Summary of the Risk Management Plan for Nubeqa®

Active substance: Darolutamide

Version number: version 2.0

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Based on the EU-RMP v1.1 dated 17-June-2020 for Nubeqa®

NUBEQA®
(Darolutamide)
Risk Management Plan

Summary of activities in 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®.

List of abbreviations

ADR	Adverse drug reaction
ADT	Androgen deprivation therapy
ALT	Alanine aminotransferase
AST	Aspartate transaminase
AUC(0-48)	Area under the plasma concentration time curve from 0 to 48 hours post dose
CV	Cardiovascular
EMA	European Medicines Agency
EPAR	European Public Assessment Report
HIV	Human immunodeficiency virus
INN	International Nonproprietary Names
nmCRPC	Non-metastatic castration-resistant prostate cancer
NYHA	New York Heart Association
RMP	Risk Management Plan
SPC	Summary of Product Characteristics
ULN	Upper limit of normal

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1. Summary of Risk Management Plan (RMP) for NUBEQA® (darolutamide)

This is a summary of the RMP for NUBEQA®. An 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 (SPC) 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.

2. 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 SPC for the full indication). 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: https://www.ema.europa.eu/en/medicines/human/EPAR/nubeqa.

3. 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 SPC 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.

3.1 List of Important Risks and Missing Information

Table 1: Summary of safety concerns

Important identified risks	• None
Important potential risks	• ADRs resulting from increased exposure in patients with severe hepatic impairment • Cardiovascular events in patients with significant CV history
Missing information	• Use in patients with severe renal impairment • Carcinogenicity potential

3.2 Summary of Important Risks and Missing Information

Important potential risk: Use in patients with severe and moderate 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 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 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 study 17712 (ARAMIS). 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 categorization system for hepatic impairment).
Risk factors and risk groups	Patients with impaired hepatic function.
Risk minimisation measures	**Routine risk communication for informed decision-making** • SPC section 4.2 Posology and method of administration • SPC section 4.8 Undesirable effects

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Important potential risk: Use in patients with severe and moderate hepatic impairment	
	• SPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** • SPC section 4.2 Posology and method of administration • SPC 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: Use in patients with significant cardiovascular history	
Evidence for linking the risk to the medicine	The 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 New York Heart Association (NYHA) Class III or IV.

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Important potential risk: Use in patients with significant cardiovascular history	
Risk minimisation measures	**Routine risk communication for informed decision-making** • SPC section 5.1 Pharmacodynamic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** • SPC section 4.2 Posology and method of administration • SPC 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 for informed decision-making** • SPC section 4.2 Posology and method of administration • SPC section 5.2 Pharmacokinetic properties **Routine risk minimisation activities recommending specific clinical measures to address the risk** • SPC section 4.2 Posology and method of administration • SPC 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

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Missing information: Carcinogenicity potential	
Evidence for linking the risk to the medicine	No carcinogenicity studies were conducted in accordance with the recommendations in the ICH S9 guideline since the proposed indication is for advanced cancer. Furthermore, the results of chronic repeat-dose toxicity studies in male and female rats and dogs at multiples up to 4 to 5-fold the therapeutic exposure did not show signs of off-target toxicity or proliferative tissue lesions indicative of a risk of secondary neoplasias following prolonged treatment with darolutamide. Also, darolutamide did not show relevant genotoxicity in a standard package of *in vitro* and *in vivo* studies. Therefore, further animal studies for the assessment of a potential carcinogenicity of darolutamide were not originally considered warranted. In order to further assess the carcinogenic potential of darolutamide, additional pharmacovigilance activities are proposed in non-clinical species. The proposed Category 3 study (A study to assess the carcinogenic potential in mice) will evaluate the effects of daily oral administration of darolutamide for a period of 6 months in tg-rasH2 transgenic mouse model.
Risk minimisation measures	**Routine risk communication for informed decision-making** • SPC 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)

3.3 Post-Authorisation Development Plan

Clinical study 17712 (ARAMIS)

Purpose of the study: to further investigate the efficacy of darolutamide in adult men with non-metastatic castration resistant prostate cancer who are at high risk of developing metastatic disease, the MAH should submit the final study report, including overall survival results.

Non-clinical study

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