

NUBEQA- darolutamide tablet, film coated
Bayer HealthCare Pharmaceuticals Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use NUBEQA safely and effectively. See full prescribing information for NUBEQA.

NUBEQA (darolutamide) tablets, for oral use
Initial U.S. Approval: 2019

INDICATIONS AND USAGE

NUBEQA is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer. (1)

DOSAGE AND ADMINISTRATION

NUBEQA 600 mg, (two 300 mg tablets) administered orally twice daily. Swallow tablets whole. Take NUBEQA with food. (2.1)

Patients should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.3)

DOSAGE FORMS AND STRENGTHS

Tablets: 300 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Embryo-Fetal Toxicity: NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception. (5.1, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions ($\geq 2\%$) are fatigue, pain in extremity, and rash. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bayer HealthCare Pharmaceuticals Inc. at 1-888-842-2937 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Combined P-gp and Strong or Moderate CYP3A Inducers: Avoid concomitant use. (7.1)
- Combined P-gp and Strong CYP3A Inhibitors: Monitor patients more frequently for NUBEQA adverse reactions. (7.1)
- BCRP Substrates: Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions and consider dose reduction of the BCRP substrate drug. (7.2).
- OATP1B1 and OATP1B3 Substrates: Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates. If used together, monitor patients more frequently for adverse reactions and consider dose reduction of these drugs (7.2)

USE IN SPECIFIC POPULATIONS

Severe Renal Impairment (not on hemodialysis): Recommended dose is 300 mg twice daily. (8.6)

Moderate Hepatic Impairment: Recommended dose is 300 mg twice daily. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2021

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dose of NUBEQA is 600 mg (two 300 mg film-coated tablets) taken orally, twice daily, equivalent to a total daily dose of 1200 mg. Swallow tablets whole with food [see *Clinical Pharmacology (12.3)*].

Patients receiving NUBEQA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had a bilateral orchiectomy.

Advise patients to take any missed dose as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose.

2.2 Dosage Modification

If a patient experiences a greater than or equal to Grade 3 toxicity or an intolerable adverse reaction, withhold dosing or reduce to 300 mg twice daily until symptoms improve. Then the treatment may be resumed at a dose of 600 mg twice daily.

Dose reduction below 300 mg twice daily is not recommended.

2.3 Recommended Dosage in Patients with Severe Renal Impairment

For patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) not receiving hemodialysis, the recommended dose of NUBEQA is 300 mg twice daily [see *Use in Specific Populations (8.6) and Clinical Pharmacology (12.3)*].

2.4 Recommended Dosage in Patients with Moderate Hepatic Impairment

For patients with moderate hepatic impairment (Child-Pugh Class B), the recommended dose of NUBEQA is 300 mg twice daily [see *Use in Specific Populations (8.7) and Clinical Pharmacology (12.3)*].

3 DOSAGE FORMS AND STRENGTHS

Tablets (300 mg): white to off-white oval film-coated tablets marked with “300” on one side and “Bayer” on the other.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see *Clinical Pharmacology (12.1)*].

Advise males with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Use in Specific Populations (8.1, 8.3)*].

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the

clinical trials of another drug and may not reflect the rates observed in practice.

ARAMIS, a 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, or a placebo, twice a day. All patients in the ARAMIS study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

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

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

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

Table 1 shows adverse reactions in ARAMIS reported in the NUBEQA arm with a $\geq 2\%$ absolute increase in frequency compared to placebo. Table 2 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 1: Adverse Reactions in ARAMIS

Adverse Reaction*	NUBEQA (n=954)		Placebo (n=554)	
	All Grades %	Grades ≥ 3 %	All Grades %	Grade ≥ 3 %
Fatigue†	16	0.6	11	1.1
Pain in extremity	6	0	3	0.2
Rash	3	0.1	1	0

* Common Terminology Criteria for Adverse Events (CTCAE) version 4.03

† Includes fatigue and asthenia

Additionally, clinically significant adverse reactions occurring in 2% or more of patients treated with NUBEQA included ischemic heart disease (4.0% versus 3.4% on placebo) and heart failure (2.1% versus 0.9% on placebo).

Table 2: Laboratory Test Abnormalities in ARAMIS

Laboratory Abnormality	NUBEQA (N=954)*		Placebo (N=554)*	
	All Grades† %	Grade 3-4† %	All Grades† %	Grade 3-4† %
Neutrophil count decreased	20	4	9	0.6
AST increased	23	0.5	14	0.2
Bilirubin increased	16	0.1	7	0

* 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.

† Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inducer

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see *Clinical Pharmacology (12.3)*]. Avoid concomitant use of NUBEQA with clinical combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see *Clinical Pharmacology (12.3)*] which may increase the risk of NUBEQA adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see *Dosage and Administration (2.2)*].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and C_{max} of BCRP substrates [see *Clinical Pharmacology (12.3)*], which may increase the risk of BCRP substrate-related toxicities.

Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of OATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of OATP1B1 or OATP1B3 substrates.

Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see *Clinical Pharmacology (12.3)*], Review the prescribing information of the BCRP, OATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy [see *Clinical Pharmacology (12.1)*]. Animal embryo-fetal developmental toxicology studies were not conducted with darolutamide. There are no human data on the use of NUBEQA in pregnant females.

8.2 Lactation

Risk Summary

The safety and efficacy of NUBEQA have not been established in females. There are no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Use in Specific Populations (8.1)*].

Infertility

Males

Based on animal studies, NUBEQA may impair fertility in males of reproductive potential [see *Nonclinical Toxicology (13.1)*].

8.4 Pediatric Use

Safety and effectiveness of NUBEQA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMIS, 88% of patients were 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

8.6 Renal Impairment

Patients with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) who are not receiving hemodialysis have a higher exposure to NUBEQA and reduction of the dose is recommended [see *Dosage and Administration (2.3)* and *Clinical Pharmacology (12.3)*]. No dose reduction is needed for patients with mild or moderate renal impairment (eGFR 30–89 mL/min/1.73 m²). The effect of end stage renal disease (eGFR ≤15 mL/min/1.73 m²) on darolutamide pharmacokinetics is unknown.

8.7 Hepatic Impairment

Patients with moderate hepatic impairment (Child-Pugh Class B) have a higher exposure to NUBEQA and reduction of the dose is recommended [see *Dosage and Administration (2.4)* and *Clinical Pharmacology (12.3)*]. No dose reduction is needed for patients with mild hepatic impairment. The effect of severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics is unknown.

10 OVERDOSAGE

There is no known specific antidote for darolutamide overdose. The highest dose of NUBEQA studied clinically was 900 mg twice daily, equivalent to a total daily dose of 1800 mg. No dose limiting toxicities were observed with this dose.

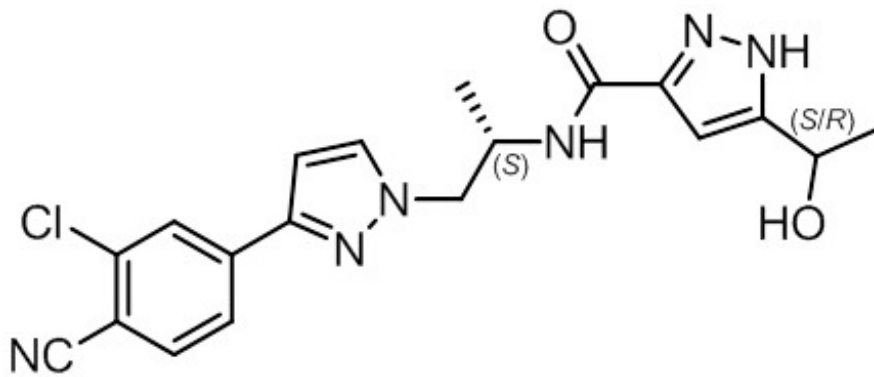
Considering the saturable absorption and the absence of evidence for acute toxicity, an intake of a higher than recommended dose of darolutamide is not expected to lead to systemic toxicity in patients with intact hepatic and renal function [see *Clinical Pharmacology (12.3)*].

In the event of intake of a higher than recommended dose in patients with severe renal impairment or moderate hepatic impairment, if there is suspicion of toxicity, interrupt NUBEQA treatment and undertake general supportive measures until clinical toxicity has been diminished or resolved. If there is no suspicion of toxicity, NUBEQA treatment can be continued with the next dose as scheduled.

11 DESCRIPTION

NUBEQA is an androgen receptor inhibitor. The chemical name is N-{(2S)-1-[3-(3-chloro-4-cyanophenyl)-1H-pyrazol-1-yl]propan-2-yl}-5-(1-hydroxyethyl)-1H-pyrazole-3-carboxamide.

The molecular weight is 398.85 and the molecular formula is C₁₉H₁₉Cl N₆O₂. The structural formula is:



Darolutamide is an optically active with a specific rotation value $[\alpha]_D^{20} = 72.2$ °*mL/(dm*g), white to greyish- or yellowish white crystalline powder, that is soluble in tetrahydrofuran, but practically insoluble in aqueous medium. Darolutamide has a pKa of 11.75.

NUBEQA (darolutamide) is supplied as film-coated tablets containing 300 mg of darolutamide for oral use. The inactive ingredients of the tablet are: calcium hydrogen phosphate, croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone K 30, hypromellose 15 cP, macrogol 3350, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Darolutamide is an androgen receptor (AR) inhibitor. Darolutamide competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription. A major metabolite, keto-darolutamide, exhibited similar *in vitro* activity to darolutamide. In addition, darolutamide functioned as a progesterone receptor (PR) antagonist *in vitro* (approximately 1% activity compared to AR). Darolutamide decreased prostate cancer cell proliferation *in vitro* and tumor volume in mouse xenograft models of prostate cancer.

12.2 Pharmacodynamics

Darolutamide exposure at 600 mg twice daily results in PSA mean reduction of more than 90% from baseline.

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.

12.3 Pharmacokinetics

Following administration of 600 mg twice daily, darolutamide mean (%CV) steady-state peak plasma concentration (C_{max}) is 4.79 mg/L (30.9%) and area under the plasma concentration-time curve from time 0 to 12 hours (AUC_{12h}) is 52.82 h•µg/mL (33.9%). Steady-state is reached 2–5 days after repeated dosing with food, with an approximate

2-fold accumulation.

The exposure (C_{max} and AUC_{12}) of the darolutamide and the active metabolite keto-darolutamide increase in a nearly dose-proportional manner in the dose range of 100 to 700 mg (0.17 to 1.17 times the approved recommended dosage). No further increase in darolutamide exposure was observed at 900 mg twice daily (1.5 times the approved recommended dosage).

Absorption

Darolutamide C_{max} is reached approximately 4 hours after administration of a single 600 mg oral dose.

The absolute bioavailability is approximately 30% following oral administration of a NUBEQA tablet containing 300 mg darolutamide under fasted conditions.

Food Effect

Bioavailability of darolutamide increased by 2.0 to 2.5-fold when administered with food. A similar increase of exposure was observed for the active metabolite keto-darolutamide.

Distribution

The apparent volume of distribution of darolutamide after intravenous administration is 119 L.

Protein binding is 92% for darolutamide and 99.8% for the active metabolite, keto-darolutamide. Serum albumin is the main binding protein for darolutamide and keto-darolutamide.

Elimination

The effective half-life of darolutamide and keto-darolutamide is approximately 20 hours in patients. The clearance (%CV) of darolutamide following intravenous administration is 116 mL/min (39.7%).

Metabolism

Darolutamide is primarily metabolized by CYP3A4, as well as by UGT1A9 and UGT1A1. Keto-darolutamide total exposure in plasma is 1.7-fold higher compared to darolutamide.

Excretion

After a single radiolabeled dose as an oral solution, a total of 63.4% of darolutamide-related material is excreted in the urine (approximately 7% unchanged) and 32.4% (approximately 30% unchanged) in the feces. More than 95% of the dose was recovered within 7 days after administration.

Specific Populations

In nmCRPC patients, no clinically significant differences in the pharmacokinetics of darolutamide were observed based on age (48-95 years), race (White, Japanese, non-Japanese Asian, Black or African American), mild to moderate renal impairment (eGFR 30-89 mL/min/1.73m²), or mild hepatic impairment.

In non-cancer subjects with severe renal impairment (eGFR 15–29 mL/min/1.73 m²) not receiving dialysis or with moderate hepatic impairment (Child-Pugh Class B), NUBEQA exposure increased by about 2.5- and 1.9-fold, respectively, compared to healthy subjects.

The effect of end-stage renal disease (eGFR <15 mL/min/1.73 m²) or severe hepatic impairment (Child-Pugh C) on darolutamide pharmacokinetics has not been studied.

Drug Interaction Studies

Clinical Studies

Combined P-gp and Strong CYP3A4 Inducers

Concomitant use of rifampicin (a combined P-gp and strong CYP3A4 inducer) decreased mean darolutamide AUC₀₋₇₂ by 72% and C_{max} by 52%. The decrease of darolutamide exposure by moderate CYP3A4 inducers is expected to be in the range of 36% – 58%.

Combined P-gp and Strong CYP3A4 Inhibitors

Itraconazole (a strong combined CYP3A4 and P-gp inhibitor) increased mean darolutamide AUC₀₋₇₂ by 1.7- and C_{max} by 1.4-fold.

CYP3A4 substrates

Concomitant use of darolutamide decreased the mean AUC and C_{max} of midazolam (CYP3A4 substrate) by 29% and 32%, respectively. No clinically relevant differences in the pharmacokinetics of midazolam were observed when used concomitantly with darolutamide.

BCRP, OATP1B1 and OATP1B3 Substrates

Concomitant use of darolutamide increased the mean AUC and C_{max} of rosuvastatin (BCRP, OATP1B1 and OATP1B3 substrate) by approximately 5-fold.

P-gp Substrates

No clinically relevant differences in the pharmacokinetics of dabigatran (P-gp substrate) were observed when used concomitantly with darolutamide.

In Vitro Studies

In vitro, darolutamide did not inhibit the major CYP enzymes (CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) or transporters (MRP2, BSEP, OATs, OCTs, MATEs, OATP2B1, and NTCP) at clinically relevant concentrations.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Darolutamide was clastogenic in an *in vitro* chromosome aberration assay in human

peripheral blood lymphocytes. Darolutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in the *in vivo* combined bone marrow micronucleus assay and the Comet assay in the liver and duodenum of the rat.

Fertility studies in animals have not been conducted with darolutamide. In repeat-dose toxicity studies in male rats (up to 26 weeks) and dogs (up to 39 weeks), tubular dilatation of testes, hypospermia, and atrophy of seminal vesicles, testes, prostate gland and epididymides were observed at doses ≥ 100 mg/kg/day in rats (0.6 times the human exposure based on AUC) and ≥ 50 mg/kg/day in dogs (approximately 1 times the human exposure based on AUC).

14 CLINICAL STUDIES

ARAMIS (NCT02200614) was a multicenter, double-blind, placebo-controlled clinical trial in 1509 patients with non-metastatic castration resistant prostate cancer with a prostate-specific antigen doubling time (PSADT) of ≤ 10 months. Randomization was stratified by PSADT and use of bone-targeted therapy at study entry. Patients with pelvic lymph nodes less than 2 cm in short axis below the aortic bifurcation were allowed to enter the study. Patients with a history of seizures were not excluded. Absence or presence of metastasis was assessed by blinded independent central review (BICR). PSA results were not blinded and were not used for treatment discontinuation.

Patients were randomized 2:1 to receive either 600 mg darolutamide orally twice daily (n=955) or matching placebo (n=554). Treatment continued until radiographic disease progression as assessed by CT, MRI, ^{99m}Tc bone scan by BICR, unacceptable toxicity or withdrawal. All patients received a gonadotropin-releasing hormone (GnRH) analog concurrently or had a bilateral orchiectomy.

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 (73%) had a Gleason score of 7 or higher at diagnosis. The median PSADT was 4.5 months. Forty-two percent of patients in both treatment arms had prior surgery or radiotherapy to the prostate. Eleven percent of patients had enlarged pelvic lymph nodes less than 2 cm at study entry. Six percent of patients were retrospectively identified by BICR as having metastases at baseline. Seventy-three percent 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 at study entry. There were 12 patients enrolled on the NUBEQA arm with a history of seizure. At baseline, 47% of patients reported no pain on the Brief Pain Inventory-Short Form (a 7-day diary average of the daily worst pain item).

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

Treatment with NUBEQA resulted in a statistically significant improvement in MFS compared to placebo. At the protocol-specified final analysis of OS, treatment with NUBEQA resulted in a statistically significant improvement in OS compared to placebo.

The final analysis of OS and time to initiation of cytotoxic chemotherapy was event-driven and conducted after 254 OS events had occurred. The efficacy results from ARAMIS are summarized in Table 3 and Figure 1.

Table 3: Efficacy Results from the ARAMIS Study

	NUBEQA (N=955)	Placebo (N=554)
Metastasis-free survival*		
Distant Metastasis or Death (%)	221 (23)	216 (39)
Median, months (95% CI)†	40.4 (34.3, NR)	18.4 (15.5, 22.3)
Hazard Ratio (95% CI)‡	0.41 (0.34, 0.50)	
P-value	<0.0001	
Overall survival§		
Deaths (%)	148 (15)	106 (19)
Median, months (95% CI)	NR (56.1, NR)	NR (46.9, NR)
Hazard Ratio (95% CI)‡	0.69 (0.53, 0.88)	
P-value¶	0.003	

NR: not reached

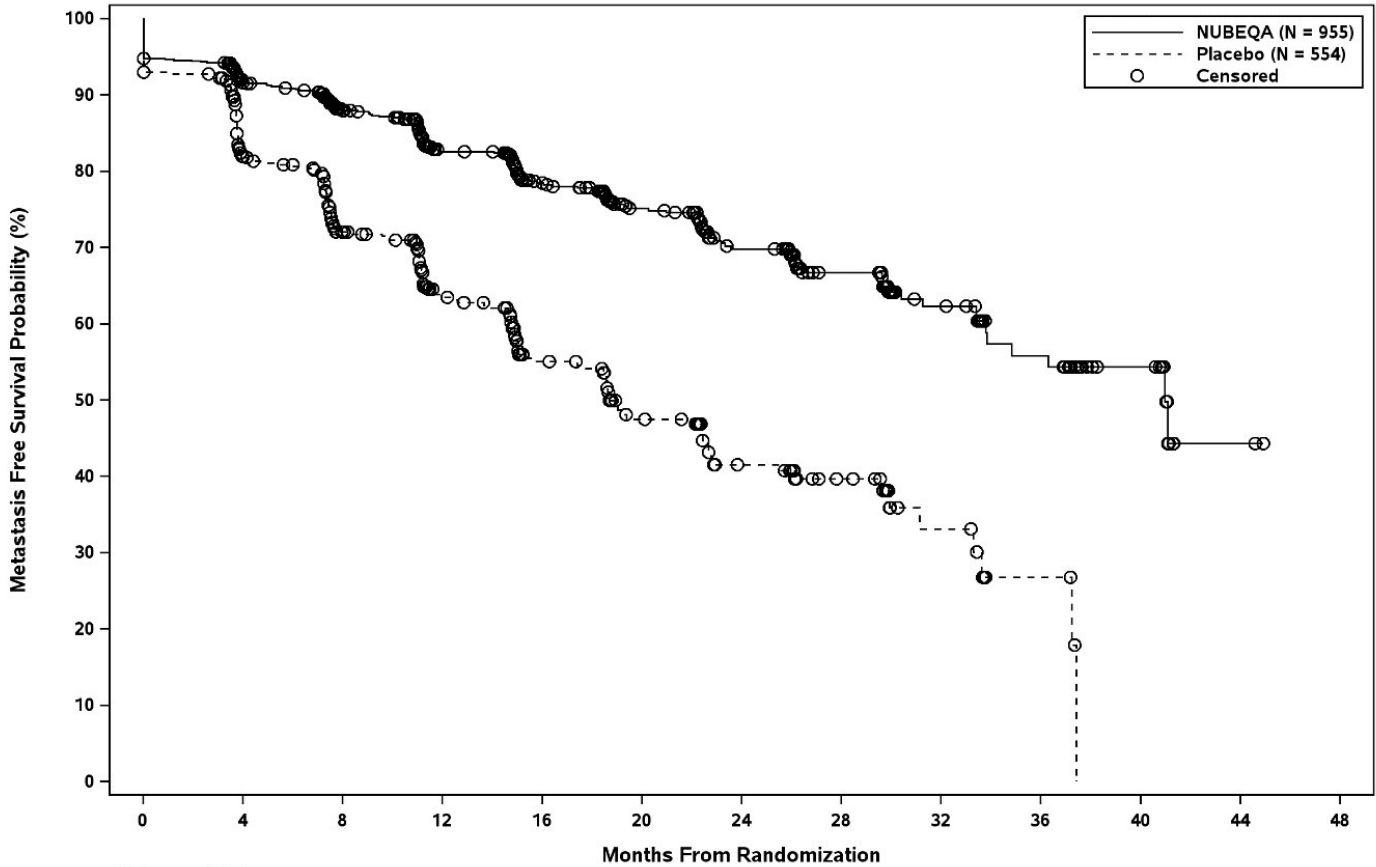
* Locoregional-only progression occurred in 6% of patients overall.

† Based on Kaplan-Meier estimates

‡ Hazard ratio is based on a stratified Cox regression model. Hazard ratio < 1 favors NUBEQA.

§ The pre-specified final OS analysis was event-driven and occurred 14 months after the MFS analysis

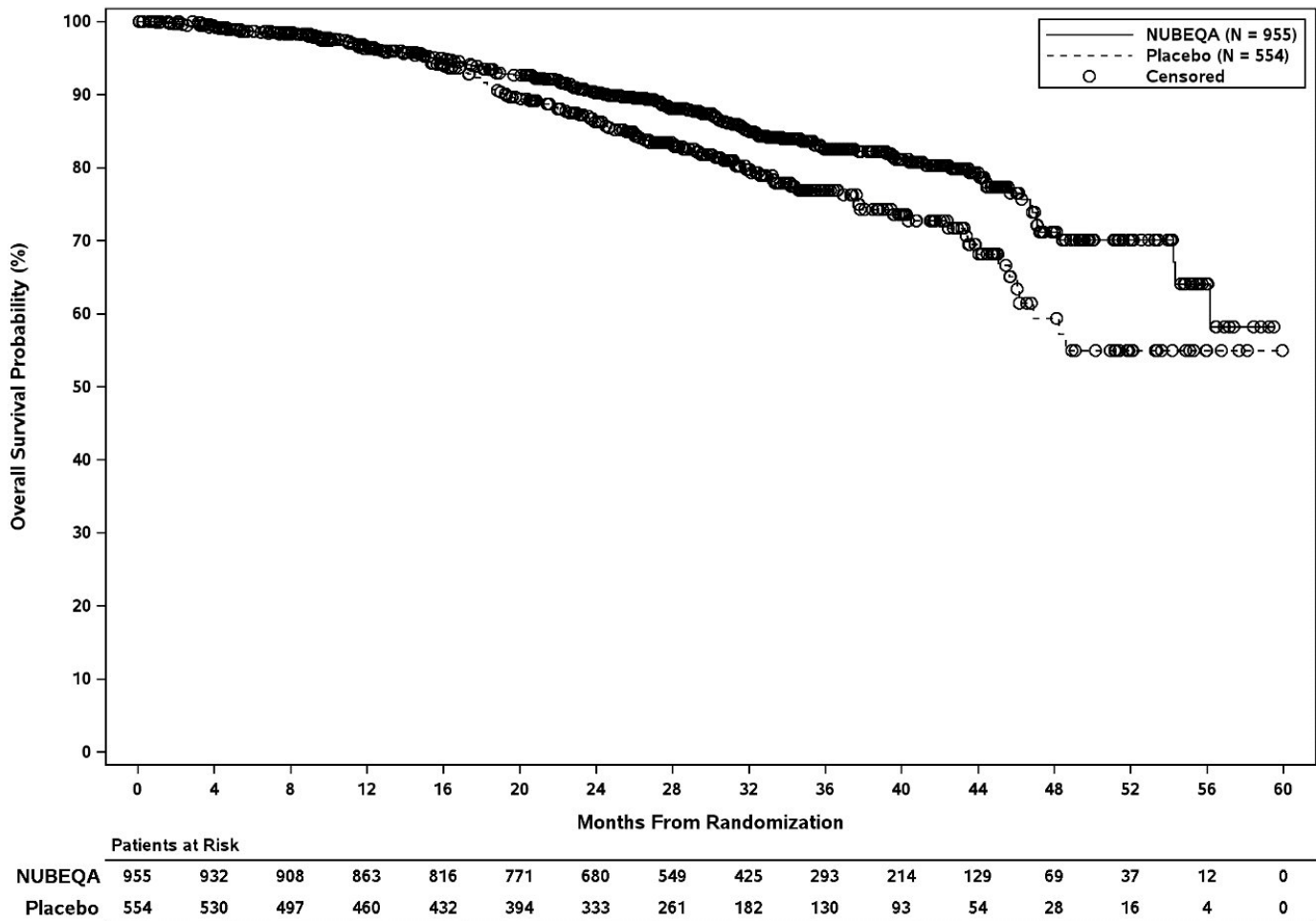
¶ P-value is based on a log-rank test stratified by PSADT (\leq 6 months vs. $>$ 6 months) and use of osteoclast-targeted therapy (yes vs. no)



	Patients at Risk												
	0	4	8	12	16	20	24	28	32	36	40	44	48
NUBEQA	955	821	678	506	378	262	189	116	68	37	18	2	0
Placebo	554	369	275	181	117	75	50	29	12	4	0	0	0

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Figure 1: Kaplan Meier Curve Metastasis Free Survival; Intent-To-Treat nmCRPC population (ARAMIS)



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Figure 2: Kaplan-Meier curves of Overall Survival; Intent-To-Treat nmCRPC population (ARAMIS)

MFS results were consistent across patient subgroups for PSADT (≤ 6 months or > 6 months) or prior use of bone-targeting agents (yes or no).

Treatment with NUBEQA resulted in a statistically significant delay in time to pain progression (HR = 0.65, 95% CI= 0.53, 0.79; $p < 0.0001$). Time to pain progression was defined as at least a 2-point worsening from baseline of the pain score on Brief Pain Inventory Short Form or initiation of opioids and reported in 28% of all patients on study.

Treatment with NUBEQA resulted in a statistically significant delay in the initiation of cytotoxic chemotherapy (HR = 0.58, 95% CI = 0.44, 0.76; $p < 0.0001$).

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

NUBEQA (darolutamide) 300 mg film-coated tablets are white to off-white, oval shaped tablets, marked with “300” on one side, and “BAYER” on the other side. NUBEQA 300 mg tablets are available in bottles of 120 tablets.

NDC 50419-395-01

16.2 Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Keep the bottle tightly closed after first opening.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with NUBEQA.

Instruct patients to take their dose of two tablets (twice daily). NUBEQA should be taken with food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of NUBEQA, to take any missed dose, as soon as they remember prior to the next scheduled dose, and not to take two doses together to make up for a missed dose [see *Dosage and Administration (2.1)*].

Embryo-Fetal Toxicity

Inform patients that NUBEQA can be harmful to a developing fetus and can cause loss of pregnancy [see *Use in Specific Populations (8.1)*].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see *Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)*].

Infertility

Advise male patients that NUBEQA may impair fertility [see *Use in Specific Populations (8.3)*].

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Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

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For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

Patient Package Insert

PATIENT INFORMATION
NUBEQA® (NŪŪ-bə-kə)
(darolutamide)

tablets

What is NUBEQA?

NUBEQA is a prescription medicine used to treat men with prostate cancer that has not spread to other parts of the body and no longer responds to a medical or surgical treatment that lowers testosterone.

It is not known if NUBEQA is safe and effective in females.

It is not known if NUBEQA is safe and effective in children.

Before taking NUBEQA, tell your healthcare provider about all your medical conditions, including if you:

- have kidney or liver problems
- are pregnant or plan to become pregnant. NUBEQA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- have a partner who may become pregnant. Males who have female partners who may become pregnant should use effective birth control (contraception) during treatment and for 1 week after the last dose of NUBEQA. Talk with your healthcare provider about birth control methods.
- are breastfeeding or plan to breastfeed. It is not known if NUBEQA passes into breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. NUBEQA may affect the way other medicines work and other medicines may affect how NUBEQA works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed NUBEQA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

How should I take NUBEQA?

- Take NUBEQA exactly as your healthcare provider tells you.
- Your healthcare provider may change your dose if needed.
- Take your prescribed dose of NUBEQA 2 times a day with food.
- Swallow NUBEQA tablets whole.
- If you are receiving gonadotropin-releasing hormone (GnRH) analog therapy, you should continue with this treatment during your treatment with NUBEQA unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of NUBEQA, take your prescribed dose as soon as you remember before the next scheduled dose. Do not take 2 doses together to make up for a missed dose.
- If you take more NUBEQA than prescribed, call your healthcare provider right away.

What are the possible side effects of NUBEQA?

The most common side effects of NUBEQA include:

- feeling more tired than usual
- arm, leg, hand or foot pain
- rash

- decreased white blood cells (neutropenia)
- changes in liver function tests

NUBEQA may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of NUBEQA.

Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store NUBEQA?

- Store NUBEQA at room temperature between 68°F to 77°F (20°C to 25°C).
- Keep the bottle tightly closed after you first open it.

Keep NUBEQA and all medicines out of the reach of children.

General information about the safe and effective use of NUBEQA.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use NUBEQA for a condition for which it was not prescribed. Do not give NUBEQA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about NUBEQA that is written for health professionals.

What are the ingredients in NUBEQA?

Active ingredient:

darolutamide

Inactive ingredients:

calcium hydrogen phosphate, croscarmellose sodium, lactose monohydrate, magnesium stearate, povidone K 30, hypromellose 15 cP, macrogol 3350, and titanium dioxide.

Manufactured by: Orion Corporation, Orion Pharma, FI-02101 Espoo, Finland

Manufactured for: Bayer HealthCare Pharmaceuticals Inc., Whippany, NJ 07981 USA

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For more information, call Bayer HealthCare Pharmaceuticals Inc. at Bayer at 1-888-842-2937 or go to www.NUBEQA-us.com

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 1/2021

PACKAGE/LABEL PRINCIPAL DISPLAY PANEL

50419-395-01

Rx Only

NUBEQA

(darolutamide) tablets

300 mg

120 film-coated tablets



NUBEQA

darolutamide tablet, film coated

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:50419-395
Route of Administration	ORAL		

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
DAROLUTAMIDE (UNII: X05U0N2RCO) (DAROLUTAMIDE - UNII:X05U0N2RCO)	DAROLUTAMIDE	300 mg

Inactive Ingredients

Ingredient Name	Strength
ANHYDROUS DIBASIC CALCIUM PHOSPHATE (UNII: L11K75P92J)	
CROSCARMELOSE SODIUM (UNII: M28OL1HH48)	
LACTOSE MONOHYDRATE (UNII: EWQ57Q8I5X)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
POVIDONE K30 (UNII: U725QWY32X)	
POLYETHYLENE GLYCOL 3350 (UNII: G2M7P15E5P)	
TITANIUM DIOXIDE (UNII: 15FIX9V2JP)	

Product Characteristics

Color	WHITE (to off white)	Score	no score
Shape	OVAL	Size	16mm
Flavor		Imprint Code	300;Bayer
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:50419-395-01	1 in 1 CARTON	07/31/2019	
1		120 in 1 BOTTLE; Type 0: Not a Combination		

1		Product		
2	NDC:50419-395-72	1 in 1 CARTON	03/03/2021	
2		120 in 1 BOTTLE; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212099	07/31/2019	

Labeler - Bayer HealthCare Pharmaceuticals Inc. (005436809)

Establishment

Name	Address	ID/FEI	Business Operations
Orion Corporation, Orion Pharma		539763727	MANUFACTURE(50419-395) , PACK(50419-395) , LABEL(50419-395)

Establishment

Name	Address	ID/FEI	Business Operations
Sharp Corporation		143696495	PACK(50419-395) , LABEL(50419-395)

Revised: 1/2021

Bayer HealthCare Pharmaceuticals Inc.