Table of Contents

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN 2

I. The medicine and what it is used for 2

II. Risks associated with the medicine and activities to minimize or further characterize the risks 3

II.A List of important risks and missing information 3

II.B Summary of important risks 4

II.C Postauthorization development plan 7

II.C.1 Studies which are conditions of the marketing authorization 7

II.C.2 Other studies in postauthorization development plan 7

PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Data-lock point for this Module	30 Aug 2018
Version when Module last updated	12.5

Summary of risk management plan for XTANDI (enzalutamide)

This is a summary of the risk management plan (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 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 nonmetastatic castration-resistant prostate cancer (CRPC), 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, 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). It is proposed that the indication be expanded to include adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy. Thus, the overall target indication is the treatment of patients with mHSPC and CRPC. 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 package leaflet 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	
Important identified risks	• Seizure • Fall • Non-pathological fracture • Ischemic heart disease
Important potential risks	• None
Missing information	• None

II.B Summary of important risks

Important identified risk: Seizure	
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. Convulsions were observed in animals in nonclinical toxicology studies (1 rat and 2 dogs) administered enzalutamide, and there was a dose-dependent increase of convulsions in mice. The event of convulsion is an uncommon adverse drug reaction that has been reported in patients treated with enzalutamide. In Study 9785-CL-0335 in patients with metastatic HSPC, the incidence of seizure was 0.3% in both the enzalutamide and placebo groups. In the pooled phase 3 studies, the incidence of seizure was 0.4% in the enzalutamide group and 0.1% in the placebo group. When adjusted for the duration of the exposure, the event rates of seizure remained higher in the enzalutamide-treated groups compared with the placebo groups.
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). 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 metastatic CRPC 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. 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 metastatic CRPC 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].
Table continued on next page	

Important identified risk: Seizure	
Risk minimization measures	Routine risk communication: • SmPC sections 4.4, 4.7, 4.8, and 4.9; • PL sections 2 and 4; • 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; • Concomitant medications associated with higher risk of seizure are described in PL Section 2. Additional risk minimization measures: • None.

CRPC: castration-resistant prostate cancer; HSPC: hormone-sensitive prostate cancer; PL: package leaflet; SmPC: summary of product characteristics.

Important identified risk: Fall	
Evidence for linking the risk to the medicine	This important identified risk is based on data from clinical studies. Fall is a common adverse reaction that has been reported in patients treated with enzalutamide. In Study 9785-CL-0335 in patients with metastatic HSPC, the incidence of fall was 3.7% in the enzalutamide group, and 2.6% in the placebo group. In the pooled phase 3 studies, the incidence of fall was 9.5% and 3.5% in the enzalutamide and placebo groups, respectively. When adjusted for the duration of the exposure, the event rates of fall remained higher in the enzalutamide-treated groups compared with the placebo groups.
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: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None

CRPC: castration-resistant prostate cancer; HSPC: hormone-sensitive prostate cancer; PL: package leaflet; SmPC: summary of product characteristics.

Important identified risk: Non-pathological fracture	
Evidence for linking the risk to the medicine	This important identified risk is based on data from clinical studies. Fracture is a common adverse reaction that has been reported in patients treated with enzalutamide. In Study 9785-CL-0335 in patients with metastatic HSPC and in the phase 3 studies including patients with nonmetastatic and metastatic CRPC, the incidence of fracture was higher in the enzalutamide groups compared with the placebo groups (6.5% vs 4.2% in Study 9785-CL-0335 and 9.7% vs 4.1% in the pooled phase 3 studies). When adjusted for the duration of the exposure, the events 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 50613 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]. 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]. 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: • SmPC Section 4.8; • PL Section 4. Additional risk minimization measures: • None.

CRPC: castration-resistant prostate cancer; HSPC: hormone-sensitive prostate cancer; PL: package leaflet; SmPC: summary of product characteristics.

Important identified risk: Ischemic heart disease	
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 enzalutamide. In Study 9785-CL-0335 in patients with metastatic HSPC, and in the pooled phase 3 studies in patients with nonmetastatic and metastatic CRPC, the incidence of any event of ischemic heart disease was higher in the enzalutamide group compared with the placebo group (1.7% vs 1.4% in Study 9785-CL-0335 and 2.8% vs 1.3% in the phase 3 studies). When adjusted for duration of the exposure, the event rates of ischemic heart disease remained higher in the enzalutamide-treated groups compared with the placebo groups.
Risk factors and risk groups	Risk factors for experiencing an ischemic event included a history 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: • SmPC Section 4.8; • PL Section 4.

ADT: androgen deprivation therapy; CRPC: castration-resistant prostate cancer; 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

The following study is a condition of the marketing authorization or specific obligation of XTANDI;

MDV3100-14 (PROSPER) long-term efficacy study follow-up

Purpose of the study: To evaluate the benefit of enzalutamide compared with placebo as measured by overall survival (OS).

II.C.2 Other studies in postauthorization development plan

There are no studies required for XTANDI.