swissmedic

*Date:* 14 October 2025
Swissmedic, Swiss Agency for Therapeutic Products

# *Swiss Public Assessment Report*
## *Extension of therapeutic indication*

# NUBEQA

| | |
|---|---|
| **International non-proprietary name:** | darolutamide |
| **Pharmaceutical form:** | film-coated tablet |
| **Dosage strength(s):** | 300 mg |
| **Route(s) of administration:** | oral |
| **Marketing authorisation holder:** | Bayer (Schweiz) AG |
| **Marketing authorisation no.:** | 67521 |
| **Decision and decision date:** | extension of therapeutic indication approved on 28 July 2025 |

**Note:**

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

**Table of contents**

# 1 Terms, Definitions, Abbreviations

| | |
|---|---|
| 1L | First-line |
| 2L | Second-line |
| ADA | Anti-drug antibody |
| ADME | Absorption, distribution, metabolism, elimination |
| ADT | Androgen deprivation therapy |
| AE | Adverse event |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| API | Active pharmaceutical ingredient |
| ARPI | Androgen receptor pathway inhibitors |
| 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 |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed plasma/serum concentration of drug |
| CYP | Cytochrome P450 |
| DCO | Data cut-off |
| DDI | Drug-drug interaction |
| DOR | Duration of response |
| ECOG | Eastern Cooperative Oncology Group |
| EMA | European Medicines Agency |
| ERA | Environmental risk assessment |
| FDA | Food and Drug Administration (USA) |
| GLP | Good Laboratory Practice |
| HPLC | High-performance liquid chromatography |
| HR | Hazard ratio |
| $IC/EC_{50}$ | Half-maximal inhibitory/effective concentration |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International non-proprietary name |
| ITT | Intention-to-treat |
| KM | Kaplan-Meier |
| LHRH | Luteinising hormone-releasing hormone |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| mCSPC | Metastatic castration-sensitive prostate cancer |
| mHSPC | Metastatic hormone-sensitive prostate cancer |
| Min | Minimum |
| MRHD | Maximum recommended human dose |
| MTD | Maximum tolerated dose |
| N/A | Not applicable |
| NCCN | National Comprehensive Cancer Network |
| NO(A)EL | No observed (adverse) effect level |
| NR | Not reached |
| ORR | Objective response rate |
| OS | Overall survival |
| PBPK | Physiology-based pharmacokinetics |
| PD | Pharmacodynamics |
| PFS | Progression-free survival |
| PIP | Paediatric Investigation Plan (EMA) |

| | |
|---|---|
| PK | Pharmacokinetics |
| PopPK | Population pharmacokinetics |
| PS | Performance status |
| PSA | Prostate-specific antigen |
| PSP | Pediatric study plan (US FDA) |
| RMP | Risk management plan |
| rPFS | Radiographic progression-free survival |
| SAE | Serious adverse event |
| SSE | Symptomatic skeletal event |
| SwissPAR | Swiss Public Assessment Report |
| TEAE | Treatment-emergent adverse event |
| TPA | Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21) |
| TPO | Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21) |
| ULN | Upper limit of normal |

# 2 Background information on the procedure

## 2.1 Applicant's request(s) and information regarding procedure

**Extension(s) of the therapeutic indication(s)**
The applicant requested the addition of a new therapeutic indication in accordance with Article 23 TPO.

**Project Orbis**
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

## 2.2 Indication and dosage

### 2.2.1 Requested indication

NUBEQA is indicated in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic, hormone-sensitive prostate cancer (mHSPC) (see 'Clinical Efficacy').

### 2.2.2 Approved indication

NUBEQA is indicated in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic, hormone-sensitive prostate cancer (mHSPC) (see "Clinical efficacy").

### 2.2.3 Requested dosage

**Summary of the requested standard dosage:**

No change to the dosage recommendation was requested with the application for extension of indication.

### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

| | |
|---|---|
| Application | 16 October 2024 |
| Formal control completed | 21 October 2024 |
| Preliminary decision | 27 May 2025 |
| Response to preliminary decision | 26 June 2025 |
| Final decision | 28 July 2025 |
| Decision | approval |

# 3 Medical context

Metastatic hormone-sensitive prostate cancer (mHSPC), also known as metastatic castration-sensitive prostate cancer (CSPC), is defined as metastatic disease in patients who have not yet received, or are continuing to respond to, antihormonal therapy.

Androgen deprivation therapy (ADT) in combination with androgen receptor pathway inhibitors (ARPI) is recommended as first-line treatment in this setting. Alternatively, in patients with high-volume disease (defined by the CHAARTED criteria: presence of visceral metastases or ≥4 bone lesions with ≥1 beyond the vertebral bodies and pelvis as assessed by conventional imaging) with either synchronous or metachronous metastases, the combination ADT with docetaxel and either abiraterone or darolutamide can be given.

# 4 Nonclinical aspects

The applicant did not submit any new nonclinical studies to support the requested new indication, which is considered acceptable. The new indication is unlikely to result in any significant risk to the environment. From the nonclinical point of view, there are no objections to the approval of the new indication applied for.

# 5 Clinical aspects

## 5.1 Clinical pharmacology

No additional clinical pharmacology data were submitted.

## 5.2 Dose Finding / Dose Recommendation

No dose-finding studies were performed.

## 5.3 Efficacy

The applicant provided results from the pivotal study ARANOTE supported by the results from study ARASENS.
Study ARANOTE is an ongoing, multicentre, randomised, double-blind, placebo-controlled, phase 3 study evaluating the efficacy and safety of darolutamide in addition to ADT compared to placebo plus ADT in patients with mHSPC.

Male patients aged 18 years or older with histologically or cytologically confirmed adenocarcinoma of the prostate and documented metastatic disease were eligible. ADT (LHRH agonist/antagonist or orchiectomy) had to be started not earlier than 12 weeks prior to randomisation.

Patients were randomised in a 2:1 ratio to receive either darolutamide 600 mg (2 tablets of 300 mg) twice daily (total dose of 1200 mg per day) or placebo in combination with ADT, respectively.

All patients must have received ADT of investigator's choice (LHRH agonist/antagonists or orchiectomy) as standard therapy, started not earlier than 12 weeks before randomisation, on a continuous basis. Patients were stratified according to presence of visceral metastases (yes/no) and prior use of local therapy (yes/no).

The primary endpoint of study ARANOTE was radiographic progression-free survival (rPFS) assessed by BICR based on RECIST v1.1 for malignant soft tissue lesions and PCWG3 criteria for malignant bone lesions. Secondary endpoints included in the hierarchical testing procedure were overall survival (OS), time to initiation of subsequent anti-cancer therapy, time to castration-resistant prostate cancer (CRPC) (defined as either PSA progression, soft tissue or bone progression, or occurrence of symptomatic skeletal event [SSE]), time to PSA progression, PSA undetectable rates, and time to pain progression.

Results were presented with a data cut-off (DCO) of June 2024 after a median follow-up time of 25.3 months in the darolutamide arm and 25.0 months in the placebo arm.

Overall n=889 patients were screened and n=669 were randomised. According to the 2:1 randomisation, n=446 were randomised to the darolutamide arm and n=223 to the placebo arm. At DCO 2024, 53.8% (n=240) of patients in the darolutamide arm vs. 28.3% (n=63) in the placebo arm were ongoing with study treatment.

Demographics and baseline characteristics were generally balanced between the treatment arms. Median age was 70 years in both arms, patients were mostly White (darolutamide 56.3%; placebo 56.1%), or Asian (darolutamide 32.3%, placebo 29.1%), had an ECOG PS of 0 (darolutamide 52.7%, placebo 43.9%) or 1 (darolutamide 44.6%, placebo 52.5%).

All patients had metastatic stage of disease at study entry, most of them stage M1b (darolutamide 77.1% vs. placebo 76.7%). The rate of patients with M1c was 19.1% in the darolutamide arm and 18.8% in the placebo arm, with M1a 3.8% and 4.5%, respectively. The majority of patients presented with de novo metastatic disease (darolutamide 71.1%; placebo 75.3%).

Gleason score ≥8 was present in 69.7% of patients in the darolutamide arm and 65.5% in the placebo arm. Disease volume at baseline (high volume defined as presence of visceral metastases or 4 or more bone lesions with at least 1 metastasis beyond the vertebral column and pelvic bones) was high in 70.6% of patients in the darolutamide arm and in 70.4% in the placebo arm.

At the DCO of June 2024 (DCO for the primary completion analysis), darolutamide demonstrated a statistically significant improvement in the primary endpoint rPFS compared to placebo with an HR of 0.54 (95% CI: 0.413, 0.707; one-sided p<0.0001). The median rPFS time was not reached in the darolutamide arm and was 25.0 months (95% CI: 19.0, NE) in the placebo arm.
Secondary endpoint overall survival was not statistically significantly improved with an HR of 0.81 (95%CI: 0.59, 1.12). In the darolutamide arm, the overall number of OS events was n=103 (23.1%) and in the placebo arm n=60 (26.9%). The median OS was not reached in either treatment arm.

During review, the final OS data with DCO of 10 Jan 2025 were provided with a median follow-up of 31.4 months for the darolutamide arm and 30.5 months for the placebo arm. At that time, n=115 (25.8%) of OS events in the darolutamide arm and n=70 (31.4%) in the placebo arm were reported. The updated OS was not statistically significant with an HR of 0.78 (95% CI: [0.58; 1.05]). The median OS was not reached in either treatment arm.

Due to the hierarchical testing procedure and no statistically significant OS results, the other secondary endpoints were not tested for statistical significance and are not presented here.

Supportive evidence in the setting of mHSPC was provided by study ARASENS, which investigated darolutamide in combination with ADT and docetaxel in patients who were candidates for chemotherapy. With a median follow-up of 43.7 months in the darolutamide arm, a statistically significant improvement in the primary endpoints OS was demonstrated in patients randomised to receive darolutamide plus docetaxel and ADT compared with placebo plus docetaxel and ADT (HR: 0.68; 95% CI: [0.57; 0.80], one-sided p<0.0001). The median OS was not reached (NR) in the darolutamide + docetaxel arm and 48.9 months (95%CI: 44.4, NR) in the placebo + docetaxel arm. PFS or rPFS was not defined as endpoint in study ARASENS. For details of this study, please refer to the attached information for healthcare professionals.

## 5.4 Safety

The safety assessment was primarily based on study ARANOTE. In addition, pooled safety data from studies ARANOTE and ARAMIS were provided.
In study ARANOTE, n=445 patients in the darolutamide arm and n=221 patients in the placebo arm were assessed for safety.
At the DCO of June 2024, the median treatment duration was 24.2 months in the darolutamide arm and 17.3 months in the placebo arm.
The number of patients with any treatment-emergent adverse events (TEAEs) was similar in both treatment arms (darolutamide 91.0%, placebo 90.0%). The most frequent events (≥ 10%) in the darolutamide arm were anaemia, arthralgia, and urinary tract infection.
The incidence of grade 3-4 TEAEs was balanced between the treatment arms (darolutamide: 30.8%, placebo: 30.3%). The most common TEAEs with worst grades 3 or 4 (≥2) in the darolutamide arm were hypertension, anaemia, AST increased, ALT increased, and bone pain.

Grade 5 TEAEs occurred in n=21 (4.7%) patients treated with darolutamide. The most frequent reasons for a G5 TEAE in the darolutamide arm were death, craniocerebral injury, myocardial infarction, and septic shock (in n=2 each).

Serious adverse events (SAEs) were reported at similar rates in both treatment arms (darolutamide 23.6%, placebo 23.5%). Most frequently reported SAEs (in ≥1%) in patients treated with darolutamide were pneumonia, urinary retention, urinary tract infection, anaemia, and spinal cord compression.

TEAEs leading to treatment discontinuation of study drug were reported in 6.1% of patients in the darolutamide arm.

One patient in the darolutamide arm met the biochemical criteria for Hy's Law (aspartate aminotransferase and/or alanine aminotransferase >3x upper limit of normal [ULN], and bilirubin ≥2xULN with alkaline phosphatase <2xULN). The study drug was discontinued and the liver enzymes returned to their normal values. No diagnostic tests were conducted to exclude other causes of the elevation in liver enzymes, including viral aetiology. The investigator assessed the case as related to the study drug.

The pooled safety data from study ARANOTE and study ARAMIS included 1399 patients treated with darolutamide and 775 patients treated with placebo. The event rates and types of TEAEs were consistent with the results provided for study ARANOTE.

## 5.5 Final benefit-risk assessment

Study ARANOTE met its primary endpoint rPFS. Efficacy was evaluated in conjunction with the clinically relevant secondary endpoint OS. Even though there was no statistically significant OS benefit, a separation of the KM curves in favour of darolutamide in the mature part of the OS KM curves was observed. The toxicity was in line with the already known safety profile of darolutamide, and no new safety signals were observed. The final benefit risk assessment was positive for darolutamide in the requested indication.

# 6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken 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. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. 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 that occur in populations or indications not included in the Swiss authorisations.

# 7 Appendix

## Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for 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 valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

**Note:**
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

# NUBEQA®

## Composition

*Active substances*

Darolutamide.

*Excipients*

Calcium hydrogen phosphate, sodium croscarmellose (produced using 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 (E 171) q.s.p. 1 film-coated tablet.

## Pharmaceutical form and active substance quantity per unit

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

## Indications/Uses

NUBEQA is indicated

- in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with non-metastatic, castration-resistant prostate cancer (nmCRPC) at high risk of developing metastases (especially with a PSADT ≤10 months; see “Clinical efficacy”).
- in combination with androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic, hormone-sensitive prostate cancer (mHSPC) (see “Clinical efficacy”).
- in combination with docetaxel and androgen deprivation therapy (ADT) for the treatment of adult patients with metastatic hormone-sensitive prostate cancer (mHSPC), for whom docetaxel therapy is indicated (see “Clinical efficacy”).

## Dosage/Administration

*Usual dosage*

NUBEQA is for oral use. The recommended dose is 600 mg (two 300 mg film-coated tablets) of darolutamide twice daily, equivalent to a total dose of 1200 mg per day.
The tablets must be taken whole together with a meal (see section “Pharmacokinetics”).
Treatment with NUBEQA must be continued until disease progression or unacceptable toxicity occurs.
Patients receiving NUBEQA should also concurrently receive a luteinising hormone-releasing hormone (LHRH) agonist or antagonist or should have had bilateral orchiectomy.

When used in combination with docetaxel in patients with mHSPC (see section “Clinical efficacy”), the first of 6 docetaxel cycles should be administered within 6 weeks after initiation of NUBEQA treatment. The recommendations in the Information for healthcare professionals for docetaxel should be followed. Treatment with NUBEQA should be continued until disease progression or unacceptable toxicity occurs, even if the administration of any docetaxel cycle is delayed, interrupted or discontinued.

If a dose of NUBEQA is missed, it should be taken as soon as the patient remembers prior to the next scheduled dose. The patient must not take two doses together to make up for a missed dose.

*Dose adjustment due to adverse reactions/interactions*

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction associated with NUBEQA, administration should be discontinued or the dose reduced to 300 mg twice daily until symptoms improve (see also section “Warnings and precautions”). 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 section “Pharmacokinetics”).

*Special dosage instructions*

*Patients with hepatic impairment*

No dose adjustment is required for patients with mild hepatic impairment.
The available data on the pharmacokinetics of darolutamide in moderate hepatic impairment are limited.
Darolutamide has not been studied in patients with severe hepatic impairment (see also section “Pharmacokinetics”).
In patients with moderate to severe hepatic impairment (Child-Pugh classes B and C), the recommended starting dose is 300 mg twice daily.

*Patients with renal impairment*

No dose adjustment is required in patients with mild to moderate renal impairment.
In patients with severe renal impairment (eGFR 15-29 mL/min/1.73 $m^2$) not receiving haemodialysis, the recommended starting dose is 300 mg twice daily.

*Elderly patients*

In clinical studies, no clinically relevant differences with regard to safety or efficacy were observed between elderly patients aged 65-74 years, 75-84 years or ≥ 85 years and younger patients

(< 65 years). No dose adjustment is therefore necessary in elderly patients (see section "Pharmacokinetics").

*Children and adolescents*

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

*Genotype/genetic polymorphisms*

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

**Contraindications**

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

**Warnings and precautions**

*Renal impairment*

The available data in patients with severe renal impairment are limited. As exposure might be increased those patients should be closely monitored for adverse reactions (see sections "Dosage/Administration" and "Pharmacokinetics").

*Hepatic impairment*

The available data in patients with moderate hepatic impairment are limited, and darolutamide has not been studied in patients with severe hepatic impairment. As exposure might be increased those patients should be closely monitored for adverse reactions (see sections "Dosage/Administration" and "Pharmacokinetics")

*Hepatotoxicity*

Cases of idiosyncratic drug induced liver injury (DILI) consisting of Grade ≥ 3 increases in ALT and/or AST, including with concomitant bilirubin ≥2x ULN (Hy's Law), have been reported with NUBEQA. Time to onset ranged approximately from 1 month up to 12 months after initiation of NUBEQA therapy. Liver function test abnormalities were mostly reversible upon discontinuation of NUBEQA. In case of liver function test abnormalities suggestive of idiosyncratic DILI, NUBEQA must be permanently discontinued (see section "Undesirable effects").

*ADT can prolong the QT interval*

In patients with risk factors such as a history of QT prolongation, torsade de pointes, hypokalaemia, or in patients on treatment with medicinal products that prolong the QT interval (see section

“Interactions”), ECG monitoring should be performed at the start of treatment and at regular intervals during treatment.

*Contraception for men and women*

If the patient is sexually active with a woman of childbearing potential, he should use a highly effective method of contraception during treatment with NUBEQA and for up to 1 week after the end of treatment, in order to prevent a pregnancy.
If the patient is sexually active with a pregnant woman, a condom must be used during treatment with NUBEQA and for up to 1 week after the end of treatment. Exposure of the fetus to an androgen receptor inhibitor through seminal transfer to the pregnant woman has to be avoided, as this could affect development of the fetus.

*Changes in bone mineral density*

In the clinical studies with darolutamide, there were no studies on bone mineral density. It can be assumed that long-term testosterone suppression during treatment with darolutamide has an impact on bone mineral density. A decrease in bone mineral density has been reported in patients treated with LHRH agonists or antagonists and in patients post orchiectomy.

*Recent cardiovascular disease*

Patients with a clinically relevant cardiovascular disease in the previous 6 months, including stroke, myocardial infarction, severe/unstable angina pectoris, coronary or peripheral artery bypass surgery and symptomatic cardiac failure, were excluded from the clinical studies. Hence, the safety of darolutamide in these patients has not been established. When NUBEQA is prescribed, patients with clinically relevant cardiovascular disease should be treated according to the current guidelines for such diseases.

This medicine contains less than 1 mmol sodium (23 mg) per oral dose (2 film-coated tablets), that is to say 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), Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 substrates*
Darolutamide is an inhibitor of BCRP, as well as OATP 1B1 and 1B3.

Administration of darolutamide (600 mg twice daily for 5 days) prior to concomitant ingestion of a single dose of rosuvastatin (5 mg), together with food, led to approximately 5-fold increase in mean exposure (AUC) and $C_{max}$ of rosuvastatin.
This indicates that co-administration of NUBEQA may increase the plasma concentrations of other substrates of BCRP, OATP1B1 and OATP1B3 (e.g. methotrexate, sulfasalazine, fluvastatin, atorvastatin). Therefore, the respective recommendation given in the Information for healthcare professionals for these substrates should be followed when co-administering with NUBEQA.
*Docetaxel*
Administration of darolutamide in combination with docetaxel in patients with mHSPC did not lead to any clinically relevant changes in the pharmacokinetics of docetaxel (see section “Clinical efficacy”). Regarding docetaxel interactions, reference should be made to the information given in the Product information for docetaxel.
*P-glycoprotein (P-gp) substrates*
With co-administration of darolutamide and dabigatran etexilate (a sensitive P-gp substrate), there was found to be no increase in dabigatran exposure (AUC and $C_{max}$).
This indicates that NUBEQA can be administered together with P-gp substrates with no clinically relevant drug-drug interactions.
*CYP substrates*
Darolutamide is a weak CYP3A4 inducer. Administration of darolutamide (600 mg twice daily for 9 days) prior to concomitant ingestion of a single 1 mg dose of midazolam (a sensitive CYP3A4 substrate) together with a meal led to a decrease in the mean exposure (AUC) and $C_{max}$ of midazolam by 29% and 32%, respectively.
*In vitro*, the metabolism of selected CYP substrates was not inhibited by darolutamide at clinically relevant concentrations.
This indicates that NUBEQA can be administered together with CYP substrates (e.g. warfarin, L-thyroxine, omeprazole) with no 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 and a P-gp inducer, with a single dose of darolutamide (600 mg), together with a meal, led to a decrease in mean exposure [AUC(0-72)] and $C_{max}$ of darolutamide by 72% and 52%, respectively.
The 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 a concomitant medicinal product with no or weak potential to induce CYP3A4 or P-gp should be considered.

*Docetaxel*

Administration of darolutamide in combination with docetaxel did not lead to any clinically relevant changes in the pharmacokinetics of darolutamide in patients with mHSPC (see section “Clinical efficacy”).

*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 a meal), led to an increase in mean exposure [AUC(0-72)] and $C_{max}$ of darolutamide by 1.7-fold and 1.4-fold, respectively.

Patients should be monitored more frequently for adverse reactions; the NUBEQA dosage should be adjusted as needed.

*Medicinal products that prolong the QT interval*

As androgen deprivation therapy can prolong the QT interval, concomitant administration of medicinal products known to prolong the QT interval or medicinal products known to cause torsade de pointes should be carefully considered. These include medicinal products such as class IA antiarrhythmics (e.g. quinidine, disopyramide) or class III antiarrhythmics (e.g. amiodarone, sotalol, dofetilide, ibutilide), methadone, moxifloxacin and antipsychotics (e.g. haloperidol).

**Pregnancy, lactation**

*Pregnancy*

NUBEQA is not indicated for treatment of women. Due to its mechanism of action, NUBEQA may cause fetal harm if used during pregnancy. No clinical data are available in pregnant women. No animal reproduction and development studies have been conducted with NUBEQA.

*Lactation*

NUBEQA is not indicated for treatment of women. There are no data on the appearance of darolutamide or its metabolites in human milk, on the effects on breastfed infants or the effects on milk production.

*Fertility*

There are no human data on the effect of NUBEQA on fertility.

Animal studies have shown that darolutamide affects the reproductive system in male rats and dogs (see section “Preclinical data”).

**Effects on ability to drive and use machines**

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

**Undesirable effects**

*NUBEQA*

The safety profile of NUBEQA is based on data from 2174 patients, 1399 of whom received at least one dose of NUBEQA in studies ARAMIS (nmCRPC) and ARANOTE (mHSPC).
According to pooled data from clinical trials of darolutamide (ARANOTE and ARAMIS), the most commonly observed adverse reaction in patients treated with NUBEQA was fatigue (14% of all patients). The most common abnormalities observed in laboratory tests were neutrophil count decreased (17%), aspartate aminotransferase (AST) increased (22%), alanine aminotransferase (ALT) increased (13%) and bilirubin increased (16%). The most serious adverse reactions (Grade ≥3) in patients with nmCRPC and mHSPC who had received NUBEQA were ischaemic heart disease (1.8%), fractures (1.1%), AST increased (1.0%), ALT increased (0.9%), cardiac failure (0.8%) and neutrophil count decreased (0.5%).

*NUBEQA in combination with docetaxel*

The safety profile of NUBEQA in combination with docetaxel is based on data from 1302 patients with mHSPC, 652 of whom received at least one dose of NUBEQA in the ARASENS study.
The most commonly observed adverse reactions in patients with mHSPC who had received NUBEQA in combination with docetaxel were rash (17% of all patients) and hypertension (14% of all patients). The most common abnormalities observed in laboratory tests were an elevated level of AST (44%), as well as elevated levels of ALT (42%) and bilirubin (20%). The most serious adverse reactions (Grade ≥3) in patients with mHSPC who received NUBEQA in combination with docetaxel were hypertension (6.7%) including hypertensive emergency (0.2%), ALT increased (2.8%) and AST increased (2.6%).
Regarding adverse reactions to medicinal products used in combination with NUBEQA, please refer to the information provided in the relevant Information for healthcare professionals.
Adverse reactions in patients with nmCRPC and mHSPC receiving NUBEQA, as well as in patients with mHSPC receiving NUBEQA in combination with docetaxel, are summarised below by system organ class and frequency. The frequencies are defined as very common (≥1/10) and common (≥1/100 to <1/10).

| | *NUBEQA* | *NUBEQA in combination with docetaxel* |
|---|---|---|
| *Blood and lymphatic system disorders* | | |

| | | |
|---|---|---|
| Very common | Neutrophil count decreased (17%)[1] | |
| *Cardiac disorders* | | |
| Common | Ischaemic heart disease[2]<br>Cardiac failure[3] | |
| *Vascular disorders* | | |
| Very common | | Hypertension (14%)[4] including hypertensive emergency (0.2%) |
| *Hepatobiliary disorders* | | |
| Very common | AST increased (22%)[1]<br>ALT increased (13%)[1]<br>Bilirubin increased (16%)[1] | AST increased (44%)[1]<br>ALT increased (42%)[1]<br>Bilirubin increased (20%)[1] |
| *Skin and subcutaneous tissue disorders* | | |
| Very common | | Rash (17%)[5, 6] |
| Common | Rash[7] | |
| *Musculoskeletal and connective tissue disorders* | | |
| Common | Pain in extremities<br>Fractures | |
| *General disorders and conditions* | | |
| Very common | Fatigue (14%)[8] | |

[1] based on laboratory test abnormalities.

[2] Includes arteriosclerosis coronary artery, coronary artery disease, coronary artery occlusion, coronary artery stenosis, acute coronary syndrome, acute myocardial infarction, angina pectoris, angina unstable, myocardial infarction, myocardial ischaemia.

[3] Includes cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive, cardiogenic shock.

[4] Includes hypertension, blood pressure increased, hypertensive emergency, heart failure with preserved ejection fraction.

[5] Incidence was highest during the first 6 months of treatment

[6] Includes skin rash, drug rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, erythema, dermatitis.

[7] Includes skin rash, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, dermatitis.

[8] Including fatigue, as well as asthenia, lethargy and malaise; in ARANOTE, the frequency of “fatigue” was lower in the NUBEQA arm than in the placebo arm.

*Description of specific adverse reactions*

*Hepatotoxicity*

Cases of idiosyncratic drug induced liver injury (DILI) with increases in alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) to ≥5 and ≥20 x upper limit of normal (ULN), including with concomitant bilirubin elevation ≥ 2x ULN (Hy's Law), have been reported with NUBEQA.

*Fractures*

In patients with nmCRPC (ARAMIS) and mHSPC (ARANOTE), fractures occurred in 4.1% of patients treated with NUBEQA and in 3.2% of patients treated with placebo.

*Ischaemic heart disease and cardiac failure*

In patients with nmCRPC (ARAMIS) and mHSPC (ARANOTE), ischaemic heart disease occurred in 3.4% of patients treated with NUBEQA and in 2.2% of patients treated with placebo. Grade 5 events occurred in 0.4% of patients treated with NUBEQA and in 0.4% of patients treated with placebo. Cardiac failure occurred in 1.6% of patients treated with NUBEQA and in 0.9% of patients treated with placebo.

*Hypertension*

In the ARASENS study hypertension was reported in 13.8% of patients treated with NUBEQA + docetaxel and 9.4% of patients treated with placebo + docetaxel. Grade 3 hypertension was reported in 6.4% of patients treated with NUBEQA + docetaxel compared to 3.5% of patients treated with placebo+docetaxel. One patient had grade 4 hypertension in each treatment arm.
One case was reported as grade 5 hypertension with grade 5 arteriosclerosis in the NUBEQA + docetaxel arm. This patient had a long-standing history of hypertension and smoking and the case occurred more than 3 years after starting NUBEQA treatment. Events of hypertension were reported more commonly in patients with no medical history of hypertension in both treatment arms.

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 dose of NUBEQA 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 section "Pharmacokinetics") 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.

In the event of intake of a higher than recommended dose, NUBEQA treatment can be continued with the next dose as scheduled.
There is no specific antidote for NUBEQA and symptoms of overdose are not established.

**Properties/Effects**

*ATC code*

L02BB06.

*Mechanism of action*

Darolutamide is a non-steroidal androgen receptor antagonist with a flexible polar-substituted pyrazole structure that binds with high affinity directly to the receptor ligand binding domain to retain strong antagonistic activity against the androgen receptor (AR).
Darolutamide competitively inhibits androgen binding, androgen receptor nuclear translocation and AR mediated transcription.
Darolutamide has strong *in vivo* anti-tumour efficacy (decreased tumour cell proliferation) leading to decreased tumour volume in xenograft models of prostate cancer including the castration-resistant prostate cancer model with VCaP cells (overexpression of AR).

*Pharmacodynamics*

A QT/QTc analysis (ECG-PK substudy based on triplicate ECG measurements with matched PK samples) as part of the pivotal phase 3 study (ARAMIS), as well as a concentration-QTc analysis, were performed. In the ECG-PK substudy of 520 patients, no prolongation of the mean QTcF interval (i.e. more than 10 ms) was observed after oral administration of 600 mg darolutamide twice daily compared to placebo. The concentration-QTc study confirmed these results by finding no clinically significant influence on cardiac repolarisation (QTc) for darolutamide.

*Clinical efficacy*

Efficacy and safety have been demonstrated in three randomised, placebo-controlled, multicentre phase III studies in patients with nmCRPC (ARAMIS) and mHSPC (ARANOTE and ARASENS). All patients received a concomitant luteinising hormone-releasing hormone (LHRH) agonist or antagonist or had undergone bilateral orchiectomy.

*Non-metastatic castration-resistant prostate cancer (nmCRPC)*

*ARAMIS: NUBEQA vs. placebo*

The efficacy and safety of NUBEQA was assessed in a randomised, double-blind, placebo-controlled multicentre phase III study (ARAMIS) in patients with non-metastatic castration resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤ 10 months. In total, 1509 patients

were randomised 2:1 to receive either 600 mg darolutamide orally twice daily (n=955) or placebo (n=554).

Only patients with pelvic lymph nodes < 2 cm (transverse diameter) below the aortic bifurcation were accepted for the study. The presence or lack of metastases based on radiological examinations was reviewed by an independent central body, with metastases being identified retrospectively in 89 patients at the point t=0. Randomisation was stratified by PSADT (≤ 6 months or > 6 months) and prior use of osteoclast-targeted therapy at study entry (yes or no).

The demographic data and disease characteristics were balanced in both treatment arms. The median age was 74 years (range 48-95) and 9% of patients were 85 years of age or older. Ethnic composition was 79% white, 13% Asian, and 3% black. Most patients (73%) had a Gleason score of 7 or higher at the time of diagnosis. The median PSADT was 4.5 months. 9% of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. 76% of patients had received more than one prior anti-hormonal treatment. Patients with a history of seizures were not excluded. In the darolutamide arm, 12 patients with a history of seizures were included. 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, Tc99m bone scan)), unacceptable toxicity or treatment withdrawal.

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 led to a statistically significant prolongation of MFS compared to placebo (see Table 1). The MFS results were uniform across all patient subgroups, irrespective of PSADT at study entry, prior osteoclast-targeted therapy or locoregional symptoms.

At the time of the final analysis with a median follow-up of 29 months, 15.5% of patients had died in the NUBEQA arm (148/955) and 19.1% (106/554) in the placebo arm; HR 0.685 (95% CI 0.533; 0.881). Median overall survival was not reached in either treatment group. The median time to pain progression was prolonged compared to placebo (see Table 1).

*Table 1: Efficacy results from the ARAMIS study*

| *Efficacy parameter* | *Number of events (%)* | | *Median in months (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 (34.3, NR) | 18.4 (15.5, 22.3) | 0.413 (0.341, 0.500) <0.000001 |
| Overall survival (OS) | 148 (15.5%) | 106 (19.1%) | NR (56.1, NR) | NR (46.9, NR) | 0.685 (0.533, 0.881) |
| Time to pain progression [b] | 251 (26.3%) | 178 (32.1%) | 40.3 (33.2, 41.2) | 25.4 (19.1, 29.6) | 0.647 (0.533, 0.785) |

[a] Hazard ratio <1 in favour of NUBEQA

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

NR not reached

*Metastatic hormone-sensitive prostate cancer (mHSPC)*

*ARANOTE: NUBEQA vs. placebo*

The efficacy and safety of NUBEQA was assessed in a multicentre, double-blind, placebo-controlled phase III study (ARANOTE) in patients with mHSPC. In total, 669 patients were randomized 2:1 to receive either 600 mg darolutamide orally twice daily (n=446) or placebo (n=223). Treatment with NUBEQA or placebo was continued until disease progression, change in antineoplastic therapy, unacceptable toxicity, death or discontinuation of treatment.

The presence of metastases was assessed by independent central radiological review. Patients with regional lymph node involvement only (M0) were excluded from the study. Randomization was stratified by the presence of visceral metastases and prior local therapy. Concomitant androgen deprivation therapy (LHRH agonist/antagonist or orchiectomy) could be started no more than 12 weeks before randomization.

The following demographic data and disease characteristics were balanced between both treatment arms. Median age was 70 years (range: 43–93), und 4.2% of patients were 85 years of age or older. 56.2% were White, 31.2% Asian, 9.7% Black or African American and 2.8% other. The majority of patients (68.3%) had a Gleason score of 8 or higher at time of diagnosis. At baseline, 49.8% of patients had an ECOG PS score of 0, 47.2% had an ECOG PS score of 1 and 3.0% had an ECOG PS score of 2. Of the patients, 72.5% had a *de novo* tumour and 21.7% recurrence. 12.0% of the patients had visceral metastases at baseline; the median PSA at baseline was 21.3 µg/L. 70.6% of the patients had high-volume disease and 29.4% had low-volume disease. High-volume disease was defined as the

presence of visceral metastases or 4 or more bone lesions with at least one metastasis outside the spine and pelvic bones. Patients with a history of seizures were eligible to participate in the study.
The primary efficacy endpoint was radiographic progression-free survival (rPFS). Key secondary endpoint was overall survival (OS).
Treatment with NUBEQA resulted in a statistically significant improvement in rPFS compared to placebo, with a p-value of <0.0001 (see Table 2). rPFS results were consistent across all subgroups, including patients with high- and low-volume disease.
At the time of the final OS analysis, the difference in overall survival was not statistically significant and the median had not been reached in either arm (HR=0.776, see Table 2).

*Table 2: Efficacy results from the ARANOTE study*

| *Efficacy parameter* | *Number of patients with events (%)* | | *Median in months (95% CI)* | | *Hazard Ratio [a] (95% confidence interval [CI]) p-value (one-sided) [b]* |
|---|---|---|---|---|---|
| | *NUBEQA (n=446)* | *Placebo (n=223)* | *NUBEQA (n=446)* | *Placebo (n=223)* | |
| Radiographic progression-free survival (rPFS) | 128 (28.7%) | 94 (42.2%) | NR (NR; NR) | 25.0 (19.0, NR) | 0.541 (0.413, 0.707) < 0.0001 |
| Overall survival (OS) | 115 (25.8%) | 70 (31.4%) | NR (NR; NR) | NR (NR; NR) | 0.776 (0.577, 1.045) |

[a] Hazard Ratio <1 in favour of NUBEQA

[b] Based on a stratified log-rank test

NR not reached

*ARASENS: NUBEQA with docetaxel vs. placebo with docetaxel*

The efficacy and safety of NUBEQA in combination with docetaxel was evaluated in a phase III, multicentre, double-blind, placebo-controlled study (ARASENS) in patients with mHSPC. Patients were required to be eligible for ADT and docetaxel therapy, as per investigator's judgment. A total of 1306 patients were randomised (1:1) and assigned to treatment with oral darolutamide 600 mg twice daily (n=651) or matched placebo (n=655), each in combination with 6 cycles of docetaxel 75 mg/m$^2$ each. Patients were excluded from the study if they had received prior treatment with either second-generation androgen inhibitors, CYP-17 enzyme inhibitors or chemotherapy for prostate cancer.
Treatment with NUBEQA or placebo was continued until symptomatic disease progression, change in antineoplastic therapy, unacceptable toxicity, death or discontinuation of treatment.
The presence of metastasis was assessed by independent central radiological review. Patients with regional lymph node involvement only (M0) were excluded from the study. Randomisation was stratified by extent of disease (non–regional lymph node metastases only (M1a), bone metastases

with or without lymph node metastases (M1b) or visceral metastases with or without lymph node metastases or with or without bone metastases (M1c)) and by alkaline phosphatase level (< or ≥ upper limit of normal, ULN)) at study entry.

The following demographic data and disease characteristics were balanced between both treatment arms. The median age was 67 years (range 41–89) and 0.5% of patients were 85 years of age or older. 52% were white, 36% Asian and 4% black. The majority of patients (78%) had a Gleason score of 8 or higher at time of diagnosis. Seventy-one percent (71%) of patients had an ECOG PS score of 0 and 29% of patients had an ECOG PS score of 1. Of the patients, 86.1% had a *de novo* tumour and 12.9% had recurrence. At inclusion in the study, 3% of patients had stage M1a, 79.5% stage M1b and 17.5% stage M1c; alkaline phosphatase was <ULN in 44.5% of patients and ≥ULN in 55.5%; the median PSA value at baseline assay was 30.3 µg/L in the NUBEQA group and 24.2 µg/L in the placebo group. Patients with a history of seizures were eligible to participate in the study and 4 patients (0.6%) were included in the NUBEQA+docetaxel treatment arm.

The primary efficacy endpoint was overall survival (OS). Another endpoint was the time to pain progression.

Pain progression was assessed using a patient questionnaire (PRO instrument), the Brief Pain Inventory-Short Form (BPI-SF), and was defined as a worsening from nadir by at least 2 points or initiation of use of a short-acting or long-acting opioid for pain over ≥7 consecutive days.

In the NUBEQA+docetaxel treatment arm, a statistically significant improvement in OS was achieved compared to the placebo+docetaxel arm, with a 32.5% (HR=0.675, p<0.0001) reduction in the risk of mortality (see Table 3 for efficacy data).

*Table 3: Efficacy results from the ARASENS study*

| *Efficacy parameter* | *Number of patients with events (%)* | | *Median in months (95% CI)* | | *Hazard Ratio [b] (95% confidence interval [CI]) p-value (one-sided) [c]* |
|---|---|---|---|---|---|
| | *NUBEQA+ Docetaxel (n=651)* | *Placebo + docetaxel (n=654) [a]* | *NUBEQA+ Docetaxel (n=651)* | *Placebo + docetaxel (n=654) [a]* | |
| Overall survival (OS) | 229 (35.2%) | 304 (46.5%) | NR (NR, NR) | 48.9 (44.4, NR) | 0.675 (0.568, 0.801) <0.0001 |
| Time to pain progression [d] | 222 (34.1%) | 248 (37.9%) | NR (30.5, NR) | 27.5 (22.0, 36.1) | 0.792 (0.660, 0.950) 0.0058 |

[a] 1 patient in the placebo arm was excluded from all analyses
[b] Hazard ratio < 1 in favour of NUBEQA
[c] Based on a stratified log-rank test
[d] Assessed by BPI-SF and initiation of use of short-acting or long-acting opioids for pain over ≥ 7 consecutive days
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%) were reached. If the same dose is taken together with a meal, 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 enhanced by 2.0- to 2.5-fold when taken with a meal. 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. The major metabolite of darolutamide, keto-darolutamide, is highly (99.8%) bound to plasma proteins.

*Metabolism*

Following administration of a single dose of 300 mg $^{14}$C-darolutamide as an oral solution, keto-darolutamide is the only relevant major metabolite. Overall exposure in the plasma is approximately twice as high in comparison with darolutamide. Darolutamide and keto-darolutamide together account 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 the 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 the active substance is excreted in the urine (approximately 7% unchanged) and 32.4% 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 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 increased 1.5-and 1.9-fold, respectively, in non-cancer patients with moderate hepatic impairment compared to healthy subjects. No data are available for patients with severe hepatic impairment

*Renal impairment*

In a clinical pharmacokinetic study, AUC and $C_{max}$ for darolutamide were increased 2.5- and 1.6-fold, respectively, 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 showed a 1.1-, 1.3- and approximately 1.5-fold higher darolutamide exposure (AUC) in patients with mild, moderate and severe renal impairment (eGFR 15 to 89 mL/min/1.73 $m^2$), respectively, 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 (41-95 years).

*Children and adolescents*

Safety and efficacy of NUBEQA have not been studied in children and adolescents below 18 years of age.

*Genetic polymorphisms*

No clinically relevant differences in the pharmacokinetics of darolutamide were observed in relation to ethnicity (white, Asian, black or African-American).

**Preclinical data**

Aside from reproductive organ changes observed in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated 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 repeated dose toxicity studies in rats (up to 26 weeks) and dogs (up to 39 weeks) at doses of ≥ 50 mg/kg/day, the main findings were changes in the male reproductive organs (decrease in organ weight with atrophy of the prostate and epididymides). These effects occurred after systemic exposures in the range of or below the anticipated human exposure (0.6-fold in rats and 1-fold in dogs, based on the AUC value). Additional changes to reproductive tissues included minimal increase in vacuolation of the pituitary gland, atrophy in seminal vesicles and mammary glands in rats, as well as hypospermia, seminiferous tubule dilatation and degeneration in dogs. Changes in the male reproductive organs in both species were consistent with the pharmacological activity of darolutamide and reversed or partially resolved after 4 to 8-week recovery periods. No effects were observed in female reproductive organs in rats and dogs. There were no significant changes in clinical pathology or histopathology observed in any other organ system, including the liver.

*Genotoxicity and carcinogenicity*

Darolutamide did not induce mutations in the microbial mutagenesis (Ames) assay. *In vitro,* darolutamide at high concentrations did induce structural chromosome aberrations in cultured human lymphocytes. However, in the *in vivo* combined bone marrow micronucleus test and the Comet assay in the liver and duodenum of the rat, no genotoxicity was observed. Overall, darolutamide did not show a relevant genotoxic potential with regard to human use.
Oral administration of darolutamide to male rasH2 transgenic mice for 6 months did not show carcinogenic potential at doses up to 1000 mg/kg/day, which is 0.9-1.3 times for darolutamide and 2.1-2.3 times for keto-darolutamide the clinical exposure (AUC) at the recommended clinical daily dose of 1200 mg/day. Based on this study carcinogenic risk of darolutamide cannot be completely excluded.

*Embryotoxicity/teratogenicity*

Studies on developmental toxicity have not been performed.

*Reproductive toxicity (fertility)*

Studies on reproductive toxicity have not been performed. In repeated dose toxicity studies in rats and dogs, atrophy and hypospermia in the male reproductive system were observed, which is 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*

Keep out of the reach of children.
Do not store above 30°C.
Store in the original packaging.

**Authorisation number**

67521 (Swissmedic).

**Packs**

Packs containing 112 film-coated tablets. (B)

**Manufacturer**

Orion Corporation, Orion Pharma, 24100 Salo, Finland.

**Marketing authorisation holder**

Bayer (Schweiz) AG, Zurich.

**Date of revision of the text**

May 2025