Date: 28 August 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

NUBEQA

International non-proprietary name: darolutamidum
Pharmaceutical form: film-coated tablet
Dosage strength: 300 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Bayer (Schweiz) AG
Marketing Authorisation No.: 67521
Decision and Decision date: approved on 19 June 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADME	Absorption, Distribution, Metabolism, Elimination
ADT	Androgen Deprivation Therapy
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AR	Androgen receptor
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
AV	Atrioventricular
BICR	Blinded independent central review
BID	Twice a day
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ECOG	Eastern Cooperative Oncology Group
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
GnRH	Gonadotropin-Releasing Hormone
HR	Hazard ratio
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MFS	Metastasis free survival
Min	Minimum
N/A	Not applicable
nmCRPC	Non-Metastatic Castration-Resistant Prostate Cancer
NO(A)EL	No Observed (Adverse) Effect Level
OS	Overall survival
PD	Pharmacodynamics
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSA	Prostate specific antigen
PSADT	PSA doubling time
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SAE	Severe adverse event
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)
TEAE	Treatment-emergent adverse event
VCaP	Vertebral-Cancer of the Prostate

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance darolutamide of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

NUBEQA, in combination with androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with non-metastatic, castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastases (in particular, PSADT ≤10 months).

2.2.2 Approved Indication

NUBEQA, in combination with androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (in particular PSADT ≤10 months; see "Clinical efficacy").

2.2.3 Requested Dosage

Patients receiving NUBEQA should also receive a gonadotropin-releasing hormone (GnRH) analogue concurrently or should have had bilateral orchiectomy.
The recommended dose is 600 mg darolutamide (two film-coated tablets of 300 mg) taken twice daily, equivalent to a total daily dose of 1200 mg.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	12 April 2019
Formal control completed	8 May 2019
List of Questions (LoQ)	9 September 2019
Answers to LoQ	5 November 2019
Predecision	24 January 2020
Answers to Predecision	24 March 2020
Final Decision	19 June 2020
Decision	approval

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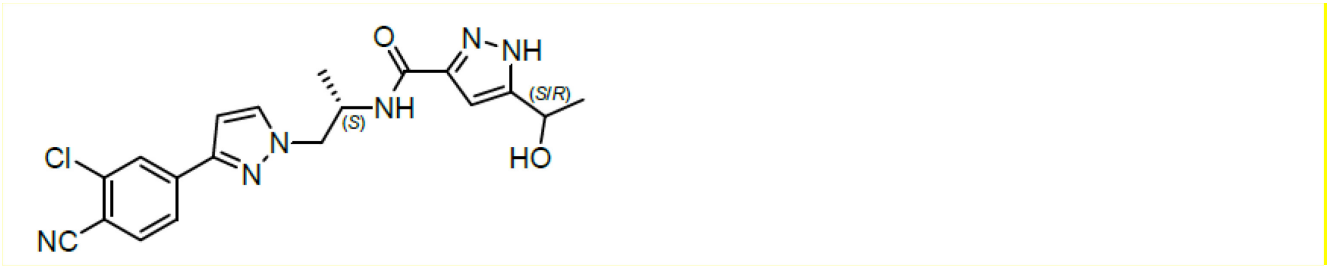
3 Medical Context

Prostate cancer is the second most common cancer in men and the third and second leading cause of cancer mortality in men in Europe and the US, respectively. In the non-metastatic castration-resistant prostate cancer (nmCRPC) patient population, the development of metastases is a major cause of complications and death. About 30% of patients with nmCRPC will develop bone metastases within 2 years, with a median overall survival (OS) of ~4 years.
Recently, FDA, EMA and Swissmedic approved other androgen receptor (AR) inhibitors for nmCRPC for the same clinical setting.

4 Quality Aspects

4.1 Drug Substance

INN:	Darolutamide
Chemical name:	N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide
Molecular formula:	$C_{19}H_{19}ClN_6O_2$
Molecular mass:	398.85g/mol
Molecular structure:	



Darolutamide is a white to greyish- or yellowish-white powder and is not hygroscopic. Crystal form I is the thermodynamically stable polymorph at ambient conditions. Darolutamide milled drug substance is a mixture of diastereomers (*S;S*)-darolutamide and (*S;R*)-darolutamide. The synthesis pathway consistently provides a 1:1 mixture of the two diastereomers. Darolutamide is categorised as a Class II drug substance (low solubility and high permeability) according to the Biopharmaceutics Classification System.
The drug substance is manufactured by a multiple-step chemical synthesis with final isolation by crystallisation. The crystallised product is milled to obtain darolutamide milled.
The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities and particle size.
Appropriate stability data have been presented and justify the established re-test period.

4.2 Drug Product

The drug product is presented as a white to off-white film-coated tablet for oral administration with a dosage strength of 300 mg darolutamide. The tablet has an oval shape and is marked “BAYER” on one side and “300” on the other side.
The composition of the drug product is adequately described, both qualitatively and quantitatively.
Suitable pharmaceutical development data have been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.

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Adequate validation data pertaining to the commercial manufacturing process will be available before marketing.

The drug product specification covers relevant physicochemical characteristics; identification, assay and purity tests are included as well. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.

The drug product tablets are packaged in blisters made of PVC and an aluminium foil.

Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a distinct assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

The applicant considered the recommendations outlined in ICH S9 for the nonclinical testing strategy. Pivotal safety pharmacology and toxicology studies were performed in compliance with GLP regulations.

5.1 Pharmacology

Darolutamide is a small molecule inhibitor of the androgen receptor. Darolutamide is a 1:1 mixture of two diastereomers, (*S,R*)-darolutamide and (*S,S*)-darolutamide, which are both pharmacologically active. The major metabolite of darolutamide, keto-darolutamide, has also a comparable pharmacological potential.

In vitro, darolutamide selectively bound to rat AR (Ki value of 9.1 nM) and antagonised human AR with an IC_{50} value of 65 nM. The compound inhibited the growth of androgen-sensitive VCaP prostate cancer cells with an IC_{50} of 500 nM.

In vivo, darolutamide inhibited testosterone-induced growth of androgen-sensitive tissues (prostate and seminal vesicles) in immature rats demonstrating antiandrogenic properties. The compound also showed antitumour activity in two VCaP xenograft tumour models in mice and lowered the serum prostate specific antigen (PSA).

Secondary pharmacology studies with darolutamide, (*S,R*)-darolutamide, (*S,S*)-darolutamide, or keto-darolutamide raised no safety concerns with respect to potential off-target effects.

Darolutamide, (*S,R*)-darolutamide, (*S,S*)-darolutamide, and keto-darolutamide were evaluated in *in vitro* and *in vivo* safety pharmacology studies to assess potential cardiovascular, respiratory and gastrointestinal effects. The central nervous system effects, as well as the arterial blood pressure and electrocardiogram (ECG) findings for darolutamide, were integrated as endpoints in the repeated-dose toxicity studies in dogs. Overall, no adverse effects on the central nervous, respiratory, cardiovascular or gastrointestinal systems were observed.

No nonclinical pharmacodynamic drug interaction studies were performed.

5.2 Pharmacokinetics

The pharmacokinetic profile of darolutamide, (*S,R*)-darolutamide, (*S,S*)-darolutamide, and keto-darolutamide following intravenous or oral administration was adequately evaluated in the rats and dogs used in the toxicology studies.

Darolutamide was completely absorbed after oral administration in rats (100%). In dogs, however, the bioavailability was below 20%, but could be increased with food. Rats, with a half-life of 4 hours, rapidly eliminated Darolutamide and both diastereoisomers (ratio 1:1). In dogs, the plasma elimination half-life was 7 hours for darolutamide and both diastereoisomers (ratio 9:1). The metabolite keto-darolutamide was eliminated from plasma with half-lives of 3.5 and 7.9 hours in rats and dogs, respectively. In humans, the absolute bioavailability reached approximately 30%, and the half-life was 12 hours at steady state. The (*S,R*)-darolutamide and (*S,S*)-darolutamide ratio in humans is 1:6.

Following repeated daily dosing in rats and dogs, no accumulation occurred. The systemic exposure to darolutamide in both species increased less than dose-proportionally and was lower in males than in females.

Tissue distribution in rats after oral administration of ^{14}C-darolutamide was rapid and extensive. The tissue/blood ratio was moderate (0.75) and low (0.079) in prostate and brain, respectively. All examined tissues were exposed to the major metabolite keto-darolutamide, with a lower tissue/plasma ratio compared to darolutamide.

The *in vitro* metabolic profile of darolutamide was investigated in hepatocytes of rats, dogs, and humans. Glucuronidation and oxidation are the primary metabolic pathways. The oxidation of darolutamide to keto-darolutamide is catalysed mainly by CYP3A4 and, to a lesser extent, by CYP1A1. Keto-darolutamide was shown to be the most abundant metabolite in hepatocytes of humans, rodents,

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and dogs. No unique metabolites were identified in human hepatocytes. *In vivo*, darolutamide and keto-darolutamide were identified as the major circulating drug-derived entities in the plasma of rats and humans, and these were also identified in dog plasma. Metabolism is the main route of elimination of darolutamide, and the major route of excretion is via the faeces in rats. Urinary excretion is the major route of elimination in humans.

No studies were performed to investigate the placental transfer and passage into milk.

5.3 Toxicology

The toxicity studies were conducted in rats and dogs, as the metabolic profile in humans was adequately represented in both species. The route of administration (i.e. oral) and the twice-daily dosing schedule were as intended for clinical use.

The toxicological profile was adequately investigated in studies for up to 26 weeks in rats (doses: 0, 100, 300, and 1000 mg/kg/day) and 39 weeks in dogs (doses: 0, 50, 150 and 400 mg/kg/day) with repeated oral gavage administration. Administration of darolutamide to rats and dogs resulted in fully or partially reversible non-adverse atrophic changes in the genital organs, consistent with the anti-androgenic activity of darolutamide. The observed effects on reproductive organs at 0.6 and 1 times the human exposure based on AUC, included decreased weight of prostate and epididymides with corresponding microscopic changes (atrophy). Based on these findings and its mechanism of action, darolutamide may impair fertility in males of reproductive potential. Atrophy of seminal vesicles and mammary glands, and increased vacuolation of the pars anterior of the pituitary (feedback effect) were observed in rats, while an increase in testicular weights, with tubular luminal sperm accumulation was observed in dogs. No noteworthy findings (clinical signs, clinical pathology and pathology) were observed in female rats and dogs. No off-target toxicities were noted.

Darolutamide tested negative for genotoxic potential *in vitro* and *in vivo*.

No carcinogenicity studies have been conducted for darolutamide in accordance with ICH S9 guidance.

Consistent with the ICH S9 guideline, neither a study of fertility and early embryonic development nor a study for effects on pre- and postnatal development have been conducted. Any risks were adequately reflected in the information for healthcare professionals, and the recommendations are considered appropriate.

Considering the requested indication, the low safety margins are acceptable.

There are no safety concerns regarding excipients and impurities or degradants. Potential impurities in drug substance and drug product are sufficiently qualified and adequately controlled.

The risk for phototoxicity is considered low based on an *in vitro* phototoxicity assay.

Based on the ERA, the risk for the environment is low.

The Nonclinical Safety Specifications in the RMP adequately address the nonclinical findings and their relevance for clinical use.

Darolutamide is not intended for use in a paediatric population. EMA/PDCO granted a class waiver.

5.4 Nonclinical conclusions

In conclusion, the pharmaco-toxicological profile of darolutamide is considered sufficiently characterised. The submitted nonclinical documentation supports the approval of Nubeqa for the applied indication. The safety margins are low but acceptable, considering the requested indication. All relevant safety concerns are listed in the Nonclinical Safety Specifications of the RMP and adequately reflected in the Information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The available assessment reports and respective product information from the US FDA were used as a basis for the clinical pharmacology evaluation.

6.2 Dose Finding and Dose Recommendation

Darolutamide is formulated at an appropriate tablet strength (300 mg), requiring two units per dosing. Clinically, darolutamide has been studied in the dose range of 100 to 900 mg b.i.d. in the dose-escalation and dose-finding study 17829 (ARADES). Dose linearity of the pharmacokinetic parameters was observed after single and repeated administration in the dose range of 100 to 700 mg darolutamide b.i.d.
A dose-related response was seen in the chemo-/CYP17i-naïve subgroup, with a higher percentage of patients in the 700 mg b.i.d. dose group achieving a decline in PSA (85.7%) compared to the lower dose groups of 100 mg (45.5%) and 200 mg b.i.d. (69.2%), indicating that the higher dose is more efficacious than the lower doses in this patient population.
The b.i.d. dosing was selected based on the half-life of darolutamide to ensure concentrations of darolutamide and its major metabolite at the target tissue during the entire dosing interval that result in sufficient occupation of the androgen receptor.

6.3 Efficacy

The single pivotal study ARAMIS (NCT02200614) was a multicentre, double-blind, placebo-controlled clinical trial in 1509 patients with nmCRPC with a PSADT of ≤ 10 months and PSA ≥2 ng/ml. Randomisation was stratified by PSADT and the use of bone-targeted therapy at study entry. Patients with pelvic lymph nodes less than 2 cm in short axis below the aortic bifurcation were allowed to enter the study. Absence or presence of metastasis was assessed by blinded independent central review (BICR). Patients were randomised 2:1 to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554). Treatment continued until radiographic disease progression as assessed by BICR, unacceptable toxicity or withdrawal. All patients received concurrent administration of a GnRH analogue or had undergone a bilateral orchiectomy. The patient demographics and disease characteristics were adequately balanced between treatment arms.

The primary efficacy endpoint was metastasis-free survival (MFS), defined as the time from randomisation to the time of first evidence of BICR-confirmed distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Distant metastasis was defined as new bone or soft tissue lesions or enlarged lymph nodes above the aortic bifurcation. OS and time to pain progression were key secondary efficacy endpoints.

The provided interim analysis (data cut-off 03.09.2018) led to the following results:

Primary Endpoint
Treatment with darolutamide resulted in a statistically significant and clinically meaningful improvement in MFS.

- In the darolutamide arm, the median MFS was 40.37 months (95% CI: [34.33; A]) with 23% MFS events and, in the placebo arm, 18.43 months (95% CI: [15.51; 22.34]) and 39%, respectively. The MFS benefit was clinically meaningful with 22 months.
- Darolutamide treatment led to a 58.7% reduction in the risk of metastases or death (HR 0.413; 95% CI 0.341 - 0.500; p<0.000001).
- The MFS benefit was observed across pre-specified subgroups, including age, geographic region, presence of pathologic lymph nodes, baseline ECOG status, race or ethnicity, number of prior hormonal therapies, Gleason score at baseline, PSA at baseline, PSADT at randomisation and use of osteoclast-targeted therapy at randomisation.

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Secondary Endpoint
The secondary efficacy variables were analysed with a hierarchical gatekeeping procedure in the aforementioned order using an alpha spending function. At the time of interim analysis, the OS data were immature, with the occurrence of 8.2% (N=78) and 10.5% (N=58) OS events in the darolutamide and placebo arms, respectively.

The MFS data were supported by a delay in the time to pain progression, defined as at least a 2-point worsening from baseline in the pain score on the Brief Pain Inventory-Short Form or initiation of opioids, in patients treated with darolutamide as compared to placebo (HR = 0.647; 95% CI: [0.533; 0.785], p = 0.000008). Pain progression was reported in 28% of all study subjects.

Uncertainty in the knowledge of the beneficial effects
Since the OS data were immature, demonstration of clinical benefit relied on improved MFS.

6.4 Safety

Darolutamide + ADT was administered to 954 study subjects in the ARAMIS study and 173 in uncontrolled Phase 1 and 2 studies. In the ARAMIS study, the median duration of treatment in the darolutamide arm was 14.80 months and, in the placebo arm, 11.04 months. The median follow-up time from randomisation to the last contact or death was 18.43 months (range: 0.1 to 46.0 months) and 16.80 months (range: 0.1 to 45.6 months), respectively.

The incidence of TEAEs in the darolutamide arm was 83.2% and, in the placebo arm, 76.9%. TEAEs leading to permanent discontinuation of study treatment was comparable in both treatment arms (8.9% vs. 8.7%, respectively). Adverse drug reactions identified for darolutamide included fatigue (very common), pain in extremity (common) and rash (common) (severity: grade 1 - 2). Additionally, darolutamide treatment was associated with laboratory test abnormalities, including AST ↑, neutrophil count ↓ and bilirubin ↑ (severity: grade 1 – 2).

Grade 3 – 4 TEAEs were reported in 24.7% and 19.5% of study subjects in the darolutamide and placebo treatment arms, respectively. Grade 3 TEAEs occurring in ≥ 1% of study subjects were hypertension (3.1% darolutamide vs. 2.2% placebo), urinary retention (1.6% vs. 2.0%) and haematuria (1.0% vs. 1.3%).
Grade 4 TEAEs occurred in 2.2% and 1.6% of study subjects in the darolutamide and placebo treatment arms, respectively. The most often reported grade 4 TEAEs in the darolutamide arm were acute myocardial infarction, hyperglycaemia, ischaemic stroke and respiratory failure, with an incidence of 0.2% each. None of these TEAEs were reported in the placebo arm.

Treatment-emergent SAEs occurred in 24.8% and 20.0% of study subjects in the darolutamide and placebo treatment arms, respectively. SAEs reported in ≥ 1% of study subjects were urinary retention (1.6% darolutamide vs. 3.2% placebo), pneumonia (1.4% vs. 1.1%) and haematuria (1.0% vs. 1.1%).

Grade 5 fatal TEAEs occurred in 3.9% and 3.2% of study subjects in the darolutamide and placebo treatment arms, respectively. Fatal TEAEs were death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for darolutamide. Drug-related grade 5 TEAEs occurred in 0.1% of study subjects in the darolutamide arm (one subject with a small intestinal perforation) and 0.4% of study subjects in the placebo arm (one subject each with myocardial infarction and intracranial haemorrhage).

Uncertainty in the knowledge of the unfavourable effects

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No significant QTc-prolongation was observed in an ARAMIS substudy. However, AV-block occurred in one of four dogs after darolutamide bolus administration.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Darolutamide is the third second-generation AR-inhibitor for nmCRPC with a high risk of metastatic disease (PSADT ≤10 months). The ARAMIS study used MFS as primary endpoint and placebo + ADT as control arm. The chosen design of the ARAMIS study was acceptable and in line with other AR inhibitors approved in Switzerland.

The primary endpoint of the ARAMIS study was met, demonstrating an MFS benefit with darolutamide of 22 months and a 58.7% reduction in the risk of developing metastases or death. The MFS data were supported by a significant delay in time to pain progression. The data for the secondary endpoint OS were immature.

The adverse drug reactions identified for darolutamide, i.e. fatigue, pain in extremity and rash, were generally mild and clinically manageable. The data from the ARAMIS study indicate that treatment with darolutamide appears not to be associated with an increase of the risk of specific safety concerns, including fracture, falls, seizure, mental impairment and hypertension. Incidences of all TEAEs were below 10%, except fatigue. In an ARAMIS QT/QTc substudy, no significant QTc-prolongation was detected. The design of the QT/QTc study did not conform to ICH E14 (no positive control and supratherapeutic dose).

In conclusion, the data indicate that the benefits of darolutamide in patients with nmCRPC outweigh the risks. Consequently, the risk / benefit for darolutamide is regarded as favourable.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Nubeqa was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

NUBEQA®

Composition

Active substances

Darolutamide.

Excipients

Calcium hydrogen phosphate, croscarmellose sodium (made from genetically modified cotton) equivalent to sodium 2.7 mg, lactose monohydrate 186 mg, magnesium stearate, povidone K 30, hypromellose 15 cP, macrogol 3350, titanium dioxide (E171) per film-coated tablet.

Pharmaceutical form and active substance quantity per unit

White to off-white, oval film-coated tablets with a length of 16 mm and a width of 8 mm, marked with “300” on one side and “BAYER” on the other side.
Each film-coated tablet contains 300 mg of darolutamide.

Indications/Uses

NUBEQA, in combination with androgen deprivation therapy (ADT), is indicated for the treatment of adult patients with non-metastatic castration-resistant prostate cancer (nmCRPC) who are at high risk of developing metastatic disease (in particular PSADT ≤10 months; see “Clinical efficacy”).

Dosage/Administration

Usual dosage

NUBEQA is for oral use. The recommended dose is 600 mg (two film-coated tablets of 300 mg) darolutamide twice daily, equivalent to a total dose of 1200 mg per day.
The tablets should be taken whole with food (see “Pharmacokinetics” section).
Patients taking NUBEQA should also receive a gonadotropin-releasing hormone (GnRH) analogue concurrently or should have had a bilateral orchiectomy.
If a NUBEQA dose is missed, the dose should be taken as soon as the patient remembers prior to the next scheduled dose. If a dose is missed, the patient should not take two doses at the same time to make up for a missed dose.

Dose adjustment following undesirable effects/interactions

If a patient experiences a ≥ grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Treatment may then be resumed at a dose of 600 mg twice daily.
Dose reduction below 300 mg twice daily is not recommended. The maximum effective daily dose is the recommended dose of 600 mg twice daily (see “Pharmacokinetics” section).

Special dosage instructions

Patients with impaired hepatic function

No clinically relevant increase in darolutamide exposure has been observed in patients with moderate hepatic impairment (Child-Pugh B) (see “Pharmacokinetics” section). No dose adjustment is necessary for patients with mild to moderate hepatic impairment.
The effects of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of darolutamide are unknown.

Patients with impaired renal function

An analysis of data from patients with nmCRPC and cancer-free subjects showed no clinically relevant increase in darolutamide exposure in patients with mild, moderate or severe (estimated glomerular filtration rate [eGFR] 15 to 89 mL/min/1.73 m^2) renal impairment (see “Pharmacokinetics” section). No dose adjustment is necessary for patients with mild, moderate or severe renal impairment.
The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m^2).

Elderly patients

In clinical studies no clinically relevant differences in safety and efficacy were seen between elderly patients aged 65-74 years, 75-84 years or ≥85 years and younger patients (<65 years). No dose adjustment is therefore necessary for elderly patients (see “Pharmacokinetics” section).

Children and adolescents

The safety and efficacy of NUBEQA in children and adolescents under 18 years of age have not been established.

Genotype/genetic polymorphism

No clinically relevant differences were observed between ethnic groups. No dose adjustment is necessary based on ethnicity (see “Pharmacokinetics” section).

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- In women who are pregnant or may become pregnant.

Warnings and precautions

ADT may prolong the QT interval

In patients with risk factors such as a history of QT prolongation, torsade de pointes, hypokalaemia or in patients receiving treatment with medicinal products that prolong the QT interval, consideration should be given to ECG monitoring at treatment initiation and periodically during treatment.

Contraception in males and females

If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method should be used during treatment with NUBEQA and for 1 week after completion of treatment in order to prevent pregnancy.
If the patient is engaged in sexual activity with a pregnant woman, a condom must be used during treatment with NUBEQA and for 1 week after completion of treatment. Exposure of the unborn child to an androgen receptor inhibitor through seminal transfer to the pregnant woman must be avoided, as this could affect development of the unborn child.

Change in bone mineral density

Bone mineral density has not been assessed in clinical studies of darolutamide. Long-term testosterone suppression during treatment with darolutamide is expected to have an impact on bone mineral density. Decreases in bone mineral density have been reported during treatment with GnRH agonists and in patients who underwent orchiectomy.
This medicinal product contains less than 1 mmol of sodium (23 mg) per dose to be taken (2 film-coated tablets), that is to say, it is essentially ‘sodium-free’.
Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not use this medicinal product.

Interactions

Effect of NUBEQA on other medicinal products

Breast cancer resistance protein (BCRP) substrates
Darolutamide is an inhibitor of BCRP.
Administration of darolutamide (600 mg twice daily for 5 days) prior to co-administration of a single dose of rosuvastatin (5 mg) together with food resulted in approximately 5-fold increase in mean exposure (AUC) and C_{max} of rosuvastatin.

This suggests that co-administration of NUBEQA may increase the plasma concentrations of other BCRP substrates (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). The related recommendation in the Information for Healthcare Professionals of the BCRP substrate should therefore be followed when co-administered with NUBEQA.

P-glycoprotein (P-gp) substrates

Co-administration of darolutamide together with the sensitive P-gp substrate dabigatran etexilate did not reveal any increase in dabigatran exposure (AUC and C_{max}).

This suggests that NUBEQA may be co-administered with P-gp substrates without any clinically relevant drug-drug interactions.

CYP substrates

Darolutamide is a mild inducer of CYP3A4. Administration of darolutamide (600 mg twice daily for 9 days) prior to co-administration of a single dose of the sensitive CYP3A4 substrate midazolam (1 mg) together with food decreased the mean exposure (AUC) and C_{max} of midazolam by 29% and 32%, respectively.

Darolutamide did not inhibit the metabolism of selected CYP substrates *in vitro* at clinically relevant concentrations.

This suggests that NUBEQA may be co-administered with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole) without any clinically relevant drug-drug interactions.

Effect of other medicinal products on NUBEQA

CYP3A4 and P-gp inducers

Darolutamide is a substrate of CYP3A4 and P-gp.

Repeated co-administration of rifampicin (600 mg), a strong CYP3A4 inducer and a P-gp inducer, with a single dose of darolutamide (600 mg) together with food resulted in a 72% decrease in mean exposure [AUC(0-72)] and a 52% decrease in C_{max} of darolutamide.

Use of strong CYP3A4 inducers and P-gp inducers (e.g. carbamazepine, phenobarbital, St. John's Wort) during treatment with NUBEQA should be avoided. Selection of an concomitant medicinal product with no or weak potential to induce CYP3A4 or P-gp should therefore be considered.

CYP3A4, P-gp and BCRP inhibitors

Darolutamide is a substrate of CYP3A4, P-gp and BCRP.

Co-administration of itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days), a strong CYP3A4, P-gp and BCRP inhibitor, with a single dose of darolutamide (600 mg on day 5 together with food) resulted in a 1.7-fold increase in mean exposure [AUC(0-72)] and a 1.4-fold increase in C_{max} of darolutamide.

Patients should be monitored more frequently for adverse reactions; the NUBEQA dose should be modified as needed.

In vitro studies

Darolutamide is an inhibitor of OATP1B1 and OATP1B3 *in vitro*.

Pregnancy, lactation

Pregnancy

NUBEQA is not indicated for treatment of women. Based on its mechanism of action, NUBEQA may cause foetal harm when used during pregnancy. No clinical data are available on use in pregnant patients. No animal reproduction and development studies have been performed with NUBEQA.

Lactation

NUBEQA is not indicated for treatment of women. No data are available as to whether darolutamide or its metabolites are excreted in human milk or whether these may have effects on a breast-fed infant or milk formation.

Fertility

There are no human data on the effect of NUBEQA on fertility.
Animal studies have shown that darolutamide impairs the reproductive system in male rats and dogs (see “Preclinical data” section).

Effects on ability to drive and use machines

No studies on the effects of darolutamide on the ability to drive and use machines have been performed. Fatigue has been observed (very commonly) during treatment with darolutamide. Patients with such symptoms should be alerted to the risk regarding their ability to drive or use machines.

Undesirable effects

The overall safety profile of NUBEQA is based on data from 1508 patients from the ARAMIS study, 954 of whom had received at least one dose of NUBEQA.
The most frequently observed adverse reaction in patients taking NUBEQA was fatigue (16% of all patients).
The most frequently reported laboratory test abnormalities were neutrophil count decreased (20%) and aspartate aminotransferase (AST) increased (23%) and bilirubin increased (16%).
Undesirable effects are summarised below by organ system and frequency. Frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10).
Musculoskeletal and connective tissue disorders
Common: pain in extremities.
Skin and subcutaneous tissue disorders
Common: skin rash.
General disorders and symptoms

Very common: fatigue (16%).

Investigations

Very common: neutrophil count decreased (20%), aspartate aminotransferase (AST) increased (23%), bilirubin increased (16%).

Description of selected adverse reactions

Laboratory test abnormalities

The table that follows summarises laboratory abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients in the ARAMIS study:

Laboratory test (in % of samples analysed)	NUBEQA (n=954)*		Placebo (n=554)*	
	All grades**	Grade 3/4**	All grades**	Grade 3/4**
Blood and lymphatic system disorders				
Neutrophil count decreased	19.6%	3.5%	9.4%	0.5%
Hepatobiliary disorders				
Bilirubin increased	16.4%	0.1%	6.9%	0
AST increased	22.5%	0.5%	13.6%	0.2%

* The number of patients tested for a specific laboratory test may vary. The incidence has been calculated accordingly for each laboratory abnormality.

** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory values (no clinical assessments) were used for grading. Grade 4 laboratory abnormalities were only reported for “neutrophil count decreased”.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected [new or serious] adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

The highest NUBEQA dose studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

Considering the saturable absorption (see “Pharmacokinetics” section) and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to toxicity.

If a higher than recommended dose has been taken, treatment with NUBEQA can be continued with the next dose as scheduled.
There is no specific antidote for NUBEQA, and symptoms of overdose have not been studied.

Properties/Effects

ATC code

L02BB06.

Mechanism of action

Darolutamide is a non-steroidal androgen receptor inhibitor with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain to maintain potent androgen receptor (AR) antagonism.
Darolutamide competitively inhibits androgen binding, AR nuclear translocation and AR-induced transcription.
In vivo, darolutamide shows potent antitumour activity (decreased tumour cell proliferation), leading to decreased tumour volume in xenograft models of prostate cancer including the VcaP cell castration-resistant prostate cancer model (AR overexpression).

Pharmacodynamics

A QT/QTc analysis (ECG/PK substudy based on three ECG measurements with suitable PK samples) as part of the pivotal phase 3 study (ARAMIS) and a concentration/QTc analysis were performed. In the ECG/PK substudy with 520 patients, no prolongation of mean QTcF interval (i.e. greater than 10 ms) was observed after oral administration of 600 mg darolutamide twice daily, compared with placebo. The concentration/QTc study confirmed these results by not finding any clinically significant effect of darolutamide on cardiac repolarisation (QTc).

Clinical efficacy

The efficacy and safety of NUBEQA were assessed in a randomised, double-blind, placebo-controlled multicentre phase 3 study (ARAMIS) in patients with non-metastatic castration-resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤10 months. A total of 1509 patients were randomised 2:1 to receive either 600 mg oral darolutamide (n=955) or placebo (n=554) twice daily.
All patients received a gonadotropin-releasing hormone (GnRH) analogue concurrently or had undergone a bilateral orchiectomy. Only patients with presence of pelvic lymph nodes <2 cm (in short axis) below the aortic bifurcation were allowed to enter the study. Absence or presence of metastasis based on radiological studies was assessed by independent central review. Eighty-nine patients were

retrospectively identified with metastasis at baseline (t=0). Randomisation was stratified by PSADT (≤6 months vs. >6 months) and use of osteoclast-targeted therapy at study entry (yes or no). Patient demographics and disease characteristics were balanced between the two treatment arms. The median age was 74 years (48-95 years) and 9% of patients were 85 years of age or older. The racial distribution was 79% White, 13% Asian and 3% Black. A majority of patients (73%) had a Gleason score of 7 or higher at the time of diagnosis. The median PSADT was 4.5 months. Nine per cent of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. Seventy-six per cent of patients had received more than one prior antihormonal treatment. Patients with a medical history of seizures were not excluded. There were 12 patients enrolled on the darolutamide arm with a history of seizures. Most patients (69%) had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 at study entry. Treatment with NUBEQA was continued until disease progression (diagnosed by conventional imaging (CT, MRI, ^{99m}Tc bone scan), unacceptable toxicity or discontinuation of therapy.

The primary endpoint of the study was metastasis free survival (MFS). The four secondary endpoints included overall survival (OS) and time to pain progression.

Treatment with NUBEQA resulted in a statistically significant prolongation of MFS compared to placebo (see Table 1). MFS results were consistent across all patient subgroups regardless of PSADT at study entry, prior use of osteoclast-targeted therapy or loco-regional disease. Median overall survival (OS) was not reached in either treatment group with a median follow-up of approximately 17.9 months. 8.2% (78/955) of the patients in the NUBEQA arm and 10.5% (55/554) in the placebo arm had died. The median time to pain progression was increased compared to placebo (see Table 1).

Table 1: Efficacy results from the ARAMIS study

Efficacy parameter	**Number of events (%)**		**Median (95% CI)**		**Hazard ratio [a] (95% confidence interval [CI]) p-value (two-sided)**
	NUBEQA (n=955)	**Placebo (n=554)**	**NUBEQA (n=955)**	**Placebo (n=554)**	
Metastasis free survival (MFS)	221 (23.1%)	216 (39.0%)	40.4 months (34.3, NR)	18.4 months (15.5, 22.3)	0.413 (0.341, 0.500) <0.000001
Overall survival (OS)	78 (8.2%)	58 (10.5%)	NR (44.5, NR)	NR (NR, NR)	0.706 (0.501, 0.994)
Time to pain progression [b]	251 (26.3%)	178 (32.1%)	40.3 months (33.2, 41.2)	25.4 months (19.1, 29.6)	0.647 (0.533, 0.785)

a Hazard ratio <1 favours NUBEQA

b Patient reported outcomes (as evaluated by Brief Pain Inventory-Short Form)

NR Not reached

Pharmacokinetics

Absorption

Following oral administration of 600 mg (2 tablets of 300 mg), peak plasma concentrations of darolutamide of 4.79 mg/L (coefficient of variation: 30.9%) are reached around 4 hours post-dose. Following oral administration of the same dose together with food, steady state is reached after 2-5 days.
The absolute bioavailability compared to an intravenous injection is approximately 30% following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions. Bioavailability of darolutamide was increased by 2.0- to 2.5-fold when administered with food.
A similar increase in exposure was observed for the major metabolite keto-darolutamide.

Distribution

The apparent volume of distribution of darolutamide after intravenous administration is 119 L, indicating that darolutamide is widely distributed throughout the body to both intracellular and extracellular fluid spaces.
Darolutamide is moderately (92%) bound to human plasma proteins. Keto-darolutamide, the major metabolite of darolutamide, is highly (99.8%) bound to plasma proteins.

Metabolism

Following administration of a single dose of 300 mg of ^{14}C-darolutamide given as an oral solution, keto-darolutamide is the only relevant major metabolite with about 2-fold higher total exposure in plasma compared to darolutamide. Darolutamide and keto-darolutamide account together for 87.4% of the ^{14}C-radioactivity in plasma, indicating that all other metabolites are of minor importance.
Darolutamide is metabolised primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1.

Elimination

The effective half-life of darolutamide and keto-darolutamide in plasma of patients is approximately 20 hours.
The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%).
A total of 63.4% of active drug is excreted in the urine (approximately 7% unchanged) and 32.4% is excreted in the faeces. More than 95% of the dose was recovered within 7 days after administration.

Linearity/non-linearity

In the dose range of 100 to 700 mg (after a single dose and at steady state), the exposure to darolutamide and the major metabolite keto-darolutamide increases linearly in a nearly dose-related manner. Based on a saturated absorption, no further increase in exposure to darolutamide was observed at 900 mg twice daily.

Kinetics in specific patient groups

Hepatic impairment

In a clinical pharmacokinetic study, C_{max} and AUC for darolutamide were 1.5- and 1.9-fold higher in patients with moderate hepatic impairment (Child-Pugh B) compared to healthy subjects. There are no data for patients with severe hepatic impairment (Child-Pugh C).

Renal impairment

In a clinical pharmacokinetic study, AUC and C_{max} for darolutamide were 2.5- and 1.6-fold higher in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/min/1.73 m^2) compared to healthy subjects.
A population pharmacokinetic analysis indicates a 1.1- and 1.3-fold higher exposure (AUC) to darolutamide in patients with mild to moderate renal impairment (eGFR 30 to 89 mL/min/1.73 m^2) compared to patients with normal renal function.
The pharmacokinetics of darolutamide has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m^2).

Elderly patients

No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on age (48-95 years).

Children and adolescents

The safety and efficacy of NUBEQA in children and adolescents under 18 years of age have not been studied.

Genetic polymorphisms

No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on ethnicity (White, Japanese, non-Japanese Asian, Black or African American).

Preclinical data

Except for the observed changes in the reproductive organs seen in all animal toxicity studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity and genotoxicity.

Safety pharmacology

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology.

Systemic toxicity

In repeat dose toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks) with testing doses ≥50 mg/kg/day, the main findings were changes in the male reproductive organs (decreases in organ weight with atrophy of the prostate and epididymides). These effects occurred after systemic exposures in the range of or below the anticipated clinical exposure (0.6-fold in rats and 1-fold in dogs, based on AUC comparison). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy of seminal vesicles and mammary glands in rats as well as hypospermia and seminiferous tubule dilatation and degeneration in dogs. The changes seen in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and fully or partially resolved after a 4- to 8-week recovery period. No effects were observed in the female reproductive organs of rats and dogs. No significant changes in the clinical pathology or histopathology of other organ systems including the liver were observed.

Genotoxicity and carcinogenicity

Darolutamide did not induce mutations in the bacterial mutagenesis (Ames) assay. At high concentrations, darolutamide did induce structural chromosomal aberrations *in vitro* in cultured human lymphocytes. However, no genotoxicity was observed based on the combined results of the *in vivo* bone marrow micronucleus test and the Comet assay in the liver and duodenum of rats. Overall, darolutamide showed no relevant genotoxic potential with regard to use in humans.
Long-term animal studies to evaluate the carcinogenic potential of NUBEQA have not been performed.

Embryotoxicity / teratogenicity

Studies on developmental toxicity have not been performed.

Reproductive toxicity (fertility)

Studies on reproductive toxicity have not been performed. In repeat dose toxicity studies in rats and dogs, atrophy and hypospermia were observed in the male reproductive system, consistent with the pharmacological activity of darolutamide.

Other data

Darolutamide was not phototoxic *in vitro*.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.

Authorisation number

67521 (Swissmedic)

Packs

Packs of 112 film-coated tablets. (B)

Manufacturer

Orion Corporation, Orion Pharma, 02101 Espoo, Finland.

Marketing authorisation holder

Bayer (Schweiz) AG, Zurich.

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