets once daily).

Further information about the evaluation of XTANDI's benefits can be found in XTANDI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002639/human_med_001663.jsp&mid=WC0b01ac058001d124

## II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of XTANDI, together with measures to minimize such risks and the proposed studies for learning more about XTANDI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

## II.A List of important risks and missing information

Important risks of XTANDI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XTANDI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

| **List of important risks and missing information** | |
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| Important identified risks | • Seizure<br>• Fall<br>• Non-pathological fracture<br>• Ischaemic Heart Disease |
| Important potential risks | • None |
| Missing information | • None |

## II.B Summary of important risks

| **Important Identified Risk: Seizure** | |
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| Evidence for linking the risk to the medicine | This important identified risk is based on data from enzalutamide toxicology studies in animals and clinical studies. Seizures were observed in animals in nonclinical toxicology studies (1 rat and 2 dogs) administered enzalutamide, and there was a dose-dependent increase of seizures in mice. The event of seizure is an uncommon adverse drug reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of seizure was 1.1% in the enzalutamide + ADT group as compared to 0.8% in the enzalutamide monotherapy group. There was no incidence of |

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| | seizure in placebo + ADT group. In 9785-CL-0335 (ARCHES) in mHSPC patients the incidence of the event of seizure was lower in the enzalutamide group compared with the placebo group (0.3% vs. 0.5%). In MDV3100-14 (PROSPER), the incidence of seizure was low in both groups, but numerically higher in the enzalutamide group compared with the placebo group (0.3% vs 0% in the double-blind portion of the study. In the phase 3 studies in patients with mHSPC and with nmCRPC and mCRPC, the incidence of any event of seizures was 0.4% in the enzalutamide group compared with 0.1% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of seizures among the enzalutamide treated patients in the double-blind plus open label group was 0.6%. When adjusted for duration of exposure, the event rates of seizure remained higher in the enzalutamide-treated groups compared with the placebo groups for the phase 3 studies but not for Study 9785-CL-0335 |
| Risk factors and risk groups | Dose appears to be an important predictor of the risk of seizure, as reflected by nonclinical data and clinical trial experience with enzalutamide at higher doses (a dose-response relationship between enzalutamide and seizure was suggested in a dose escalation study).<br>In a single-arm postmarketing safety study to assess the risk of seizure in patients with predisposing factors for seizure (9785-CL- 0403), the seizure event rate among enzalutamide-treatment mCRPC patients who were potentially at an increased risk of seizure was 1.1%, which was comparable with the seizure rate in the other studies, despite the inclusion of patients with potential risk factors for seizure.<br>The occurrence of seizure in patients diagnosed with prostate cancer has been reported in the literature mainly in association with central nervous system metastases, which are exceedingly rare in prostate cancer. In a retrospective cohort study, the incidence of seizure in mCRPC patients was higher in patients with at least 1 risk factor than in those with no risk factors, with the highest incidence occurring among patients with a history of seizure plus a history of anticonvulsant use. History of seizure but no history of anticonvulsant use, dementia, history of loss of consciousness, transient ischemic attack or cerebrovascular accident, and treated brain metastases were also associated with increased incidences of seizure [Bonafede, 2013]. |
| Risk minimization measures | Routine risk communication:<br>• SmPC Sections 4.4, 4.7, 4.8, and 4.9;<br>• PL Sections 2 and 4;<br>• Recommendation that the decision to continue treatment in patients who develop seizure should be taken case by case, is provided in SmPC Section 4.4 and PL sections 2 and 4;<br>• Concomitant medications associated with higher risk of seizure are described in PL Section 2. |

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| | Additional risk minimization measures:<br>• None. |

ADT: Androgen Deprivation Therapy; CRPC: Castration-Resistant Prostate Cancer; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

| **Important Identified Risk: Fall** | |
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| Evidence for linking the risk to the medicine | This important identified risk is based on data from clinical studies. Fall is a very common adverse reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of fall was 21% in the enzalutamide + ADT group, 14.4% in placebo + ADT group and 15.8% in the enzalutamide monotherapy group. In study 9785-CL- 0335 (ARCHES) in metastatic HSPC patients and in the pooled phase 3 studies, the incidence of fall was 6.5% versus 3.3% in Study 9785-CL-0335 (ARCHES) and 11.5% versus 5.1 % for enzalutamide and placebo group respectively. In MDV3100-14 (PROSPER), the incidence of fall was 17.6% versus 5.4% in the enzalutamide and placebo groups for the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fall among the enzalutamide treated patients in the double-blind plus open label group was 12.7%. When adjusted for the duration of the exposure, the event rates of fall remained higher in the enzalutamide-treated groups compared with the placebo. |
| Risk factors and risk groups | In phase 3 studies, the incidence of fall increased with increasing patient age in all treatment groups. The events of fall among enzalutamide-treated patients did not appear to be associated with prior events of syncope, presyncope, loss of consciousness, dizziness, or postural dizziness. |
| Risk minimization measures | Routine risk communication:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None |

ADT: Androgen Deprivation Therapy; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

| **Important Identified Risk: Non-pathological fracture** | |
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| Evidence for linking the risk to the medicine | This important identified risk is based on data from clinical studies. Fracture is a very common adverse reaction that has been reported in patients treated with enzalutamide. In MDV3100-13 (EMBARK), the incidence of fracture was 18.4% in the enzalutamide + ADT group, 13.6% in placebo + ADT group and 11% in the enzalutamide monotherapy group. In 9785-CL-0335 (ARCHES) in mHSPC patients and in the pooled phase 3 studies, the incidence of fracture was 9.6% versus 5.4% in Study 9785-CL-0335 (ARCHES) and 12.3% versus 5.8% for enzalutamide and placebo group respectively. In MDV3100-14 (PROSPER), |

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| | the incidence of fracture was 17.6% versus 6.0% for enzalutamide and placebo groups in the double-blind portion of the study. From the pooled phase 3 studies and phase 2 studies, the incidence of fracture among the enzalutamide treated patients in the double-blind plus open label group was 12.5%. When adjusted for the duration of the exposure, the event rates of fracture remained higher in the enzalutamide-treated groups compared with the placebo groups. |
| Risk factors and risk groups | In prostate cancer, ADT is a risk for fracture. The incidences of all fractures and hip fractures requiring hospitalization in males treated with LHRH agonists were 9.8 and 6.3/1000 PY higher than the general population [Thorstenson et al, 2012]. In a review of 50 613 males in the SEER-Medicare linked database diagnosed with prostate cancer between 1992 and 1997 who had survived at least 5 years after diagnosis, the incidence of fracture (both pathological and non-pathological) was 19.4% in patients who had been treated with ADT (medical or surgical); whereas the rate was 12.6% in patients who had not received treatment [Shahinian et al, 2005].<br>Age is an independent risk factor for fractures in males with osteoporosis. Decreased lean body mass attributed to ADT, and, in general in patients with cancer, non-oncologic factors such as smoking, excessive alcohol use, inadequate exercise, calcium and vitamin D deficiency, parental history of hip fracture, use of glucocorticoids, proton pump inhibitors and anticoagulants are associated with increased risk of fracture [Lipton et al, 2012].<br>In general, in enzalutamide clinical trials, an increased incidence of fracture was observed with increasing age, consistent with the increased incidence of fall. The higher risk of fracture associated with fall in the enzalutamide group may be related to longer exposure time on study along with the bone effects of prolonged androgen deprivation. |
| Risk minimization measures | Routine risk communication:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None |

ADT: Androgen Deprivation Therapy; LHRH: Luteinizing Hormone-Releasing Hormone; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; PY: Patient-Years; SEER: Surveillance Epidemiology and End Results; SmPC: Summary of Product Characteristics.

| **Important Identified Risk: Ischemic Heart Disease** | |
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| Evidence for linking the risk to the medicine | This important identified risk is based on data from clinical studies. Ischemic heart disease (including the following events observed in at least 2 patients in randomized placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarction, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischemia, and arteriosclerosis coronary artery) is a common adverse drug reaction that has been reported in patients treated with |

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| | enzalutamide. In MDV3100-13 (EMBARK), the incidence of IHD was higher in the enzalutamide monotherapy group (9%), as compared 5.4% in the enzalutamide + ADT group and 5.6% in placebo + ADT. In 9785-CL-0335 (ARCHES) in metastatic HSPC patients the incidence of ischaemic heart disease was 2.8% in the enzalutamide group, and in 1.9% in the placebo group. In PROSPER, the incidence of ischemic heart disease was 6.5% vs 1.7% in enzalutamide and placebo groups. In the phase 3 studies, the incidence of any event of ischemic heart disease was 3.5% in the enzalutamide group compared with 2.0% in the placebo group. From the pooled phase 3 studies and phase 2 studies, the incidence of ischaemic heart disease among the enzalutamide treated patients in the double-blind plus open label was 4.6%. When adjusted for duration of the exposure, the event rates of ischemic heart disease remained higher in the enzalutamide-treated group in the phase 3 studies compared with the placebo group. |
| Risk factors and risk groups | Risk factors for experiencing an ischemic event included a history<br>of one or more of the following: cardiovascular disease, dyslipidemia, and age ≥ 75 years. Adverse cardiac events are a recognized risk with ADT. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.8;<br>• PL Section 4.<br>Additional risk minimization measures:<br>• None |

ADT: Androgen Deprivation Therapy; HSPC: Hormone-Sensitive Prostate Cancer; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

# II.C Postauthorization development plan

## II.C.1 Studies which are conditions of the marketing authorization

There are no studies that are conditions of the marketing authorization or specific obligation of XTANDI.

## II.C.2 Other studies in postauthorization development plan

There are no studies required for XTANDI.