PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrNUBEQA®

Darolutamide tablets

Tablet, 300mg, oral

Anti-androgen

ATC Code: L02BB06

Bayer Inc.
2920 Matheson Blvd East,
Mississauga, Ontario
L4W 5R6
www.bayer.ca

Submission Control No: 243046

Date of Initial Approval:
February 19, 2020

Date of Revision:
July 14, 2021

RECENT MAJOR LABEL CHANGES

Not applicable.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1. INDICATIONS

NUBEQA (darolutamide) is indicated for:

- The treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

NUBEQA has not been studied in patients with nmCRPC at low risk of developing metastases (see CLINICAL TRIALS). The benefit and risk profile in these patients is unknown.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥ 65 years of age): Evidence from clinical studies do not suggest clinically relevant differences in safety or efficacy associated with the use of NUBEQA in the geriatric population.

2. CONTRAINDICATIONS

NUBEQA is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4. DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- The tablets should be taken whole with food (see Pharmacokinetics).
- Patients receiving NUBEQA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

4.2 Recommended Dose and Dosage Adjustment

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

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, dosing should be withheld or reduced to 300 mg twice daily until symptoms improve. 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 daily dose is 1200 mg (600 mg twice daily).

Health Canada has not authorized an indication for pediatric use.

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 NUBEQA twice daily (see Pharmacokinetics). The effect of severe hepatic impairment (Child-Pugh C) on NUBEQA pharmacokinetics has not been studied.

Patients with renal impairment

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

The recommended dose for patients with severe renal impairment not receiving hemodialysis (estimated glomerular filtration rate (eGFR) of 15 to 29 mL/min/1.73m^2) is 300 mg NUBEQA twice daily (see Pharmacokinetics). Clinical experience in patients with severe renal impairment is limited.

The pharmacokinetics of NUBEQA has not been studied in patients with end-stage renal disease receiving dialysis (eGFR <15 mL/min/1.73 m^2).

4.3 Administration

For oral use.

4.4 Missed Dose

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.

5. OVERDOSAGE

There is no specific antidote for NUBEQA and symptoms of overdose are not established.

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.

In the event of an overdose, closely monitor patients for signs and symptoms of adverse reactions, and initiate appropriate symptomatic and supportive treatment (see ADVERSE REACTIONS; ACTION AND CLINICAL PHARMACOLOGY; NON-CLINICAL TOXICOLOGY).

For management of a suspected drug overdose, contact your regional poison control centre.

6. DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	tablet, 300 mg	Calcium hydrogen phosphate, croscarmellose sodium, hypromellose 15 cP, lactose monohydrate, Macrogol 3350, magnesium stearate, povidone K 30, titanium dioxide

NUBEQA (darolutamide) 300 mg tablet is presented as white to off-white film-coated oval tablets. The tablets are marked with BAYER on one side and with 300 on the other side. The product is supplied in 120 mL bottles of 120 tablets or blisters containing 112 tablets.

7. WARNINGS AND PRECAUTIONS

Monitoring and Laboratory Tests

Monitoring for laboratory or clinical parameters should be conducted as per routine practice.

Patients should be monitored for disease progression radiographically in addition to Prostate Specific Antigen (PSA), as 141 out of 221 patients treated with NUBEQA who reported radiographic progression (distant metastasis) did not have PSA progression in the ARAMIS trial.

Sexual Health

Reproduction

Based on the mechanism of action, darolutamide can cause harm to the developing fetus or lead to loss of pregnancy. If the patient is engaged in sexual activity with a pregnant woman, a condom should be used during and for 3 months after completion of treatment with NUBEQA.

If the patient is engaged in sexual activity with a woman of childbearing potential, a highly effective contraceptive method (<1% failure rate per year) should be used during and for 3 months after completion of treatment with NUBEQA to prevent pregnancy.

Fertility

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential (see NON-CLINICAL TOXICOLOGY). Male patients should not donate sperm during treatment and for 3 months after the last dose of NUBEQA.

7.1 Special Populations

7.1.1 Pregnant Women

NUBEQA is not indicated in women. There are no human data on the use of NUBEQA in pregnant women. Animal embryo fetal toxicology studies have not been performed. However, based on the mechanism of action, NUBEQA can cause embryo/fetal harm or loss of pregnancy. Therefore, NUBEQA is not to be used in women who are or may become pregnant.

7.1.2 Breast-feeding

NUBEQA is not indicated in women. No data exist on the presence of NUBEQA or its metabolites in human milk, its effects on the breast fed infant, or the effect on milk production. However, because many drugs are excreted in human milk, NUBEQA is not to be used in women who are breast-feeding.

7.1.3 Pediatrics

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Evidence from clinical studies do not suggest clinically relevant differences in safety or efficacy associated with the use of NUBEQA in the geriatric population.

8. ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of NUBEQA has been assessed in randomized, double-blind, placebo-controlled, multi-centre clinical study, ARAMIS, a Phase 3 trial consisting of 1509 patients with non-metastatic castration-resistant prostate cancer (nmCRPC), (see CLINICAL TRIALS).

The most frequently observed adverse reaction (≥ 10%) in patients receiving NUBEQA was fatigue.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1 % of patients who received NUBEQA included urinary retention, pneumonia and hematuria. Overall 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, 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 reactions occurred in 8.9% of patients treated with NUBEQA and 8.7% of patients who received placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%)

Adverse reactions leading to dose interruption occurred in 12.5% of patients treated with NUBEQA and in 8.8% of patients who received placebo. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hypertension (0.6%), diarrhea (0.5%), and pneumonia (0.5%).

Adverse reactions leading to dose reduction occurred in 4.8% of patients treated with NUBEQA and in 1.6% of patients who received placebo. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

ARAMIS, a phase III, randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic, castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg twice a day, or a placebo. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. Patients with uncontrolled hypertension or recent (in the past 6 months) stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft, congestive heart failure New York Heart Association (NYHA) Class III or IV were excluded from the study. 64.4% of patients on NUBEQA and 36.1% of patients on placebo were receiving ongoing treatment at the time of the primary analysis. The median duration of exposure at the time of the primary analysis was 14.8 months (range: 0.0 to 44.3 months) in patients who received NUBEQA and 11.0 months (range: 0.1 to 40.5 months) in patients who received placebo.

Table 2 shows the incidence of adverse drug reactions reported in patients treated with NUBEQA in ARAMIS that occurred with a ≥2% absolute increase in frequency compared to placebo.

Table 2 – Incidence of adverse drug reactions reported in patients treated with NUBEQA in ARAMIS that occurred with a ≥2% absolute increase in frequency compared to placebo

System/Organ Class Preferred Term MedDRA Version 21.0	NUBEQA (n=954)		Placebo (n=554)	
	Grade		Grade	
	All n (%)	3-4 n (%)	All n (%)	3-4 n (%)
General disorders and administration site conditions				
Fatigue[a]	151 (15.8%)	6 (0.6%)	63 (11.4%)	6 (1.1%)
Musculoskeletal and connective tissue disorders				
Pain in Extremity	55 (5.8%)	0	18 (3.2%)	1 (0.2%)
Skin and subcutaneous tissue disorders				
Rash[b]	28 (2.9%)	1 (0.1%)	5 (0.9%)	0

a includes Asthenia, Fatigue, Malaise, Lethargy
b includes Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pustular, Erythema, Dermatitis

At the final analysis, the median treatment duration was 25.8 months (range: 0.0 to 58.9) in patients who received NUBEQA and 11.6 months (range: 0.1 to 45.1 months) in patients who received placebo. The safety profile of NUBEQA remained consistent with the data presented in the primary analysis.

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.

Fractures

At the final analysis of the ARAMIS study, during the double blind period, bone fractures occurred in 5.5% of patients treated with NUBEQA and in 3.6% of patients treated with placebo. Grade 3 or 4 reactions occurred in 1.0% of patients treated with NUBEQA and 0.9% of patients treated with placebo. Bone fractures occurred in 8.3% of patients treated in the combined double blind and open label period with NUBEQA and Grade 3 or 4 reactions occurred in 1.4% of patients. No Grade 4 bone fracture reactions were reported with NUBEQA.

8.3 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and other Quantitative Data

Table 3 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMIS study.

Table 3 – Laboratory test abnormalities in NUBEQA-Treated Patients Occurring at a Higher Incidence than Placebo (Between Arm Difference of >5%) in ARAMIS

Laboratory parameter	NUBEQA (N=954)[1]		Placebo (N=554)[1]	
	All Grades[2] (%)	Grade 3/4[2] (%)	All Grades[2] (%)	Grade 3/4[2] (%)
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

1 The denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value

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

9. DRUG INTERACTIONS

9.2 Overview

Darolutamide is primarily metabolized by CYP3A4, which can be induced or inhibited by concomitant medications. Darolutamide is also a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). Concomitant use of darolutamide with combined P-gp and strong CYP3A4 inducers can decrease darolutamide exposure. Concomitant use of darolutamide with combined P-gp, BCRP and strong inhibitors of CYP3A4 can increase darolutamide exposure.

Darolutamide is also an inhibitor of BCRP, Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 and P-gp *in vitro*. Co-administration of darolutamide with a BCRP substrate can significantly increase exposure of the BCRP substrate. Co-administration of darolutamide with OATP1B1 and OATP1B3 substrates may increase exposure of the OATP1B1 and OATP1B3 substrates. Co-administration of darolutamide with a P-gp substrate (i.e. dabigatran etexilate) does not result in a clinically significant drug-drug interaction. This indicates that NUBEQA may be given concomitantly with P-gp substrates.

Darolutamide is a weak inducer of CYP3A4. Co-administration of darolutamide with a CYP3A4 substrate does not result in a clinically significant drug-drug interaction.

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

9.3 Drug-Drug Interactions

The drugs listed in this table are based drug interaction studies.

Table 4 - Established or Potential Drug-drug Interactions

Proper / Common name	Source of Evidence	Effect	Clinical Comment
Effect of CYP3A4 and P-gp inducers on darolutamide			
Rifampicin (600 mg)	CT	AUC ↓ 72% C_{max} ↓ 52%	Avoid concomitant use of strong CYP3A4 inducers and P-gp inducers during treatment with NUBEQA, unless there is no therapeutic alternative.
Effect of CYP3A4, P-gp and BCRP inhibitors on darolutamide			
Itraconazole (200 mg twice daily on day 1 and once daily on the following 7 days)	CT	AUC ↑ 1.7-fold C_{max} ↑ 1.4-fold	Consider alternative therapies that do not strongly inhibit CYP3A4 and/or P-gp activity. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for darolutamide related adverse events.
Effect of darolutamide on BCRP, OATP1B1 and OATP1B3 substrates			
Rosuvastatin (5 mg)	CT	AUC ↑ 5-fold C_{max} ↑ 5-fold	BCRP substrates: Avoid concomitant use if clinically feasible. If co-administration with NUBEQA is required, the related recommendation and monitoring advice in the Product Monograph of the BCRP substrate should be followed. OATP1B1 and OATP1B3 substrates: Concomitant use of NUBEQA may increase plasma exposure, therefore, the related recommendation and monitoring advice in the Product Monograph of the OATP1B1 and OATP1B3 substrates should be followed.
Effect of darolutamide on CYP3A4 substrates			
Midazolam (1 mg)	CT	AUC ↓ 29% C_{max} ↓ 32%	NUBEQA may be given concomitantly with CYP3A4 substrates.

Legend: CT=Clinical Trial

9.4 Drug-Food Interactions

Administration of darolutamide (2 x 300 mg) with a high-fat high-calorie meal resulted in a 2.5 fold increase in AUC_T and a 2.0 fold increase in C_{max} relative to administration of darolutamide (2 x 300 mg) under fasted conditions.

Administration of darolutamide (2 x 300 mg) with a low-fat low-calorie meal resulted in a 2.5 fold increase in AUC_T and a 2.8 fold increase in C_{max} relative to administration of darolutamide (2 x 300 mg) under fasted conditions.

9.5 Drug-Herb Interactions

Avoid concomitant use of St. John's Wort during treatment with NUBEQA, unless there is no therapeutic alternative.

9.6 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10. ACTION AND CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Darolutamide is an orally administered, non-steroidal androgen receptor (AR) inhibitor 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 AR.

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

Darolutamide inhibited prostate cancer cell proliferation and resulted in tumor growth inhibition in xenograft animal models of prostate cancer.

10.2 Pharmacodynamics

In the ARAMIS study, during the double-blind period, the confirmed prostate-specific antigen (PSA) response rate (defined as a ≥ 50% reduction from baseline) was 84.0%. The median PSA reduction at 16 weeks from baseline was 87.4% for the darolutamide arm.

Cardiac Electrophysiology

The effect of darolutamide (600 mg twice daily) on the QTc interval was evaluated in a subgroup of 500 patients in the ARAMIS study. No large mean increase in QTc (i.e., >20 ms) was detected.

10.3 Pharmacokinetics

Darolutamide is poorly soluble in aqueous solvents over a large pH range and generally more soluble in organic solvents.

Table 5 - Geometric mean (CV [%]), PK parameters at steady state in study 17712 using the selected Phase 3 popPK model (Study 18651)

	Darolutamide (n=388)	Keto-darolutamide (n=388)
C_{max}, µg/L	4786 (30.9)	8475 (35.4)
t_{max}, h	3.64 (4.4)	2.06 (3.3)
AUC(0-12), µg·h/L	52817 (33.9)	87640 (42.1)
Effective $t_{1/2}$, h	19.6 (29.7)	20.0 (37.9)

Abbreviations: AUC(0-12) = area under the plasma concentration time curve from time 0 to 12 hours; C_{max} = peak concentration; CV% = coefficient of variation; PK = pharmacokinetics; popPK = population pharmacokinetics; tmax = time to peak concentration; $t_{1/2}$ = half-life.

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. Following oral administration together with food, steady-state is reached after 2-5 days of repeated twice-daily dosing, with a 2.9-fold accumulation.

The absolute bioavailability following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions is approximately 30%. 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. Binding to plasma proteins is 92% for darolutamide and 99.8% for keto-darolutamide. Serum albumin is the main binding protein for darolutamide and keto-darolutamide.

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 1.9-3.9% 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:

Following single oral administration of 300 mg 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 together accounted for 87.4% of the 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.

Elimination:

The effective half-life of darolutamide and keto-darolutamide in plasma of patients is approximately 20 hours. The clearance of darolutamide following intravenous administration was 116 mL/min (39.7%). Following administration of a radiolabeled oral solution of 300 mg darolutamide, a total of 63.4% of drug related material is excreted in the urine (6.7% unchanged), 32.4% is excreted in the feces (approximately 30% unchanged).

Linearity / Non-linearity:

In the dose range of 100 to 700 mg (after single dose and at steady state), the exposure (based on C_{max} and AUC_{0-12}) to darolutamide and the major metabolite keto-darolutamide increases linearly in a nearly dose-related manner. No notable increase in exposure to darolutamide was observed beyond 700 mg twice daily.

Special Populations and Conditions

Pediatrics:

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

Geriatrics:

A population pharmacokinetic analysis indicates increased darolutamide exposure with increasing age. Darolutamide AUC_{0-12} is 1.6-fold greater in patients aged above 85 years compared to patients aged below 65 years. The increased exposure was not associated with increased toxicity.

Ethnic origin:

A population pharmacokinetic analysis indicates a 1.4-fold greater AUC_{0-12} in Japanese patients. The increased exposure was not associated with increased toxicity.

Hepatic Insufficiency:

In a clinical pharmacokinetic study, C_{max} and AUC_{0-48} 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).

Renal Insufficiency:

In a clinical pharmacokinetic study, C_{max} and AUC_{0-48} for darolutamide were 1.6 and 2.5-fold higher in non-cancer 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-, 1.3- and an approximately 1.5-fold higher exposure (AUC) of darolutamide in patients with mild, moderate and severe renal impairment (eGFR 15 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).

11. STORAGE, STABILITY AND DISPOSAL

Store bottles or blisters at room temperature 15°C to 30°C. Keep out of sight and reach of children.

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

12. SPECIAL HANDLING INSTRUCTIONS

There are no special handling requirements for this product.

PART II: SCIENTIFIC INFORMATION

13. PHARMACEUTICAL INFORMATION

13.1 Drug Substance

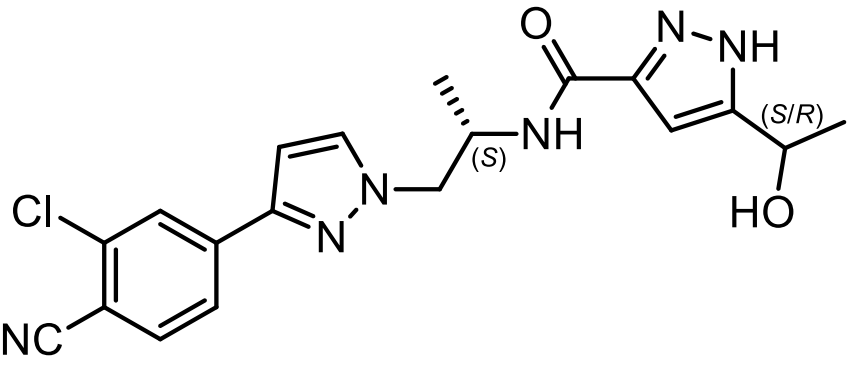
Proper/Common name: darolutamide

Chemical name: N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide

Molecular formula and molecular mass: $C_{19}H_{19}Cl N_6O_2$

398.85 g/mol

Structural formula:



Physicochemical properties: Darolutamide is a white to greyish- or yellowish-white powder. Darolutamide milled drug substance is practically insoluble in water. Using the method described in the Ph. Eur. a saturated solution in water gives a pH-value of 6.4. The pKa value was found to be 11.75 ± 0.06. The aqueous solubility of darolutamide milled drug substance is practically not dependent on pH. Theoretically, darolutamide milled drug substance has another pKa under pH 2, but experimental solubility results show only slight effect within pH 1.0 – 6.8.

14. CLINICAL TRIALS

14.1 Trial Design and Study Demographics

The efficacy and safety of NUBEQA was assessed in a randomized, double-blind, placebo-controlled multicenter phase III study (ARAMIS) in patients with non-metastatic castration resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤ 10 months (considered to be at high risk of developing metastatic disease). In total, 1509 patients were randomized 2:1 to receive either 600 mg NUBEQA orally twice daily (n=955) or matching placebo (n=554). Randomization was stratified by PSADT (≤ 6 months or > 6 months) and use of osteoclast-targeted therapy at study entry (yes or no).

All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a bilateral orchiectomy. 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 metastases at baseline.

The following patient demographics and disease characteristics were balanced between treatment arms (see Table 6). 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-three percent (73%) of patients received prior treatment with an anti-androgen (bicalutamide or flutamide). All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 (69% and 31%, respectively) at study entry.

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) which was defined as the time from randomization to confirmed evidence of distant metastasis or death from any cause within 33 weeks after the last evaluable scan, whichever occurred first. Distant metastasis was defined as new bone or soft tissue lesions or enlarged lymph nodes above the aortic bifurcation. Secondary endpoints, evaluated in a hierarchical order, were overall survival (OS), time to pain progression, and time to initiation of first cytotoxic chemotherapy for prostate cancer.

Table 6 - Demographic and baseline cancer characteristics (ARAMIS)

	NUBEQA N = 955	**Placebo N = 554**
Age: years, median (range)	74.0 (48-95)	74.0 (50-92)
Age group (years), n (%)		
<65	113 (11.8%)	84 (15.2%)
65-74	373 (39.1%)	216 (39.0%)
75-84	384 (40.2%)	209 (37.7%)
≥85	85 (8.9%)	45 (8.1%)
Race, n (%)		
White	760 (79.6%)	434 (78.3%)
Asian	122 (12.8%)	71 (12.8%)
Black or African American	28 (2.9%)	24 (4.3%)
Missing	36 (3.8%)	19 (3.4%)
Other	9 (0.9%)	6 (1.1%)
Geographical region, n (%)		
North America	108 (11.3%)	76 (13.7%)
Asia Pacific	119 (12.5%)	67 (12.1%)
Rest of the World	728 (76.2%)	411 (74.2%)
PSA central laboratory: ng/mL, median (range)	9.030 (0.31-858.30)	9.670 (1.46-885.21)
Categories, n (%)		
≤10 ng/mL	508 (53.2%)	285 (51.4%)
>10 to ≤20 ng/mL	215 (22.5%)	122 (22.0%)
>20 ng/mL	232 (24.3%)	147 (26.5%)

Table 6 - Demographic and baseline cancer characteristics (ARAMIS)

	NUBEQA N = 955	Placebo N = 554
Baseline value of PSADT, n (%)		
≤6 months	669 (70.1%)	371 (67.0%)
>6 months	286 (29.9%)	183 (33.0%)
PSADT (months); median (range)	4.389 (0.744-10.991)	4.650 (0.662-13.194)
ECOG PS, n (%)		
0	650 (68.1%)	391 (70.6%)
1	305 (31.9%)	163 (29.4%)
Gleason score at diagnosis (factor1+factor2), n (%)		
Missing	27 (2.8%)	17 (3.1%)
<7	217 (22.7%)	142 (25.6%)
≥7	711 (74.5%)	395 (71.3%)
Baseline presence of regional pathological lymph nodes by central imaging review, n (%)[a,b]		
No	855 (89.5%)	488 (88.1%)
Yes	100 (10.5%)	66 (11.9%)
Time since initial diagnosis to start of study treatment (months) median (range)	86.15 (2.6 – 337.5)	84.23 (0.5 – 344.7)
Baseline osteoclast-targeted therapy, Yes, n (%)	36 (3.8%)	28 (5.1%)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; PSA = prostate-specific antigen; PSADT = prostate-specific antigen doubling time.

a pathological lymph nodes were defined according to RECIST criteria as having the short axis >=15mm as measured by CT scan. The protocol allowed presence at baseline of lymph nodes with short axis of <2cm below the aortic bifurcation

b Baseline values are observed at Screening Visit

14.2 Study Results

The median treatment duration at the time of the primary analysis for NUBEQA-treated patients was 14.8 months compared to 11.0 months for placebo-treated patients. The median treatment duration at the time of the final analysis for NUBEQA-treated patients was 25.8 months (combined double blind + open-label) compared to 11.6 months for placebo-treated patients.

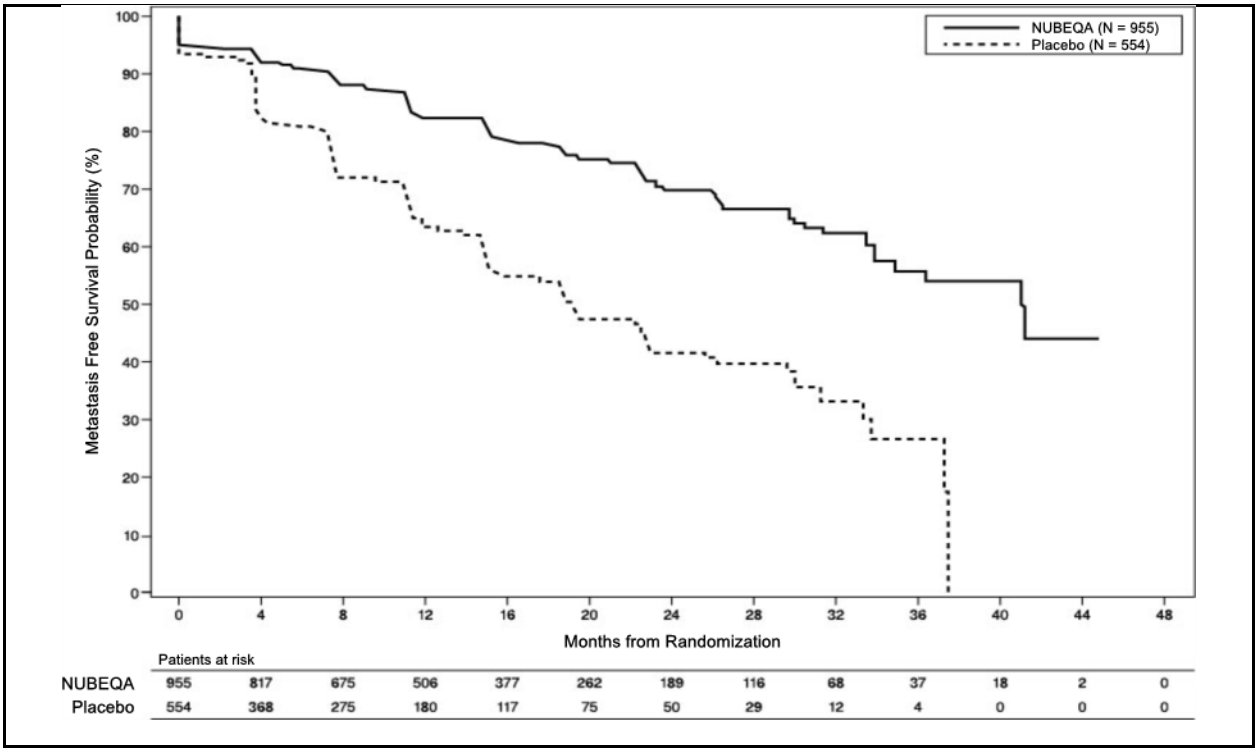
At the primary analysis, treatment with NUBEQA resulted in a statistically significant improvement in MFS compared to placebo (median MFS 40.4 vs. 18.4 months) with a p-value of <0.000001 and a hazard ratio (HR) of 0.413 (see Table 7 and Figure 1).

Table 7 - Efficacy Results from the ARAMIS study

Efficacy parameter[a]	Number of events (%)		Median (95% CI)		Hazard Ratio[c, d] (95% Confidence Interval [CI]) p-value (two-sided)
	NUBEQA (N=955)	Placebo (N=554)	NUBEQA (N=955)	Placebo (N=554)	
Metastasis free survival[e]	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[f]	148 (15.5%)	106[b] (19.1%)	NR (56.1, NR)	NR[b] (46.9, NR)	0.685 (0.533, 0.881) 0.003048
Time to pain progression[e, f]	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 first cytotoxic chemotherapy[e]	127 (13.3%)	98[b] (17.7%)	NR (NR, NR)	NR[b] (NR, NR)	0.579 (0.444, 0.755) 0.000044

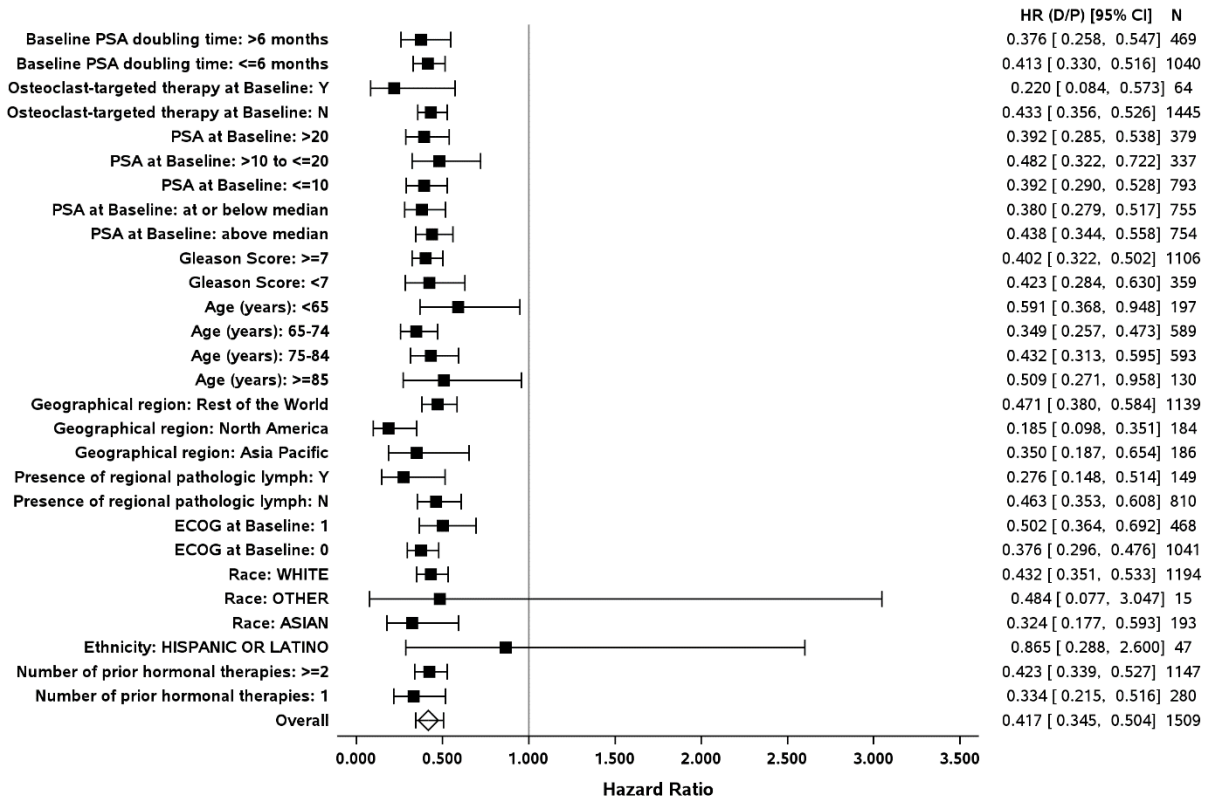
a Analyses were performed in the full analysis set
b including 170 patients who crossed over to open-label darolutamide
c Hazard ratio < 1 favors NUBEQA.
d P-value is based on a log-rank test stratified by PSADT (≤ 6 months vs. > 6 months) and use of osteoclast-targeted therapy (yes vs. no).
e MFS and time to pain progression endpoints were performed at the time of primary analysis and time to initiation of first cytotoxic chemotherapy was performed at the time of final OS analysis.
f Patient reported outcome as evaluated by Brief Pain Inventory-Short Form questionnaire
NR not reached

Figure 1: Kaplan Meier curves of Metastasis Free Survival



MFS results were consistent across patient subgroups (see Figure 2) 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.

Figure 2: Forest plot of subgroup analysis: Metastasis Free Survival



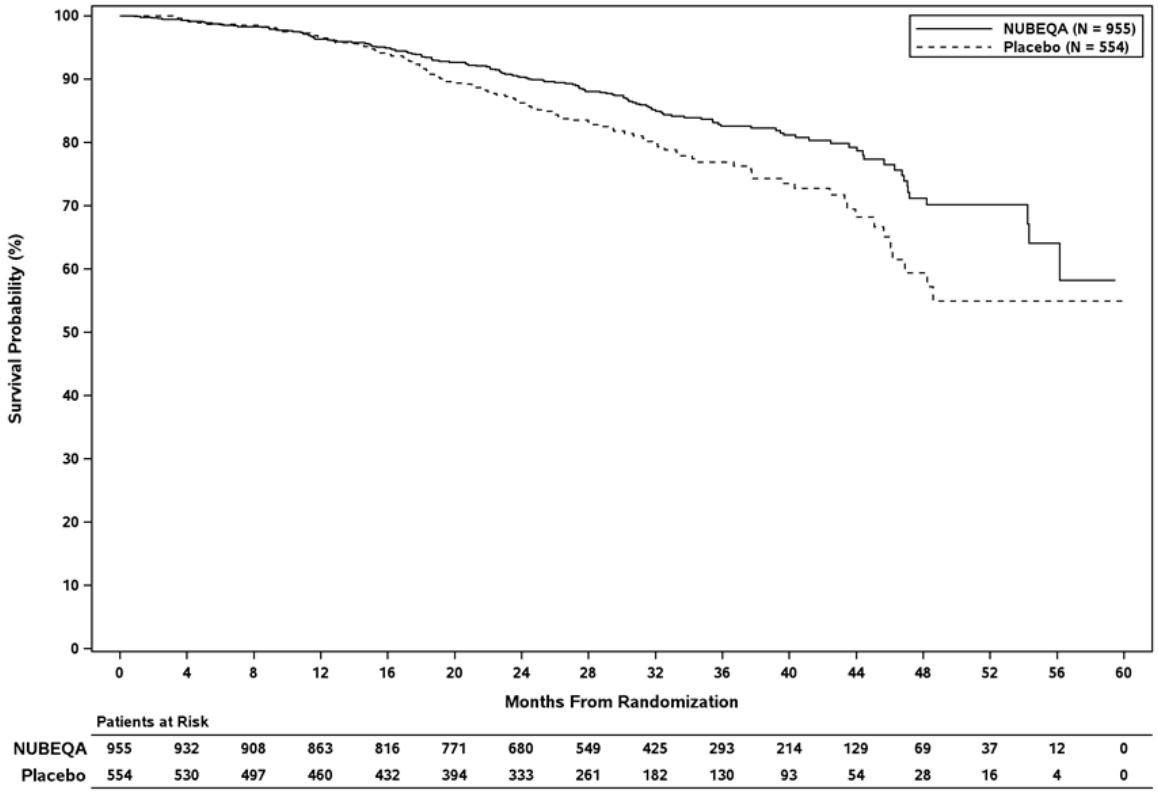
A Hazard ratio < 1 indicates superiority of Darolutamide over Placebo.
Hazard ratio and CI were obtained from univariate analysis using Cox regression (unstratified).

The final analysis of OS was event-driven conducted after 254 OS events had occurred, 14 months after the primary analysis of MFS. After the primary analysis of MFS, all patients receiving placebo at time of database cut-off were offered treatment with open-label NUBEQA (cross-over option) once the study was unblinded. Among the 554 patients randomized to placebo, 170 (31%) crossed over to receive NUBEQA treatment. The OS analysis was not adjusted for confounding effects of cross-over.

For patients who crossed over from placebo to NUBEQA after study unblinding, the median treatment duration was 11.0 months.

At the protocol-specified final OS analysis, treatment with NUBEQA resulted in a statistically significant improvement in OS compared to placebo (HR=0.685, p=0.003048, median was not reached in either arm (see Table 7 and Figure 3). The treatment effect for overall survival favored NUBEQA in pre-specified subgroups, including patients with PSA doubling time less than or equal to 6 months and greater than 6 months, presence or absence of lymph node involvement at baseline, and ECOG performance status of 0 or 1.

Figure 3: Kaplan-Meier curves of Overall Survival



Treatment with NUBEQA also resulted in statistically significant delays in time to pain progression (median 40.3 vs. 25.4 months, HR=0.647, p=0.000008), and time to initiation of first cytotoxic chemotherapy (HR=0.579, p=0.000044) compared to placebo (see Table 7).

14.3 Comparative Bioavailability Studies

Not applicable.

15. MICROBIOLOGY

Not applicable.

16. NON-CLINICAL TOXICOLOGY

General Toxicology

In repeated dose toxicity studies in rats and dogs, the main findings were changes in the male reproductive organs (decreases in organ weight with atrophy of the prostate and epididymides). 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 testicular hypospermia, seminiferous tubule dilatation and degeneration in dogs. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison). 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. In addition, a slight decrease of body weight gain in the highest dose group in male rats (2x500 mg/kg/d) after 26-weeks and male dogs (2x200 mg/kg/d) after 39 weeks was observed. In male and female dogs decreases of small magnitude in mean red blood cell parameters (red blood cell, hemoglobin, packed cell volume) within or close to the background control range were seen at the highest dose during 39-weeks treatment.

Carcinogenicity

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

Genotoxicity

Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay. Additionally, darolutamide did not induce genotoxicity in the *in vivo* combined bone marrow rat micronucleus assay or the Comet assay in the liver and duodenum of the rat. However, clastogenicity was observed in the *in vitro* chromosome aberration assay in human lymphocytes.

Reproduction and Developmental Toxicology

Studies on reproductive toxicity have not been performed. However, 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. These effects occurred at systemic exposures in the range of or below the anticipated human exposure (based on AUC comparison).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

PrNUBEQA®

darolutamide tablets

Read this carefully before you start taking **NUBEQA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **NUBEQA**.

What is NUBEQA used for?
NUBEQA is used in adults to treat prostate cancer that:
- has not spread to other parts of the body, and
- no longer responds to a medicine or surgery that lowers testosterone.

NUBEQA has not been studied in patients with low risk of the cancer spreading to other parts of the body. Talk to your healthcare professional if you have any questions about this.

How does NUBEQA work?
NUBEQA contains darolutamide. Darolutamide works by blocking the activity of androgens (like testosterone). This will slow the spread of your prostate cancer and the start of disease symptoms.

What are the ingredients in NUBEQA?
Medicinal ingredients: darolutamide
Non-medicinal ingredients: calcium hydrogen phosphate, croscarmellose sodium, hypromellose 15 cP, lactose monohydrate, macrogol 3350, magnesium stearate, povidone K 30, titanium dioxide

NUBEQA comes in the following dosage forms:
Tablet (film-coated): 300 mg

Do not use NUBEQA if:
- you are allergic to darolutamide or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take NUBEQA. Talk about any health conditions or problems you may have, including if you:
- suffer from a lactose intolerance. This is because NUBEQA contains lactose.
- have or have had liver or kidney problems.
- have a partner who is pregnant or may become pregnant. NUBEQA may harm your unborn baby or may make your partner lose the baby. Men who are sexually active with a pregnant woman must use a condom during and for 3 months after the last dose. If your sexual partner may become pregnant, highly effective birth control must be used during and for 3 months after treatment. Talk with your healthcare professional if you have questions about birth control. If your sexual partner becomes pregnant while you are taking NUBEQA, tell your healthcare professional right away.

Other warnings you should know about:

Fertility:
- NUBEQA may affect your ability to have a child. Talk to your doctor if this is a concern for you.
- Do NOT donate sperm while taking NUBEQA and for 3 months after stopping NUBEQA.

Women, pregnancy and breast-feeding:
- NUBEQA is NOT for use in women.
- NUBEQA is NOT to be used in women who are or may become pregnant. NUBEQA can harm the unborn baby or make a woman lose the baby.
- NUBEQA is NOT to be used in women who are breast-feeding. This is because it may get into breast milk and harm the baby.

Children and adolescents:
- NUBEQA is NOT for use in patients under the age of 18 years.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with NUBEQA:
- rifampicin – used to treat bacterial infections
- carbamazepine, phenobarbital – used to treat epilepsy
- St. John's Wort (hypericum perforatum) – a herbal product used mainly to treat depression
- rosuvastatin, fluvastatin, and atorvastatin – used to treat high cholesterol
- methotrexate – used to treat severe joint inflammation, severe cases of the skin disease psoriasis, and cancers
- sulfasalazine – used to treat inflammatory bowel disease
- itraconazole – used to treat fungal infections

How to take NUBEQA:
- Always take exactly as your healthcare professional tells you. Check with your doctor or pharmacist if you are not sure.
- Take your prescribed dose twice a day with food (a snack or meal) at about the same time each day.
- Do NOT stop taking NUBEQA without talking to your doctor first.
- Swallow the tablets whole.
- Your doctor may also prescribe a gonadotropin-releasing hormone (GnRH) analog therapy while you are taking NUBEQA, unless you have had surgical castration. This is a surgery to remove your testicles in order to lower the amount of testosterone in your body.

Usual dose:

Usual daily adult dose:
1200 mg (600 mg twice daily): Take two 300 mg tablets (600 mg) by mouth twice a day. This is a total daily dose of 1200 mg.

Your doctor may reduce your NUBEQA dose if needed.

Reduced daily adult dose:
600 mg (300 mg twice daily): Take one 300 mg tablet by mouth twice a day. This is a total daily dose of 600 mg.

Overdose:

If you think you have taken too much NUBEQA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
If you are late in taking NUBEQA, take it as soon as you remember before the next scheduled dose. Do NOT take a double dose to make up for the missed dose.

What are possible side effects from using NUBEQA?
These are not all the possible side effects you may feel when taking NUBEQA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects of NUBEQA may include:
- fatigue (tiredness)
- rash
- pain in arms and legs
- bone fracture

NUBEQA may cause abnormal blood test results. This includes abnormal blood cell counts and liver enzymes. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Cardiac problems (including heart attack, heart disease and heart failure): pressure or pain in your chest or arms that may spread to neck, jaw or back, chest pain or discomfort or shortness of breath at rest or with activity, changes in heart rate, dizziness or lightheadedness, nausea			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store bottles or blisters at room temperature (15°C to 30°C).
- Do NOT use this medicine after the expiry date stated on the product labels.
- Keep the bottle tightly closed after you first open it.
- Do NOT throw away any medicines away in the garbage, down the sink or in the toilet. Ask your pharmacist how to throw away expired or unused NUBEQA. These measures will help protect the environment.
- **Keep out of sight and reach of children.**

If you want more information about NUBEQA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website http://www.bayer.ca or by calling Bayer Medical Information at 1-800-265-7382 or emailing canada.medinfo@bayer.com.

This leaflet was prepared by

Bayer Inc.
2920 Matheson Blvd East
Mississauga, Ontario
L4W 5R6
Canada

Last Revised: July 14, 2021