Johnson&Johnson

**Janssen-Cilag AG**,
a Johnson & Johnson company
Gubelstrasse 34
6300 Zug

Tel: +41 (0)58 231 34 34
Fax: +41 (0)58 231 35 81
janssen.com/switzerland/

# Summary of the Risk Management Plan (RMP) for ERLEADA® (apalutamide)

Marketing Authorisation Holder (MAH): Janssen-Cilag AG

Document version 1.0

Document date 06-03-2025

Based on EU RMP version 7.1, 10-01-2025

Disclaimer:
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 ERLEADA® 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 ERLEADA® in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Janssen-Cilag AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of ERLEADA®.

# PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

## Summary of Risk Management Plan for ERLEADA (Apalutamide)

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

ERLEADA's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how ERLEADA should be used.

This summary of the RMP for ERLEADA 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 ERLEADA's RMP.

## I. The Medicine and What it is Used For

ERLEADA is authorized for the treatment of non-metastatic castration-resistant prostate cancer (NM-CRPC) in adult men who are at high risk of developing metastatic disease and for the treatment of metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see SmPC for the full indication). It contains apalutamide as the active substance and it is given as an oral tablet.

Further information about the evaluation of ERLEADA's benefits can be found in ERLEADA's EPAR, including in its plain-language summary.

## II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of ERLEADA, together with measures to minimize such risks and the proposed studies for learning more about ERLEADA'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 (eg, 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 analyzed regularly, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of ERLEADA is not yet available, it is listed under 'missing information' below.

## II.A. List of Important Risks and Missing Information

Important risks of ERLEADA 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 ERLEADA. 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 (eg, on the longterm use of the medicine).

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | Seizures<br>Fall<br>Non-pathological fracture<br>Ischemic heart disease<br>Ischemic cerebrovascular disorders |
| Important potential risks | None |
| Missing information | Use in patients with severe hepatic impairment |

## II.B. Summary of Important Risks

| **Important Identified Risk: Seizures** | |
|---|---|
| Evidence for linking the risk to the medicine | In nonclinical studies in animals, apalutamide was given at high doses and seizures were observed. Seizures have also been reported in apalutamide clinical trials. As a precautionary measure, patients who had any prior history of seizure or had conditions that might predispose to seizures were excluded from clinical trials with apalutamide. Additionally, medications known to lower seizure threshold were also prohibited while on trial medication. Seizures are described in the current SmPC for ERLEADA. |
| Risk factors and risk groups | Some conditions that may predispose patients to seizures such as: infantile onset of seizures, masses or lesions in the brain, a prior history of seizures, or the use of certain medication that may lower the seizure threshold, may increase a patient's risk of seizures when administered ERLEADA. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.7<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Advice on the use of ERLEADA if a seizure develops is provided in SmPC Section 4.4 and PL Section 4<br>• Advice on the use of ERLEADA in patients with a history of seizures or other predisposing factors is provided in SmPC Section 4.4<br>• Warning to the use of ERLEADA with concomitant medicinal products that lower the seizure threshold is provided in SmPC Section 4.4 and PL Section 2<br>• Legal status<br>Additional risk minimization measures:<br>• None |

| **Important Identified Risk: Fall** | |
|---|---|
| Evidence for linking the risk to the medicine | Fall is considered an important identified risk, based on clinical trial data in men with NM-CRPC (Trial ARN-509-003).<br><br>In Trial ARN-509-003 (NM-CRPC population), 22.0% of apalutamide-treated subjects versus 9.5% of placebo-treated subjects experienced fall (clinical cut-off date of 1 February 2020).<br><br>In Trial PCR3002 (mHSPC population), fall occurred with a similar frequency in the apalutamide (9.4%) and placebo (7.4%) arm (clinical cut-off date of 07 September 2020).<br><br>Fall is described in the current SmPC for ERLEADA. |
| Risk factors and risk groups | Being older, being on prolonged ADT, potentially having impaired musculoskeletal function, and possibly being treated with multiple concomitant therapies, or having a combination of any of these variables, may place a patient at risk to fall. |
| Risk minimization measures | Routine risk minimization measures:<br><br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation to evaluate patients for fall risk is provided in SmPC Section 4.4 and PL Section 4<br>• A warning for patients to take extra care to reduce risk of fall is provided in PL Section 2<br>• Legal status<br><br>Additional risk minimization measures:<br><br>• None |
| **Important Identified Risk: Non-pathological fracture** | |
| Evidence for linking the risk to the medicine | Non-pathological fracture is considered an important identified risk, based on clinical trial data in men with NM-CRPC (Trial ARN-509-003).<br><br>In Trial ARN-509-003 (NM-CRPC population), 18.1% of apalutamide-treated subjects versus 7.5% of placebo-treated subjects reported fracture (clinical cut-off date of 1 February 2020).<br><br>In Trial PCR3002 (mHSPC population), fracture occurred for 10.3% of subjects in the apalutamide arm and 5.9% in the placebo arm (clinical cut-off date of 07 September 2020).<br><br>Non-pathological fracture is described in the current SmPC for ERLEADA. About half of the fractures reported in clinical trials (for both subjects treated with apalutamide and placebo) were reported within 7 days of a fall. |

| | |
|---|---|
| Risk factors and risk groups | Androgen deprivation therapy is associated with significant bone loss and increased risk for low trauma or fragility fractures; effects are cumulative with prolonged use of ADT. In addition, as fall is likely to increase the risk of fractures, the following risk factors for fall are also risk factors for fractures: being older, potentially having impaired musculoskeletal function, and possibly being treated with multiple concomitant therapies, or having a combination of any of these variables. |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation to evaluate patients for fracture risk is provided in SmPC Section 4.4 and PL Section 4<br>• Recommendation to monitor and manage patients at risk for fractures according to established treatment guidelines, and to consider use of bone targeted agents is provided in SmPC Section 4.4<br>• Legal status<br>Additional risk minimization measures:<br>• None |
| **Important Identified Risk: Ischemic heart disease** | |
| Evidence for linking the risk to the medicine | Ischemic heart disease is considered an important identified risk, based on clinical trial data in men with mHSPC (Trial PCR3002).<br>In Trial PCR3002 (mHSPC population), 5.9% of apalutamidetreated subjects versus 2.3% of placebo-treated subjects experienced ischemic heart disease; the exposure-adjusted incidence (events per 100 person-years) was 3.3 versus 1.6. In Trial ARN-509-003 (NM-CRPC population), ischemic heart disease was reported in 5.5% of apalutamide-treated subjects versus 2.8% of placebo-treated subjects; the exposure-adjusted incidence was numerically lower in the apalutamide arm (2.5) as compared with the placebo arm (3.6).<br>Ischemic heart disease is described in the current SmPC for ERLEADA. |
| Risk factors and risk groups | Risk factors for ischemic heart disease include hypertension, diabetes, and dyslipidemia. |

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation to monitor for signs and symptoms of ischemic heart disease is provided in SmPC Section 4.4, PL Section 2, and PL Section 4<br>• Recommendation to optimize management of risk factors for ischemic heart disease is provided in SmPC Section 4.4<br>• Advice for patients experiencing signs and symptoms of heart disease is provided in PL Section 2 and PL Section 4<br>• Legal status<br>Additional risk minimization measures:<br>• None |
| **Important Identified Risk: Ischemic cerebrovascular disorders** | |
| Evidence for linking the risk to the medicine | Ischemic cerebrovascular disorders is considered an important identified risk based on clinical trial data in men with NM-CRPC (Trial ARN-509-003).<br>In Trial ARN-509-003 (NM-CRPC population), 4.0% of apalutamide-treated subjects versus 1.0% of placebo-treated subjects experienced ischemic cerebrovascular disorders; the exposure-adjusted incidence (events per 100 person-years) was 1.9 versus 0.9. In Trial PCR3002 (mHSPC population), ischemic cerebrovascular disorders were reported for 2.5% of subjects in the apalutamide group and 2.3% of subjects in the placebo group; the exposure-adjusted incidence was numerically the same for the apalutamide (1.3) and the placebo (1.3) arms.<br>Ischemic cerebrovascular disorders is described in the current SmPC for ERLEADA. |
| Risk factors and risk groups | Risk factors for cerebrovascular disorders include hypertension, diabetes, and dyslipidemia. |

| | |
|---|---|
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.4<br>• SmPC Section 4.8<br>• PL Section 2<br>• PL Section 4<br>• Recommendation to monitor for signs and symptoms of ischemic cerebrovascular disorders is provided in SmPC Section 4.4, PL Section 2, and PL Section 4<br>• Recommendation to optimize management of risk factors for cerebrovascular disorders is provided in SmPC Section 4.4<br>• Advice for patients experiencing signs and symptoms of stroke or mini-stroke is provided in PL Section 2 and PL Section 4<br>• Legal status<br>Additional risk minimization measures:<br>• None |
| **Missing Information: Use in patients with severe hepatic impairment** | |
| Risk minimization measures | Routine risk minimization measures:<br>• SmPC Section 4.2<br>• SmPC Section 5.2<br>• Legal status<br>Additional risk minimization measures:<br>• None |
| Additional pharmacovigilance activities | Additional pharmacovigilance activities:<br>• 56021927PCR1026<br>Final report: 31 January 2026<br>See section II.C of this summary for an overview of the post-authorization development plan. |

## II.C. Post-authorization Development Plan

### II.C.1. Studies Which are Conditions of the Marketing Authorization

Not applicable.

### II.C.2. Other Studies in Post-authorization Development Plan

**56021927PCR1026**

Purpose of the study: To characterize the single dose PK and safety of apalutamide in subjects with severe hepatic impairment relative to subjects with normal hepatic function.