NEWS RELEASE

Bayer Submits Supplemental New Drug Application to U.S. FDA Seeking Expanded Indication for NUBEQA® (darolutamide) in Metastatic Hormone-Sensitive Prostate Cancer

2024-09-26

- Submission is based on positive results from the investigational pivotal Phase III ARANOTE trial that showed NUBEQA ® (darolutamide) plus androgen deprivation therapy (ADT) demonstrated an improvement in radiological progression-free survival (rPFS), significantly reducing in the risk of progression or death in patients with metastatic hormone-sensitive prostate cancer (mHSPC) compared to placebo plus ADT; no new safety signals were observed 1
- NUBEQA is currently indicated for the treatment of adult patients with mHSPC in combination with docetaxel and for non-metastatic castration-resistant prostate cancer (nmCRPC) 2

WHIPPANY, N.J.--(BUSINESS WIRE)-- Bayer today announced the submission of a supplemental new drug application (sNDA) to the U.S. Food and Drug Administration (FDA) for the oral androgen receptor inhibitor (ARi) NUBEQA ® (darolutamide) in combination with androgen deprivation therapy (ADT) for the treatment of patients with metastatic hormone-sensitive prostate cancer (mHSPC).

“Simply put, our ambition is to help more patients with prostate cancer,” said Christine Roth, Executive Vice President, Global Product Strategy and Commercialization and Member of the Pharmaceuticals Leadership Team at Bayer. “We are proud of the role NUBEQA currently plays in the treatment of mHSPC and with this FDA submission, hope to expand the use of NUBEQA to more patients with the disease, regardless of chemotherapy use.”

The submission is based on positive results from the investigational pivotal Phase III ARANOTE trial. Data from the trial were presented at the 2024 European Society for Medical Oncology (ESMO) Congress and published in **The**

Journal of Clinical Oncology .

NUBEQA is developed jointly by Bayer and Orion Corporation, a globally operating Finnish pharmaceutical company.

About the ARANOTE Trial [1]

The ARANOTE trial (NCT04736199) was a randomized, double-blind, placebo-controlled Phase III study designed to assess the efficacy and safety of NUBEQA plus androgen deprivation therapy (ADT) in patients with metastatic hormone-sensitive prostate cancer (mHSPC). 669 patients were randomized to receive 600mg of NUBEQA twice daily or matching placebo in addition to ADT.

The primary endpoint of this study was radiological progression-free survival (rPFS), measured as time from the date of randomization to the date of first documentation of radiological disease progression or death due to any cause, whichever occurs first. Secondary endpoints included overall survival (time from randomization to the date of death from any cause), time from randomization to the date of first castration-resistant event, time to initiation of subsequent anti-cancer therapy, time to prostate-specific antigen (PSA) progression, PSA undetectable rates, time to pain progression, and safety assessments.

About NUBEQA ® (darolutamide) [2]

NUBEQA ® (darolutamide) is an androgen receptor inhibitor (ARi) with a distinct chemical structure that competitively inhibits androgen binding, AR nuclear translocation, and AR-mediated transcription.

In addition to the ARANOTE trial, NUBEQA is being evaluated in a robust clinical development program, which includes studies across various stages of prostate cancer, including in the ARASTEP Phase III trial evaluating NUBEQA plus ADT versus ADT alone in HSPC patients with high-risk biochemical recurrence (BCR) and no evidence of metastatic disease by conventional imaging and a positive PSMA PET/CT at baseline, as well as in the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) led international Phase III co-operative group DASL-HiCaP (ANZUP1801) trial evaluating NUBEQA as an adjuvant treatment for localized prostate cancer with very high risk of recurrence. Information about these trials can be found at **www.clinicaltrials.gov.**

INDICATIONS

NUBEQA ® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of adult patients with:

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

IMPORTANT SAFETY INFORMATION

Warnings & Precautions

Ischemic Heart Disease – In a study of patients with nmCRPC (ARAMIS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA versus 2.5% receiving placebo, including Grade 3-4 events in 1.7% vs. 0.4%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA vs. 0.2% receiving placebo. In a study of patients with mHSPC (ARASENS), ischemic heart disease occurred in 3.2% of patients receiving NUBEQA with docetaxel vs. 2% receiving placebo with docetaxel, including Grade 3-4 events in 1.3% vs. 1.1%, respectively. Ischemic events led to death in 0.3% of patients receiving NUBEQA with docetaxel vs. 0% receiving placebo with docetaxel. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue NUBEQA for Grade 3-4 ischemic heart disease.

Seizure – In ARAMIS, Grade 1-2 seizure occurred in 0.2% of patients receiving NUBEQA vs. 0.2% receiving placebo. Seizure occurred 261 and 456 days after initiation of NUBEQA. In ARASENS, seizure occurred in 0.6% of patients receiving NUBEQA with docetaxel, including one Grade 3 event, vs. 0.2% receiving placebo with docetaxel. Seizure occurred 38 to 340 days after initiation of NUBEQA. It is unknown whether antiepileptic medications will prevent seizures with NUBEQA. Advise patients of the risk of developing a seizure while receiving NUBEQA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others. Consider discontinuation of NUBEQA in patients who develop a seizure during treatment.

Embryo-Fetal Toxicity – Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

Adverse Reactions

In ARAMIS, serious adverse reactions occurred in 25% of patients receiving NUBEQA vs. 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA included urinary retention, pneumonia, and hematuria. Fatal adverse reactions occurred in 3.9% of patients receiving NUBEQA vs. 3.2% of patients receiving placebo. Fatal adverse reactions in patients who received NUBEQA included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%). The most common adverse reactions (>2% with a ≥2% increase over placebo), including laboratory test abnormalities, were increased AST, decreased neutrophil count, fatigue, increased bilirubin, pain in extremity and rash. Clinically relevant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease and heart failure.

In ARASENS, serious adverse reactions occurred in 45% of patients receiving NUBEQA with docetaxel vs. 42% of patients receiving placebo with docetaxel. Serious adverse reactions in ≥2% of patients who received NUBEQA with docetaxel included febrile neutropenia (6%), decreased neutrophil count (2.8%), musculoskeletal pain (2.6%), and

pneumonia (2.6%). Fatal adverse reactions occurred in 4% of patients receiving NUBEQA with docetaxel vs. 4% of patients receiving placebo with docetaxel. Fatal adverse reactions in patients who received NUBEQA included COVID-19/COVID-19 pneumonia (0.8%), myocardial infarction (0.3%), and sudden death (0.3%). The most common adverse reactions (≥10% with a ≥2% increase over placebo with docetaxel) were constipation, rash, decreased appetite, hemorrhage, increased weight, and hypertension. The most common laboratory test abnormalities (≥30%) were anemia, hyperglycemia, decreased lymphocyte count, decreased neutrophil count, increased AST, increased ALT, and hypocalcemia. Clinically relevant adverse reactions in <10% of patients who received NUBEQA with docetaxel included fractures, ischemic heart disease, seizures, and drug-induced liver injury.

Drug Interactions

Effect of Other Drugs on NUBEQA – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible. If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the Prescribing Information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

For important risk and use information about NUBEQA, please see the accompanying full **Prescribing Information** .

About Metastatic Hormone-Sensitive Prostate Cancer

Prostate cancer is the second most common cancer in men and the fifth most common cause of cancer death in men worldwide. 3 In 2020, an estimated 1.4 million men were diagnosed with prostate cancer, including almost 300,000 cases in the U.S., and about 375,000 died from the disease worldwide. 4,5

At the time of diagnosis, most men have localized prostate cancer, meaning their cancer is confined to the prostate

gland and can be treated with curative surgery or radiotherapy. Upon relapse when the disease will metastasize or spread, androgen deprivation therapy (ADT) is the cornerstone of treatment for this hormone-sensitive disease. Approximately 10% of men will already present with mHSPC when first diagnosed. 6,7,8 Men with metastatic hormone-sensitive prostate cancer (mHSPC) will start their treatment with hormone therapy, such as ADT, androgen receptor inhibitor (ARi) plus ADT or a combination of the chemotherapy docetaxel and ADT. Despite this treatment, most men with mHSPC will eventually progress to castration-resistant prostate cancer (CRPC), a condition with limited survival.

About Oncology at Bayer

Bayer is committed to delivering science for a better life by advancing a portfolio of innovative treatments. The oncology franchise at Bayer includes six marketed products and several other assets in various stages of clinical development. Together, these products reflect the company's approach to research, which prioritizes targets and pathways with the potential to impact the way that cancer is treated.

About Bayer

Bayer is a global enterprise with core competencies in the life science fields of health care and nutrition. In line with its mission, "Health for all, Hunger for none," the company's products and services are designed to help people and the planet thrive by supporting efforts to master the major challenges presented by a growing and aging global population. Bayer is committed to driving sustainable development and generating a positive impact with its businesses. At the same time, the Group aims to increase its earning power and create value through innovation and growth. The Bayer brand stands for trust, reliability and quality throughout the world. In fiscal 2023, the Group employed around 100,000 people and had sales of 47.6 billion euros. R&D expenses before special items amounted to 5.8 billion euros. For more information, go to **www.bayer.com** .

Find more information at **www.pharma.bayer.com**
Our online press service is just a click away: **www.bayer.us/en/newsroom**
Follow us on Facebook: **http://www.facebook.com/pharma.bayer**
Follow us on X: **https://X.com/BayerUS**

Forward-Looking Statements

This release may contain forward-looking statements based on current assumptions and forecasts made by Bayer management. Various known and unknown risks, uncertainties and other factors could lead to material differences between the actual future results, financial situation, development or performance of the company and the estimates given here. These factors include those discussed in Bayer's public reports which are available on the

Bayer website at **www.bayer.com** . The company assumes no liability whatsoever to update these forward-looking statements or to conform them to future events or developments.

References

1. NUBEQA (darolutamide) [Prescribing Information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; October 2023.
2. Journal of Clinical Oncology (ascopubs.org). **Darolutamide in Combination With Androgen-Deprivation Therapy in Patients With Metastatic Hormone-Sensitive Prostate Cancer From the Phase III ARANOTE Trial** . **https://ascopubs.org/doi/10.1200/JCO-24-01798** . September 2024.
3. Hyuna S et al. Ca Cancer J Clin 2021 ; 71:209–249.
4. Prostate Cancer: Statistic. Cancer.Net. **https://www.cancer.net/cancer-types/prostate-cancer/statistics** . September 2024.
5. American Cancer Society. Cancer Facts & Figures 2024. **https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/2024-cancer-facts-figures.html** . September 2024.
6. Piombino C et al. Cancers (Basel). 2023 Oct 11;15(20):4945.
7. Helgstrand JT et al. Cancer. 2018;124(14):2931-2938.
8. Buzzoni C et al. Eur. Urol. 2015;68:885–890.

PP-NUB-US-3569-1 9/24

Media:

Elaine Colón, Tel +1.732.236.1587

Email: **elaine.colon@bayer.com**

Source: Bayer