Summary of the Risk Management Plan for NUBEQA®

Active substance: Darolutamide

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NUBEQA®
(Darolutamide)
Risk Management Plan
Summary of the risk management plan

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 NUBEQA® 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 NUBEQA® in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. Bayer (Schweiz) AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of NUBEQA®.

Summary of risk management plan for Nubeqa (Darolutamide)

This is a summary of the RMP for Nubeqa. A Risk Management Plan (RMP) details important risks, how these risks can be minimised, and how more information will be obtained about these risks and uncertainties (missing information).

Nubeqa's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Nubeqa should be used.

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

I. The medicine and what it is used for

Nubeqa is authorised for the treatment of adult men with non-metastatic castration resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (see SmPC for the full indication) and for the treatment of adult men with metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel. It contains darolutamide as the active substance and it is administered orally.

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

II. Risks associated with the medicine and activities to minimise or further characterise the risks

No important identified risks are known for Nubeqa at this point in time. All identified risks are classified as non-important and are managed by the following *routine risk minimisation measures*:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- The medicine's legal status — the way a medicine is supplied to the patient (*e.g.*, with or without prescription) can help to minimise its risks.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, 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 Nubeqa is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Nubeqa are risks that need special risk management activities to further investigate or minimise 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 Nubeqa. 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).

Table Part VI.1: Summary of safety concerns

List of important risks and missing information	
Important identified risks	• None
Important potential risks	• Adverse drug reactions resulting from increased exposure in patients with severe hepatic impairment • Cardiovascular events in patients with significant cardiovascular history
Missing information	• Use in patients with severe renal impairment • Carcinogenicity potential

II.B Summary of important risks

Important potential risk: ADRs resulting from increased exposure in patients with severe hepatic impairment	
Evidence for linking the risk to the medicine	It is uncertain whether patients with moderate to severe hepatic impairment may be at higher risk of adverse drug reactions (ADRs) when exposed to darolutamide in comparison to general target population. Patients with active viral hepatitis, active human immunodeficiency virus (HIV), chronic liver disease or with screening values of serum alanine aminotransferase (ALT) and aspartate transaminase (AST) ≥2.5 x ULN, total bilirubin ≥1.5 x ULN (except patients with a diagnosis of Gilbert's disease) were not eligible for inclusion in the pivotal phase III Studies 17712 (ARAMIS) and 17777 (ARASENS). Based on the single dose data in non-cancer patients a 1.9-fold increase in darolutamide exposure AUC (0-48) was observed in 9 subjects with moderate hepatic impairment compared to 10 healthy, age- and body weight-matched subjects (Study 17721, using Child-Pugh categorisation system for hepatic impairment).

Important potential risk: ADRs resulting from increased exposure in patients with severe hepatic impairment	
Risk factors and risk groups	Patients with impaired hepatic function.
Risk minimisation measures	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.8 Undesirable effects SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Important potential risk: Cardiovascular events in patients with significant CV history	
Evidence for linking the risk to the medicine	The androgen deprivation therapy (ADT) associated changes in body composition, lipids, and insulin sensitivity are suspected to increase the risk for diabetes and cardiovascular disorders in prostate cancer patients. The overall evidence is, however, conflicting and the relationship between ADT and cardiovascular disorders remains unclear. Patients with recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the pivotal clinical Study 17712. It is uncertain whether patients with the medical history of recent significant cardiovascular events may be at higher risk for cardiovascular disorders (progression) in association with darolutamide exposure.
Risk factors and risk groups	Patients with clinically significant cardiovascular disease in the past 6 months including stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and congestive heart failure NYHA Class III or IV.

Important potential risk: Cardiovascular events in patients with significant CV history	
Risk minimisation measures	**Routine risk communication** SmPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Missing information: Use in patients with severe renal impairment	
Risk minimisation measures	**Routine risk communication** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warnings and precautions for use SmPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** SmPC section 4.2 Posology and method of administration SmPC section 4.4 Special warning and precautions for use **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None

Missing information: Carcinogenicity potential	
Risk minimisation measures	**Routine risk communication** SmPC section 5.3 Preclinical safety data **Routine risk minimisation activities recommending specific clinical measures to address the risk** None proposed **Other routine risk minimisation measures beyond the Product Information** Nubeqa is a prescription-only medicine **Additional risk minimisation measures** None
Additional pharmacovigilance activities	Non-clinical study to assess the carcinogenic potential in mice (Category III)

II.C Post-authorisation development plan

Non-clinical study

Purpose of the study: To assess the carcinogenic potential of darolutamide in mice.

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Nubeqa.

II.C.2 Other studies in post-authorisation development plan

Category 3 - Studies to assess the carcinogenic potential in mice

Study short name and title:

- 28-Day oral Range Finding Toxicity Study in CByB6F1-Tg(HRAS)2Jic Wild Type [rasH2] Transgenic Mice
- 26-Week i.g. Oncogenicity Study in CByB6F1 Tg(HRAS)2Jic Mice

Rationale and study objectives:

The 4-week pilot study in wild type mice is performed to get data on the safety profile and toxicokinetics in this strain of mice in order to support dose selection for the pivotal study in CByB6F1-Tg (HRAS)2Jic Mice. The pilot study assesses general tolerability based on body weight, clinical pathology and necropsy data. In addition, toxicokinetics are evaluated for the dose levels tested. The pivotal study over 26-weeks is performed to assess the

carcinogenic potential of darolutamide in CByB6F1-Tg(HRAS)2Jic Mice. In the main study, tumour incidence will be assessed in darolutamide-treated CByB6F1 Tg (HRAS)2Jic Mice compared to a vehicle control group.