▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

NUBEQA (DAROLUTAMIDE) TABLET

1 NAME OF THE MEDICINE

Darolutamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 300 mg of darolutamide.

Excipients with known effect:

Contains sugars as lactose.

For a full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

NUBEQA is indicated for the treatment of patients with:

- non-metastatic castration resistant prostate cancer (nmCRPC)
- metastatic hormone-sensitive prostate cancer (mHSPC) in combination with docetaxel

4.2 DOSE AND METHOD OF ADMINISTRATION

Method of administration

For oral use.

Dosage regimen

nmCRPC and mHSPC

The recommended dose is 600 mg (two film-coated tablets of 300 mg) darolutamide taken twice daily, equivalent to a total daily dose of 1200 mg.

The tablets should be taken whole with food (see section **5.2 PHARMACOKINETIC PROPERTIES**).

NUBEQA should be continued until disease progression or unacceptable toxicity.

Patients receiving NUBEQA should also receive a luteinizing hormone releasing hormone (LHRH) analog concurrently or should have had bilateral orchiectomy.

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

mHSPC

mHSPC patients should start NUBEQA in combination with docetaxel (see section **5.1 PHARMACODYNAMIC PROPERTIES**). The first of 6 cycles of docetaxel should be administered within 6 weeks after the start of NUBEQA treatment. The recommended dosage of docetaxel for prostate cancer is 75 mg/m^2 administered as a one-hour infusion every three weeks. Treatment with NUBEQA should be continued until disease progression or unacceptable toxicity even if a cycle of docetaxel is delayed, interrupted, or discontinued.

Dose modification

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction related to NUBEQA, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. Then treatment may be resumed at a dose of 600 mg twice daily.

Dose reduction below 300 mg twice daily is not recommended. The maximum efficacious daily dose is the recommended dose of 600 mg twice daily (see section **5.2 PHARMACOKINETIC PROPERTIES**).

Additional information on special populations

Paediatric patients

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

Elderly

In clinical studies, no clinically relevant differences in safety or efficacy were observed between elderly patients aged 65-74 years, 75-84 years or ≥ 85 years and younger patients (aged < 65 years). No dose adjustment is necessary in elderly patients (see also section **5.2 PHARMACOKINETIC PROPERTIES**).

Patients with hepatic impairment

No dose adjustment is necessary for patients with mild hepatic impairment.

The recommended dose for patients with moderate hepatic impairment (Child-Pugh B) is 300 mg twice daily.

The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

Patients with renal impairment

No dose adjustment is necessary for patients with mild and moderate renal impairment.

The recommended dose for patients with severe renal impairment (eGFR 15-29 mL/min/1.73m^2) is 300 mg twice daily.

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).

4.3 CONTRAINDICATIONS

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1

4.4 Women who are or may become pregnant

4.5 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Cardiovascular

The safety of darolutamide has not been characterised in patients with recent (within 6 months) cardiovascular events, including uncontrolled hypertension, stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, and NYHA Class III or IV congestive heart failure, as these patients were excluded from the pivotal study (ARAMIS).

Ischemic heart disease, including fatal cases, occurred in patients receiving NUBEQA.

In a randomised study of patients with nmCRPC (ARAMIS), ischaemic heart disease occurred in 3.2% of patients receiving NUBEQA and 2.5% receiving placebo, including Grade 3-4 events in 1.7% and 0.4%, respectively. Ischaemic events led to death in 0.3% of patients receiving NUBEQA and 0.2% receiving placebo.

In a randomised study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 2.9% of patients receiving NUBEQA with docetaxel and 2% receiving placebo with docetaxel. This included Grade 3-4 events in 1.3% and 1.1%, respectively. Ischaemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel and 0.1% receiving placebo with docetaxel.

Patients should be monitored for signs and symptoms of ischemic heart disease. Optimise management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidaemia.

Seizure

Seizure occurred in patients receiving NUBEQA. Patients with a history of seizure were permitted to enrol in the clinical trials. However, all seizure events in patients receiving NUBEQA occurred in patients without prior history of seizure. In clinical trials, none of the patients permanently discontinued therapy due to seizure.

In a randomised study of patients with nmCRPC, seizure (grade 1-2) occurred in 0.2% of patients receiving NUBEQA or placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA.

In a randomised study of patients with mHSPC, seizure occurred in 0.6% of patients receiving NUBEQA+docetaxel, including one grade 3 event, and 0.2% of patients receiving placebo+docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA.

Use in hepatic impairment

See section 4.2 DOSE AND METHOD OF ADMINISTRATION - Additional information on special populations in Patients with hepatic impairment

Use in renal impairment

See section 4.2 DOSE AND METHOD OF ADMINISTRATION - Additional information on special populations in Patients with renal impairment

Use in the elderly

See section 4.2 DOSE AND METHOD OF ADMINISTRATION - Additional information on special populations in Geriatric patients

Paediatric use

See section 4.2 DOSE AND METHOD OF ADMINISTRATION - Additional information on special populations in Paediatric patients

Effects on laboratory tests

See section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS).

4.6 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other medicinal products on darolutamide

CYP3A4 and P-gp inducers

Darolutamide is a substrate of CYP3A4 and P-glycoprotein (P-gp).

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

Concomitant use of darolutamide with combined strong CYP3A4 inducers and P-gp inducers (*e.g.,* carbamazepine, phenobarbital, St. John's Wort) should be avoided (as this decreases darolutamide exposure) unless there is no therapeutic alternative. Selection of an alternate 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 resulted in no clinically relevant changes in the pharmacokinetics of darolutamide in mHSPC patients (see section **5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials**).

CYP3A4, P-gp and BCRP inhibitors

Darolutamide is a substrate of CYP3A4, P-gp and Breast Cancer Resistance Protein (BCRP).

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 of Cmax of darolutamide.

Consider alternative therapies that do not strongly inhibit CYP3A4 and/or P-gp activity and thus may increase darolutamide exposure. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for darolutamide related adverse events.

Effects of darolutamide on other medicinal products

BCRP, OATP1B1 and OATP1B3 substrates

Darolutamide is an inhibitor of Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3

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 Cmax of rosuvastatin.

This indicates that co-administration of NUBEQA may increase the plasma concentrations of other concomitant BCRP, OATP1B1 or OATP1B3 substrates (*e.g.,* methotrexate, sulfasalazine, fluvastatin, atorvastatin).

Avoid concomitant use with BCRP substrates where possible.

If used together, the related monitoring advice and recommendations in the product information of the BCRP, OATP1B1, or OATP1B3 substrates should be followed.

Docetaxel

Administration of darolutamide in combination with docetaxel resulted in no clinically relevant changes in the pharmacokinetics of docetaxel in mHSPC patients (see section **5.1 PHARMACODYNAMIC PROPERTIES – Clinical Trials**)

P-gp substrates

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

This indicates that NUBEQA may be given concomitantly with P-gp substrates without a clinically relevant drug-drug interaction.

CYP substrates

Darolutamide is a weak 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 Cmax of midazolam by 29% and 32%, respectively.

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

This indicates that NUBEQA may be given concomitantly with CYP substrates (*e.g.,* warfarin, L-thyroxine, omeprazole) without a clinically relevant drug-drug interaction.

Substrates for other transporters

In vitro data indicate darolutamide administration may inhibit OAT3, MATE1, MATE2K and intestinal MRP2. Darolutamide did not inhibit the transporters, BSEP, OAT1, OCTs, OATP2B1 and NTCP at clinically relevant concentrations.

4.7 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

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

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.

Use in pregnancy (Category D)

Pregnancy and breast-feeding

NUBEQA is contraindicated in women who are or may become pregnant. Based on its mechanism of action, NUBEQA may cause foetal harm when administered during pregnancy. There are no data available with the use of NUBEQA during pregnancy in humans. It is not known whether darolutamide or its metabolites are present in semen. Exposure of the foetus to an androgen receptor inhibitor through seminal transfer to the pregnant woman has to be avoided, as this could affect development of the foetus. Patients having sex with pregnant women should use a condom during and for three months after the last dose of NUBEQA.

Women of childbearing potential / Contraception in males and females

NUBEQA may be harmful to a developing foetus. Patients having sex with female partners of reproductive potential should use a condom along with another highly effective contraceptive method during treatment and for three months after the last dose of NUBEQA.

Use in lactation

NUBEQA is not indicated in women. NUBEQA is not to be used in women who are, or may be, pregnant or breast-feeding.

4.8 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no evidence that NUBEQA will affect the ability to drive or use machines.

4.9 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems (Australia) or https://nzphvc.otago.ac.nz/reporting/ (New Zealand).

Summary of the safety profile

nmCRPC (ARAMIS)

The safety profile of NUBEQA in nmCRPC is based on data from 1508 patients of whom 954 received at least one dose of NUBEQA in the ARAMIS study.

The **most frequently** observed adverse drug reaction (≥ 10 %) in patients with nmCRPC receiving NUBEQA is fatigue.

Serious adverse events occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse events, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse events occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse events requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dosage interruptions due to adverse events occurred in 13% of patients treated with NUBEQA. The most frequent adverse events requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhoea (0.5%), and pneumonia (0.5%).

Dosage reductions due to adverse events occurred in 6% of patients treated with NUBEQA. The most frequent adverse events requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

mHSPC (ARASENS)

The safety profile of NUBEQA in mHSPC is based on data from 1302 patients of whom 652 received at least one dose of NUBEQA in the ARASENS study.

The **most frequently** observed adverse drug reaction (≥10%) in patients with mHSPC receiving NUBEQA in combination with docetaxel were constipation (23%), decreased appetite (19%), rash (19%) and hypertension (14%).).

The most frequently observed adverse events (≥20%) in patients receiving NUBEQA+docetaxel were alopecia (40.5%), fatigue (33.1%), anaemia (27.8%), arthralgia (27.3%), oedema peripheral (26.5%), neutrophil count decreased (26.1%), diarrhoea (25.6%), white blood cell count decreased (23.8%), and constipation (22.5%). Serious adverse events occurred in 44.8% of patients receiving NUBEQA+docetaxel and in 42.3% of patients receiving placebo+docetaxel. Serious adverse events in ≥2% of patients who received NUBEQA+docetaxel included febrile neutropenia (6.1%), neutrophil count decreased (2.8%), and pneumonia (2.5%). Overall, 4.1% of patients receiving NUBEQA+docetaxel and 4.0% receiving placebo+docetaxel died from adverse events. Deaths reported in ≥2 patients in the NUBEQA+docetaxel arm included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%).

Permanent discontinuation of study drug due to adverse events occurred in 13.5% of patients who received NUBEQA+docetaxel and 10.6% of patients who received placebo+docetaxel. The most

frequent adverse events requiring discontinuation in patients who received NUBEQA+docetaxel included rash (1.1%), aspartate aminotransferase (AST) increased (0.9%), and alanine aminotransferase (ALT) increased (0.8%).

Dose interruption of study drug due to adverse events occurred in 22.9% of patients treated with NUBEQA+docetaxel and in 15.7% of patients who received placebo+docetaxel. The most frequent adverse events requiring dosage interruption in patients who received NUBEQA+docetaxel included ALT increased (3.2%), AST increased (3.1%), and febrile neutropenia (2.1%).

Dose reductions of study drug due to adverse events occurred in 8.7% of patients treated with NUBEQA+docetaxel and in 4.3% of patients who received placebo+docetaxel. The most frequent adverse events requiring dosage reduction in patients treated with NUBEQA+docetaxel included ALT increased (2.8%), and AST increased (2.5%).

Tabulated list of adverse reactions

The adverse drug reactions observed in patients with nmCRPC treated with NUBEQA are listed in **Table 1, Table 2,** and **Table 4**. The adverse drug reactions observed in patients with mHSPC treated with NUBEQA in combination with docetaxel are listed in **Table 3** and **Table 5**.

They are classified according to System Organ Class (MedDRA). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

Adverse drug reactions are grouped according to their frequencies. Frequency groups are defined by the following convention: very common: ≥ 1/10; common: ≥ 1/100 to < 1/10.

Within each frequency group, adverse drug reactions are presented in order of decreasing seriousness.

nmCRPC (ARAMIS)

Table 1: Adverse drug reactions reported in patients treated with NUBEQA in the ARAMIS study

System Organ Class (MedDRA version 21.0)	Very common	Common
Skin and subcutaneous tissue disorders		Rash[a]
Musculoskeletal and connective tissue disorders		Pain in extremity
General disorders and administration site conditions	Fatigue[b]	

[a] Included rash, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, dermatitis

[b] Included asthenia, fatigue, malaise, lethargy

Table 2: Incidence of adverse drug reactions (≥1%) reported in patients treated with NUBEQA in ARAMIS and reported more frequently than in patients receiving placebo

System Organ Class Preferred Term	NUBEQA (n=954)		Placebo (n=554)	
	Grade		Grade	
	All %	3-4 %	All %	3-4 %
Musculoskeletal and Connective Tissue Disorders				
Pain in Extremity	5.8	0	3.2	0.2
Skin and subcutaneous tissue disorders				
Rash	2.9	0.1	0.9	0
General disorders and administration site conditions				
Fatigue	15.8	0.6	11.4	1.1

Cardiovascular

Ischaemic heart disease occurred in 3.2% of patients treated with NUBEQA and in 2.5% of patients treated with placebo. Grade 3 or 4 reactions occurred in 1.7% of patients treated with NUBEQA and 0.4% of patients treated with placebo. Heart failure occurred in 1.9% of patients treated with NUBEQA and in 0.9% of patients treated with placebo. Grade 3 or 4 reactions occurred only in the NUBEQA arm in 0.5% of patients.

mHSPC (ARASENS)

Table 3: Adverse drug reactions that occurred at an incidence of ≥10% in patients treated with NUBEQA+docetaxel with a ≥2% absolute increase in frequency compared to placebo+docetaxel in ARASENS[a]

System/Organ Class Preferred Term MedDRA Version 24.1	NUBEQA+docetaxel (n=652)		Placebo+docetaxel (n=650)	
	Grade		Grade	
	All n (%)	3-4 n (%)	All n (%)	3-4 n (%)
Gastrointestinal disorders				
Constipation[b]	147 (23%)	2 (0.3%)	130 (20%)	2 (0.3%)
Investigations				
Weight increased	116 (18%)	14 (2%)	102 (16%)	8 (1%)
Metabolism and nutrition disorders				
Decreased appetite[b]	121 (19%)	1 (0.2%)	85 (13%)	4 (0.6%)
Musculoskeletal and connective tissue disorders				
Pain in extremity[b]	98 (15%)	2 (0.3%)	78 (12%)	2 (0.3%)
Vascular disorders				
Haemorrhage[c]	115 (18%)	9 (1%)	85 (13%)	9 (1%)
Hypertension[d]	90 (14%)	43 (7%)	61 (9%)	24 (4%)
Skin and subcutaneous tissue disorders				
Rash [b,e]	125 (19%)	12 (2%)	98 (15%)	1 (0.2%)

a. Adverse drug reaction incidence presented in Table 3 may not be attributable to NUBEQA alone but may contain contributions from other medicinal products used in combination
b. The incidence was highest during the first 6 months of treatment
c. Includes haematuria, epistaxis, anal haemorrhage, haemorrhoidal haemorrhage, rectal haemorrhage, upper gastrointestinal haemorrhage, haemoptysis, haemorrhage urinary tract, haemorrhagic stroke, subarachnoid haemorrhage, lower gastrointestinal haemorrhage, cystitis haemorrhagic, gastrointestinal haemorrhage, haemorrhage subcutaneous, intra-abdominal haemorrhage, nail bed bleeding, subdural haemorrhage
d. Includes hypertension, blood pressure increased, hypertensive crisis, hypertensive emergency
e. Includes rash, rash maculo-papular, palmar-plantar erythrodysaesthesia syndrome, eczema, dermatitis, skin exfoliation, dermatitis acneiform, drug eruption, rash pruritic, rash erythematous, erythema multiforme, rash macular, dermatitis exfoliative generalized, penile rash, dyshidrotic eczema, rash papular, dermatitis bullous, rash follicular, rash pustular, rash vesicular, toxic skin eruption

Laboratory test abnormalities

Hepatic Impairment

Drug-induced liver injury with increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to ≥5x and ≥20x upper limit of normal (ULN) has been reported in patients treated with NUBEQA in clinical trials. Time to onset ranged from 1 month to 10.5 months after initiation of NUBEQA. The ALT and AST elevations were reversible upon NUBEQA discontinuation. Monitor ALT and AST as per routine clinical practice.

In case of hepatic transaminase elevations suggestive of idiosyncratic drug-induced liver injury related to NUBEQA, permanently discontinue NUBEQA.

nmCRPC (ARAMIS)

Table 4: Laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study

Laboratory parameter (in % of samples investigated)	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 parameter may be different. The incidence of each laboratory test abnormality was calculated accordingly.

** Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory test values (no clinical assessments) were used for the grading. Grade 4 laboratory test values were limited to neutrophil count decreased.

mHSPC (ARASENS)

Table 5: Laboratory test abnormalities occurring in ≥30% of NUBEQA+docetaxel - Treated Patients and at a Higher Incidence than Placebo+docetaxel in ARASENS[1] (mHSPC)

Laboratory parameter	NUBEQA+docetaxel (N=652)[2]		Placebo+docetaxel (N=650)[2]	
	All Grades[3] (%)	Grade 3/4[3] (%)	All Grades[3] (%)	Grade 3/4[3] (%)
Blood and lymphatic system disorders				
Anaemia	96	6	94	7
Investigations				
White blood cell count decreased	56	27	52	26
Neutrophil count decreased	51	34	46	31
ALT increased	42	4	38	3
AST increased	44	4	39	2

Metabolism and nutrition disorders				
Hyperglycaemia	75	9	71	12
Hypocalcaemia	35	3	31	2

1 Laboratory test abnormalities presented in Table 5 may not be attributable to NUBEQA but may contain contributions from other medicinal products used in combination.
2 The number of patients tested for a specific laboratory test parameter may be different. The incidence of each laboratory test abnormality was calculated accordingly.
3 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Only laboratory test values (no clinical assessments) were used for the grading.

4.10 OVERDOSE

For general advice on overdose management, contact the Poisons Information Centre, telephone number 13 11 26 (Australia) or the National Poisons Centre, 0800 POISON or 0800 764 766 (New Zealand).

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 **5.2 PHARMACOKINETIC PROPERTIES**) 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Anti-androgens ATC code: L02BB06

Mechanism of action

Darolutamide is a non-steroidal androgen receptor antagonist with a flexible polar-substituted pyrazole structure that binds with nanomolar affinity directly to the receptor ligand binding domain to retain antagonistic activity against the androgen receptor (AR).

Darolutamide competitively inhibits androgen binding, androgen receptor nuclear translocation and AR mediated transcription.

Darolutamide had significant in vivo anti-tumour efficacy (decreased tumour cell proliferation) leading to decreased tumour volume in xenograft models of prostate cancer implemented in mice, including the castration-resistant model VCaP which overexpresses the AR.

Pharmacodynamic effects

Patients receiving darolutamide in the ARAMIS study demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 84% versus 7.9% (difference = 76.1%, $p < 0.000001$).

Patients receiving darolutamide+docetaxel in the ARASENS study had a significantly higher PSA response rate (defined as a ≥ 50% reduction from baseline) at 12 months after randomisation compared with patients receiving placebo + docetaxel, 89.6% versus 80.4% (difference = 9.2, $p < 0.0001$).

No prolongation of the mean QTcF interval (*i.e.*, greater than 10 ms) was observed after oral administration of 600 mg darolutamide twice daily compared to placebo in a subgroup of 500 patients in the phase III study (ARAMIS).

Clinical trials

Non-metastatic castration resistant prostate cancer (nmCRPC)

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 matching placebo (n=554).

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 was assessed by independent central radiological review. Included in these analyses were 89 patients that were retrospectively identified with metastasis at baseline. Randomisation was stratified by PSADT (≤ 6 months or > 6 months) and use of osteoclast-targeted therapy at study entry (yes or no).

The following patient demographics and disease characteristics were balanced between treatment arms. The median age was 74 years (range 48-95) 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 had a Gleason score of 7 or higher at diagnosis (73%). The median PSADT was 4.5 months. Nine percent (9%) of patients had prior orchiectomy, 25% of patients had prior prostatectomy and 50% of patients had at least one prior radiotherapy. Seventy-six percent (76%) of patients received more than one prior anti-hormonal treatment. Most patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 (69%) at study entry. Patients with a medical history of seizure were allowed to enter the study, and 12 patients (0.21%) were enrolled in the darolutamide arm.

Treatment with NUBEQA continued until radiographic disease progression as assessed by conventional imaging (CT, MRI, Tc99m bone scan) by blinded central review, unacceptable toxicity, or withdrawal.

The primary efficacy endpoint was metastasis free survival (MFS). Secondary endpoints were overall survival (OS), time to pain progression, time to initiation of first cytotoxic chemotherapy for prostate cancer, and time to first symptomatic skeletal events (defined as occurrence of any of the following: external beam radiotherapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumour-related orthopaedic surgical intervention).

Treatment with NUBEQA resulted in a statistically significant improvement in MFS compared to placebo with a p-value of <0.000001 and a hazard ratio (HR) of 0.413 (see Table 6 and Figure 1).

MFS results were consistent across patient subgroups regardless of PSADT, prior use of bone-targeting agents or loco-regional disease. Additional subgroups with consistent MFS results included PSA at baseline, Gleason score at diagnosis, age, geographical region, ECOG PS at baseline, race, and number of prior hormonal therapies.

After the primary analysis of MFS, patients receiving placebo were offered treatment with open-label NUBEQA (cross-over option) once the study was unblinded. Among the 554 patients randomised to placebo, 170 (31%) crossed over to receive NUBEQA treatment. The OS analysis was not adjusted for confounding effects of cross-over.

At the time of the final analysis, treatment with NUBEQA resulted in a statistically significant improvement in overall survival compared to placebo (HR=0.685, p=0.003048, median was not reached in either arm, see Table 6 and Figure 2.

Treatment with NUBEQA also resulted in statistically significant delays in time to pain progression (HR=0.647, p=0.000008), time to initiation of first cytotoxic chemotherapy (HR=0.579, p=0.000044) and time to first symptomatic skeletal event (HR=0.484, p=0.005294) compared to placebo, see Table 6.

All analyses were performed in the full analysis set.

Table 6: Efficacy Results from the ARAMIS study

Efficacy parameter	Number of events (%)		Median (95% CI)		Hazard Ratio [b] (95% Confidence Interval [CI]) p-value (two-sided)
	NUBEQA (N=955)	Placebo [a] (N=554)	NUBEQA (N=955)	Placebo [a] (N=554)	
Metastasis free survival [c]	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	148 (15.5%)	106 (19.1%)	NR (56.1, NR)	NR (46.9, NR)	0.685 (0.533, 0.881) 0.003048
Time to pain progression [c, d]	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) 0.000008
Time to initiation of cytotoxic chemotherapy	127 (13.3%)	98 (17.7%)	NR (NR, NR)	NR (NR, NR)	0.579 (0.444, 0.755) <0.000044
Time to first symptomatic skeletal event	29 (3.0%)	28 (5.1%)	NR (NR, NR)	NR (NR, NR)	0.484 (0.287, 0.815) 0.005294

a Including 170 patients who crossed over to open-label darolutamide

b Hazard ratio < 1 favours NUBEQA

c For MFS and time to pain progression, the analysis performed at the time of primary completion is considered as the final analysis

d Patient reported outcome as evaluated by Brief Pain Inventory-Short Form questionnaire

NR not reached

Figure 1: Kaplan-Meier curves of metastasis free survival (ARAMIS)

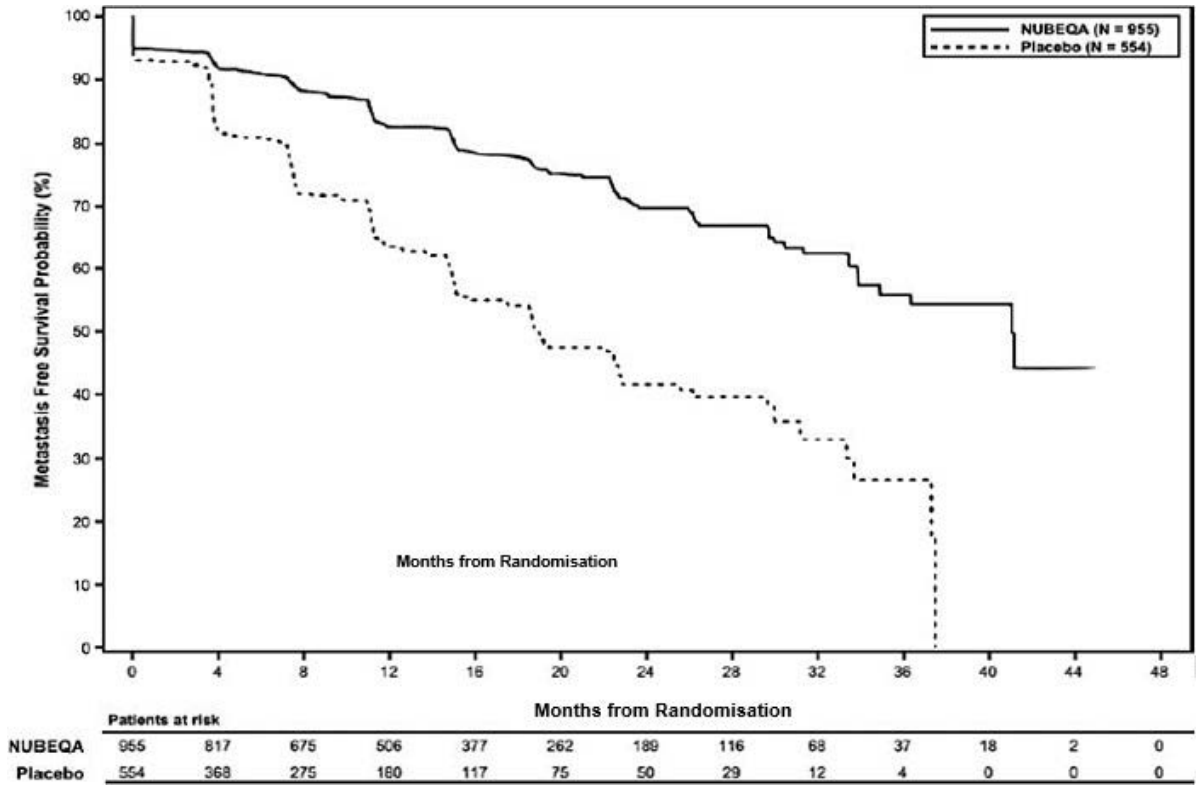
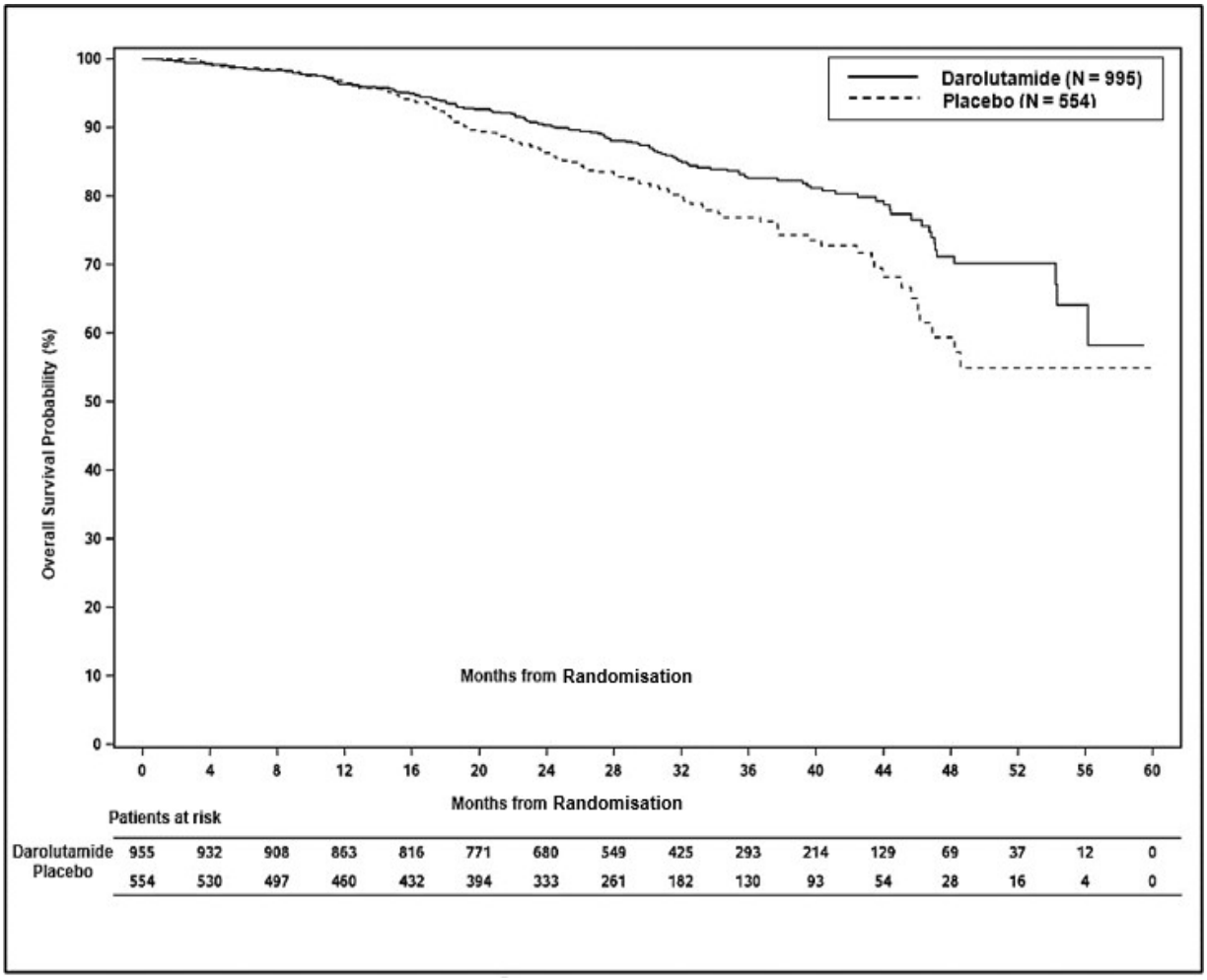


Figure 2: Kaplan-Meier curves of overall survival (ARAMIS)



Metastatic hormone sensitive prostate cancer (mHSPC)

The efficacy and safety of NUBEQA in combination with docetaxel was assessed in a multicentre, double-blind, placebo-controlled phase III study (ARASENS) in patients with mHSPC. In total, 1305 patients were randomised (1:1) to receive 600 mg darolutamide orally twice daily (n=651) or matching placebo (n=654), concomitantly with 75 mg/m2 of docetaxel, for 6 cycles. All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a bilateral orchiectomy. Patients should receive ADT (LHRH agonist/ antagonists or orchiectomy) as standard therapy started ≤12 weeks before NUBEQA and docetaxel (if combined with a first–generation anti-androgen, such as bicalutamide, flutamide, nilutamide, or cyproterone acetate, it must be stopped before treatment). For those receiving LHRH agonists, treatment in combination with a first-generation anti-androgen for at least 4 weeks prior to commencing NUBEQA and docetaxel was recommended.

Treatment with NUBEQA or placebo continued until symptomatic progressive disease, change of antineoplastic therapy, unacceptable toxicity, death, or withdrawal.

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 nodes 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) at study entry.

The following patient demographics and disease characteristics were balanced between treatment arms. The median age was 67 years (range 41-89) and 17% of patients were 75 years of age or older. The racial distribution was 52% White, 36% Asian, and 4% Black. A majority of patients had a Gleason score of 8 or higher at diagnosis (78%). Seventy-one percent (71%) of patients had an ECOG PS score of 0 and 29% of patients had an ECOG PS score of 1. There were 86.1% of patients with de novo and 12.9% with recurrent disease. At study entry, 3% of patients had M1a, 79.5% had M1b and 17.5% had M1c; alkaline phosphatase was <ULN in 44.5% of patients and ≥ ULN in 55.5% of patients; median PSA level at baseline was 30.3 µg/L and 24.2 µg/L for NUBEQA vs placebo group, respectively. Patients with a medical history of seizure were allowed to enter the study, and 4 patients (0.6%) were enrolled in the NUBEQA+docetaxel arm and 2 patients (0.3%) in the placebo+docetaxel arm.

The primary efficacy endpoint was overall survival (OS). Secondary endpoints evaluated in hierarchical order were time to castration–resistant prostate cancer, time to pain progression, symptomatic skeletal event free survival (SSE–FS), time to first symptomatic skeletal event (SSE), time to initiation of subsequent antineoplastic therapy, time to worsening of disease-related physical symptoms, and time to initiation of opioid use for ≥7 consecutive days.

A statistically significant improvement in OS with a 32.5% reduction in risk of death (HR=0.675, p<0.0001) was observed in the NUBEQA+docetaxel arm compared to the placebo+docetaxel arm (see Table 7 and Figure 3). OS results were consistent across all patient subgroups, including stratification subgroups (extent of disease and alkaline phosphatase level).

The following secondary efficacy endpoints showed a statistically significant advantage in favour of NUBEQA+docetaxel: time to castration–resistant prostate cancer (HR=0.357, p<0.0001), time to pain progression (HR=0.792, p=0.0058), symptomatic skeletal event free survival (HR=0.609, p<0.0001, time to first symptomatic skeletal event (HR=0.712, p=0.0081), and time to initiation of subsequent antineoplastic chemotherapy (HR=0.388, p<0.0001), see Table 7.

For the time to castration-resistant prostate cancer endpoint, although PSA progression represented the majority of events in both treatment arms, the proportion of radiological progression events in the absence of PSA progression was higher in the darolutamide+docetaxel arm.

Table 7: Efficacy Results from the ARASENS study[h]

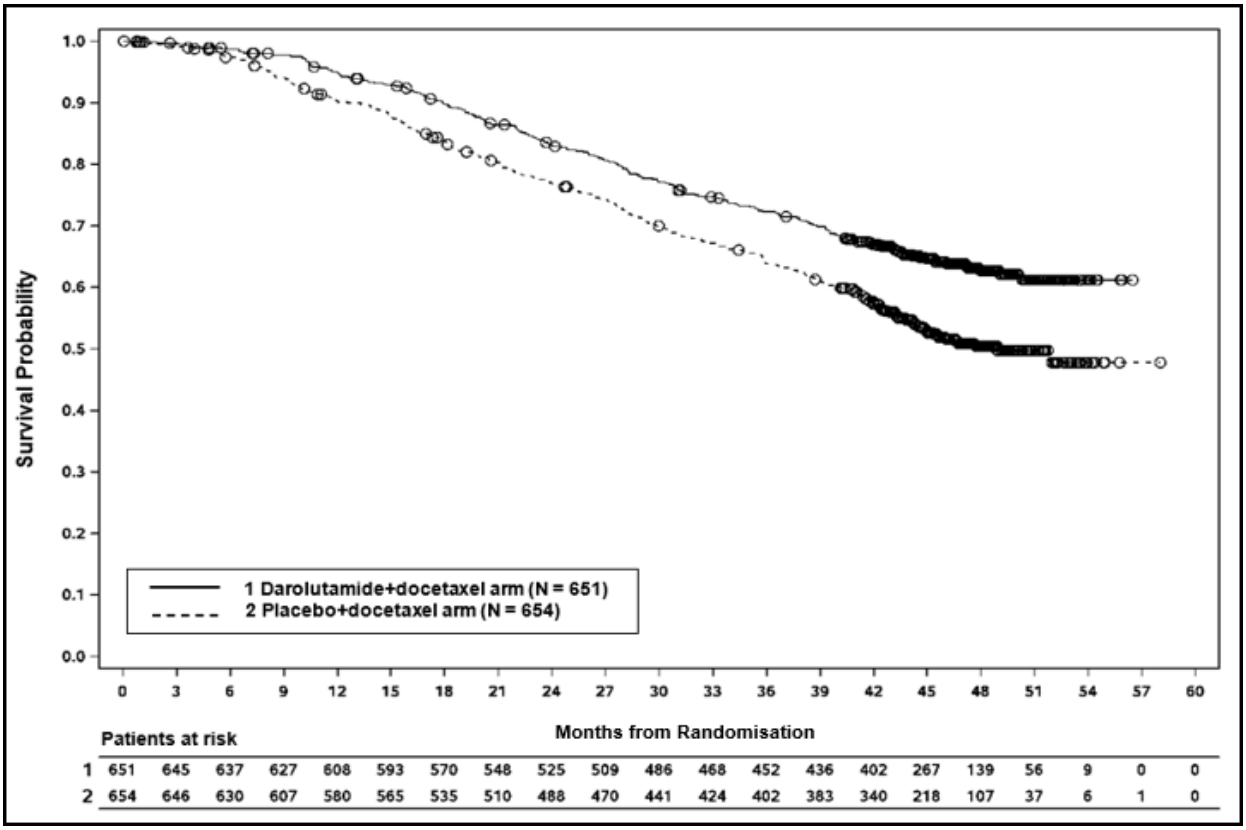
Efficacy parameter	Number (%) of patients with events		Median in months (95% CI)		Hazard Ratio[b] (95%Confidence Interval [CI]) p-value (one-sided)[c]
	NUBEQA+ docetaxel (N=651)	Placebo+ docetaxel (N=654)[a]	NUBEQA+ docetaxel (N=651)	Placebo+ docetaxel (N=654)[a]	
Primary Endpoint					
Overall survival	229 (35.2%)	304 (46.5%)	NR (NR, NR)	48.9 (44.4, NR)	0.675 (0.568, 0.801) <0.0001
Key Secondary Endpoints					
Time to CRPC[d]	225 (34.6%)	391 (59.8%)	NR (NR, NR)	19.1 (16.5, 21.8)	0.357 (0.302, 0.421) <0.0001
Time to pain progression[e]	222 (34.1%)	248 (37.9%)	NR (30.5, NR)	27.5 (22.0, 36.1)	0.792 (0.660, 0.950) 0.0058
Symptomatic skeletal event free survival (SSE–FS)[f]	257 (39.5%)	329 (50.3%)	51.2 (47.2, NR)	39.7 (36.0, 42.3)	0.609 (0.516, 0.718) <0.0001
Time to first	95	108	NR	NR	0.712

symptomatic skeletal event (SSE)[g]	(14.6%)	(16.5%)	(NR, NR)	(NR, NR)	(0.539, 0.940) 0.0081
Time to initiation of subsequent antineoplastic therapy	219 (33.6%)	395 (60.4%)	NR (NR, NR)	25.3 (23.1, 28.8)	0.388 (0.328, 0.458) <0.0001

a One patient in the placebo arm was excluded from all analyses
b Hazard ratio < 1 favours NUBEQA
c Based on stratified log-rank test
d Time to CRPC defined as time from randomisation to first occurrence of: PSA progression (≥25% increase and an absolute increase of 2 ng/mL or more from nadir), radiological progression by soft tissue and visceral lesions according to RECIST version 1.1, or radiological progression by bone lesions.
e Evaluated by BPI-SF and initiation of short- or long-acting opioid for pain for ≥7 consecutive days. Analysis included patients who received subsequent anti-cancer therapies.
f SSE-FS defined as time from randomisation to first occurrence of an SSE or death from any cause. SSE defined as first occurrence of: external beam radiation therapy (EBRT) to relieve skeletal symptoms, new symptomatic pathologic bone fracture, spinal cord compression, or tumor-related orthopaedic surgical intervention. The number of deaths in this analysis was 162 for the NUBEQA+docetaxel arm and 221 for the docetaxel+placebo arm. Analysis included patients who received subsequent anti-cancer therapies.
g Time to first SSE defined as time from randomisation to first occurrence of an SSE. Analysis included patients who received subsequent anti-cancer therapies.
h 87.6% and 85.5% of patients received full 6 cycles of docetaxel and 1.5% and 2.0 % of patients did not receive docetaxel, in darolutamide+docetaxel and placebo+docetaxel arm, respectively (based on SAF population).

CRPC=castration-resistant prostate cancer
NR=not reached

Figure 3: Kaplan-Meier curves of overall survival; mHSPC population (ARASENS)[a]



[a] OS rate at 36 months was 72.3% (95% CI, 68.8 to 75.8) in the NUBEQA+docetaxel arm versus 63.8% (95% CI, 60.1 to 67.6) in the placebo+docetaxel arm. OS rate at 48 months was 62.7% (95% CI, 58.7 to 66.7) in the NUBEQA+docetaxel arm versus 50.4% (95% CI, 46.3 to 54.6) in the placebo+docetaxel arm.

5.2 PHARMACOKINETIC PROPERTIES

Darolutamide consists of two diastereomers [(S,R) darolutamide and (S,S) darolutamide] which interconvert via the main circulating metabolite called keto-darolutamide. *In vitro*, all three substances show similar pharmacological activity. Darolutamide is poorly soluble in aqueous solvents over a large pH range and generally more soluble in organic solvents.

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 usually reached around 4 hours after administration. The ratio of the two diastereomers, (S,R) darolutamide to (S,S) darolutamide, changed from a 1:1 ratio in the tablet to an approximately 1:9 ratio in plasma based on AUC(0-12) data at steady-state. Following oral administration together with food, steady-state is reached after 2-5 days of repeated twice-daily dosing.

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 administered with food. A similar increase of 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 without any difference between the two diastereomers. The major metabolite of darolutamide, keto-darolutamide, is highly (99.8%) bound to plasma proteins.

Passage of darolutamide across the blood-brain barrier has not been studied clinically. However, brain exposures to darolutamide in terms of AUC (0 - 24) are very low with 4.5% of plasma exposure after single dose in rats and 2-4% after repeated dose in mice. This indicates low passage of darolutamide across the intact blood-brain barrier in rats and mice and a low likelihood that darolutamide crosses the intact blood-brain barrier in humans to a clinically relevant extent.

Metabolism

The diastereomers (S,R) darolutamide and (S,S) darolutamide are able to interconvert via the metabolite keto-darolutamide with a preference for (S,S) darolutamide.

Following single oral administration of 300 mg ^{14}C-darolutamide given as an oral solution, keto darolutamide is the only major metabolite with about 2-fold higher total exposure in plasma compared to darolutamide. Darolutamide and keto-darolutamide accounted together for 87.4% of the ^{14}C-radioactivity in plasma indicating that all other metabolites are of minor importance.

Darolutamide is metabolized primarily by oxidative metabolism mediated mainly by CYP3A4, as well as by direct glucuronidation mediated preferentially by UGT1A9 and UGT1A1. In addition, mainly the AKR1C3 to a lesser extent AKR1C1 and AKR1D1 aldo-keto reductase isoforms were shown to catalyse the reduction of keto-darolutamide to primarily the S,S-diastereomer.

Excretion

The effective half-life of darolutamide and keto-darolutamide in plasma of patients is approximately 20 hours. Of the two diastereomers comprising darolutamide, (S,R) darolutamide has a shorter effective half-life of 9 hours compared to (S,S) darolutamide with an effective half-life of 22 hours.

The clearance of darolutamide following intravenous administration was 116 mL/min (CV: 39.7%). A total of 63.4% of drug related material is excreted in the urine (approximately 7% unchanged), 32.4% is excreted in the faeces. More than 95% of the dose was recovered within 7 days after administration.

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure to the two diastereomers 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.

Additional information on special populations

Pediatric patients

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

Elderly

No clinically relevant differences in the pharmacokinetics of darolutamide were observed based on age (41-95 years).

Patients with hepatic impairment

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

Patients with renal impairment

In a clinical pharmacokinetic study, AUC and Cmax 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 volunteers.

A population pharmacokinetic analysis indicates a 1.1 and 1.3-fold higher exposure (AUC) of darolutamide in patients with mild and 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).

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Darolutamide did not induce mutations in the microbial mutagenesis (Ames) assay. At high concentrations, darolutamide did induce structural chromosome aberrations in vitro 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 for human use.

Carcinogenicity

Long-term animal studies to evaluate the carcinogenic potential of darolutamide have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet core
Calcium hydrogen phosphate dihydrate
Croscarmellose sodium
Lactose monohydrate
Magnesium stearate
Povidone

Film coat
Hypromellose
Lactose monohydrate
Macrogol 3350
Titanium dioxide

6.2 INCOMPATIBILITIES

Not applicable.

6.3 SHELF LIFE

Bottle: Keep the bottle tightly closed after first opening. Once the bottle is opened the medicinal product has shown to be stable for 3 months.

Information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30˚C. Store in original container.

6.5 NATURE AND CONTENTS OF CONTAINER

Blister: Each package contains 112 film coated tablets in PVC/Aluminium foil blisters (7 x 16).

Bottle*: Each 120 mL PE white opaque bottle contains 120 tablets and closed with PP/PP white opaque seal PE child-resistant screw cap

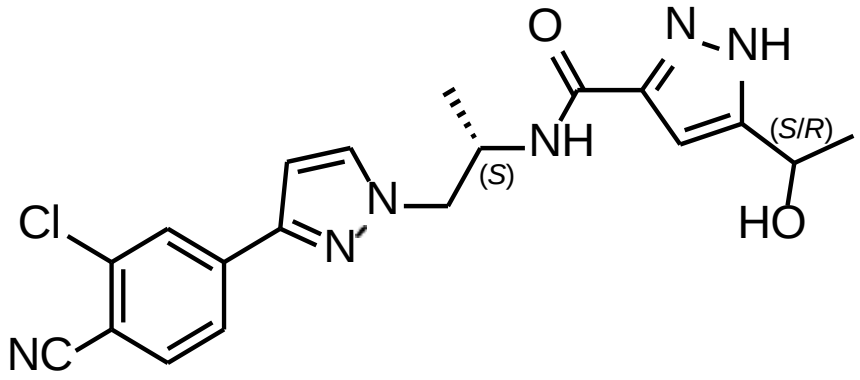
* Not currently marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure



Chemical name:	N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide
Empirical formula:	$C_{19}H_{19}ClN_6O_2$
Molecular weight:	398.85
CAS:	1297538-32-9

7 MEDICINE SCHEDULE (POISONS STANDARD)

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9 DATE OF FIRST APPROVAL

26 February 2020

10 DATE OF REVISION

DD Month YYYY

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All sections	Editorial update to fonts and lay-outs
2	Change statement to 'Contains sugars as lactose'
4.1	Inclusion of additional indication (treatment of mHSPC patients)
4.2	Inclusion of information related to the additional indication (dosing with docetaxel)
4.4	Inclusion of additional information on cardiovascular and seizure
4.5	Inclusion of docetaxel information
4.8	Inclusion of information related to the additional indication; safety profile from ARASENS study (mHSPC) Inclusion of Hepatic transaminase elevations (Hepatic impairment)
4.1	Inclusion of updated information related to the additional indication: pharmacodynamic effects (darolutamide+docetaxel) and clinical trials
5.1	Inclusion of additional indication (treatment of mHSPC patients)
5.2	Update to elderly population age range