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Pfizer and Astellas' XTANDI® Approved by U.S. FDA in Earlier Prostate Cancer Treatment Setting

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XTANDI becomes the first and only androgen receptor signaling inhibitor approved for use with or without a GnRH analog therapy* in nonmetastatic castration-sensitive prostate cancer

TOKYO and NEW YORK, November 16, 2023 – Astellas Pharma Inc. (TSE: 4503, President and CEO: Naoki Okamura, "Astellas") and Pfizer Inc. (NYSE: PFE) today announced that the companies received an approval by the U.S. Food and Drug Administration (FDA) of a supplemental New Drug Application for XTANDI® (enzalutamide), following FDA expedited development and review programs (Priority Review designation, Fast Track designation, Real-time Oncology Review), based on results from the Phase 3 EMBARK trial. With this approval, XTANDI becomes the first and only androgen receptor signaling inhibitor approved by the FDA for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR). Patients with nmCSPC with high-risk BCR may be treated with XTANDI with or without a gonadotropin-releasing hormone (GnRH) analog therapy.

Of men who have undergone definitive prostate cancer treatment, including radical prostatectomy, radiotherapy, or both, an estimated 20-40% will experience biochemical recurrence (BCR) within 10 years.[1] About nine out of 10 men with high-risk BCR will develop metastatic disease, and one in three will die as a result of their metastatic prostate cancer.[2]

"For patients who were previously treated for prostate cancer and had achieved remission, only to later receive the distressing news of disease recurrence with a risk of metastasis, the emotional toll can be profound," said Courtney Bugler, President and CEO of ZERO Prostate Cancer. "This approval of XTANDI is a promising treatment option for the community, offering a ray of hope to patients and their caregivers during these challenging times."

"Having had the privilege of taking care of patients with prostate cancer for nearly 40 years, I have been fortunate to have participated in many of the prostate cancer landscape changing trials; notably, we have not progressed our evidenced-based care for patients with biochemical recurrence (BCR), also known as nmCSPC, until the completion of the EMBARK trial," said Neal Shore, MD, FACS, Chief Medical Officer of Strategic Innovation and Pharmacy, GenesisCare USA, Director, CPI, Carolina Urologic Research Center, and Primary Investigator for the EMBARK trial. "Previously, treatment options for these BCR patients, especially those who have a high likelihood of developing metastases were limited. The FDA approval of XTANDI for patients with nmCSPC with BCR at high risk of metastasis represents an important advancement whereby an androgen deprivation signaling inhibitor, enzalutamide, has achieved standard of care discussion for patient-physician decision-making."

The approval is based on results from the Phase 3 EMBARK trial, which evaluated XTANDI plus leuprolide, placebo plus leuprolide, and XTANDI (single agent) in patients with nonmetastatic hormone- (or castration-)

sensitive prostate cancer (nmHSPC or nmCSPC) with high-risk BCR. Detailed results from the trial were presented as a plenary session during the 2023 American Urological Association Annual Meeting and subsequently published in the New England Journal of Medicine.

“Today’s FDA approval is the culmination of over a decade of research and development as we’ve worked to bring XTANDI forward for as many patients with prostate cancer as possible who may benefit,” said Ahsan Arozullah, M.D., MPH, Senior Vice President and Head of Oncology Development, Astellas. “With every milestone, our clinical development program has played an instrumental role in changing the course of patients’ lives. We are proud that XTANDI can now be offered to a subset of men with nonmetastatic castration-sensitive prostate cancer with biochemical recurrence and at high risk for metastases.”

“More than 300,000 men in the U.S. have been prescribed XTANDI, and we are excited to have this approval expand the indication for the first time into an earlier setting of the disease,” said Chris Boshoff, M.D., Ph.D., Chief Oncology Research and Development Officer and Executive Vice President at Pfizer. “This milestone is a testament to XTANDI’s legacy and robust clinical profile, with overall survival demonstrated for patients with metastatic castration-resistant prostate cancer, nonmetastatic castration-resistant prostate cancer, and metastatic castration-sensitive prostate cancer. With today’s approval, we look forward to bringing this therapy to even more patients who have nonmetastatic castration-sensitive prostate cancer at high risk for their cancer metastasizing.”

XTANDI is currently under review with other regulatory authorities around the world, including the European Medicines Agency, to support an expanded indication in nmHSPC (or nmCSPC) with high-risk BCR based on the results of EMBARK.

About EMBARK
The Astellas- and Pfizer-led Phase 3, randomized, double-blind, placebo-controlled, multi-national trial enrolled 1,068 patients with nonmetastatic hormone- (or castration-) sensitive prostate cancer (nmHSPC or nmCSPC) with high-risk BCR at sites in the U.S., Canada, Europe, South America, and the Asia-Pacific region. Patients who were considered to experience high-risk BCR had a prostate-specific antigen doubling time (PSA-DT) ? 9 months; serum testosterone ? 150 ng/dL (5.2 nmol/L); and screening PSA by the central laboratory ? 1 ng/mL if they had a radical prostatectomy (with or without radiotherapy) as primary treatment for prostate cancer, or at least 2 ng/mL above the nadir if they had radiotherapy only as primary treatment for prostate cancer. Patients in the EMBARK trial were randomized to receive enzalutamide 160 mg daily plus leuprolide (n=355), enzalutamide 160 mg as a single agent (n=355), or placebo plus leuprolide (n=358). Leuprolide 22.5 mg was administered every 12 weeks.

EMBARK met its primary endpoint of metastasis-free survival (MFS) for the XTANDI plus leuprolide arm, demonstrating a statistically significant reduction in the risk of metastasis or death over placebo plus leuprolide. MFS is defined as the duration of time in months between randomization and the earliest objective evidence of radiographic progression by central imaging or death due to any cause, whichever occurred first.

The study also met a key secondary endpoint, by demonstrating that patients treated with XTANDI (single agent) had a statistically significant reduction in the risk of metastasis or death versus placebo plus leuprolide, meeting its MFS endpoint.

In EMBARK, Grade 3 or higher adverse events (AEs) were reported in 46% of XTANDI plus leuprolide patients, 50% of patients treated with XTANDI (single agent), and 43% of patients receiving placebo plus leuprolide. Permanent discontinuation due to AEs as the primary reason was reported in 21% of XTANDI plus leuprolide patients, 18% in XTANDI (single agent) patients, and 10% in placebo plus leuprolide patients.

For more information on the EMBARK trial (NCT02319837) go to www.clinicaltrials.gov.

About Nonmetastatic Castration-Sensitive Prostate Cancer with High-Risk Biochemical Recurrence
In nonmetastatic castration- (or hormone-) sensitive prostate cancer (nmCSPC or nmHSPC), no evidence of the cancer spreading to distant parts of the body (metastases) is detectable with conventional radiological methods (CT/MRI), and the cancer still responds to medical or surgical treatment designed to lower testosterone levels.[3,4] Of men who have undergone definitive prostate cancer treatment, including radical prostatectomy, radiotherapy, or both, an estimated 20-40% will experience a BCR within 10 years.[1] About 9 out of 10 men with high-risk BCR will develop metastatic disease, and 1 in 3 will die as a result of their metastatic prostate cancer.[2] The EMBARK trial focused on men with high-risk BCR. Per the EMBARK protocol, patients with nmCSPC and high-risk BCR are those initially treated by radical prostatectomy or radiotherapy, or both, with a PSA-DT ? 9 months. High-risk BCR patients with a PSA-DT of ? 9 months have a higher risk of metastases and death.[5] In the U.S., it is estimated that 12,000-16,000 patients are diagnosed with nmCSPC with high-risk BCR annually.[6]

About XTANDI® (enzalutamide)
XTANDI® (enzalutamide) is an androgen receptor signaling inhibitor. XTANDI is a standard of care and has received regulatory approvals in one or more countries around the world for use in men with metastatic castration-sensitive prostate cancer (mCSPC; also known as metastatic hormone-sensitive prostate cancer or mHSPC), metastatic castration-resistant prostate cancer (mCRPC), non-metastatic castration-resistant prostate cancer (nmCRPC) and nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR). XTANDI is currently approved for one or more of these indications in more than 90 countries, including in the U.S., European Union and Japan. Over one million patients have been treated with XTANDI globally.[6]

U.S. Important Safety Information
XTANDI (enzalutamide) is indicated in the U.S. for the treatment of patients with castration-resistant prostate cancer (CRPC), metastatic castration-sensitive prostate cancer (mCSPC) and nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR).

Warnings and Precautions

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Posterior Reversible Encephalopathy Syndrome (PRES) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that can present with rapidly evolving symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in eight randomized clinical trials. Pharyngeal edema has been reported in post-

marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

Ischemic Heart Disease In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on XTANDI versus 1.1% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

Falls and Fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo.

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

Adverse Reactions (ARs)
In the data from the five randomized placebo-controlled trials, the most common ARs (? 10%) that occurred more frequently (? 2% over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. In the bicalutamide-controlled study, the most common ARs (? 10%) reported in XTANDI-treated patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated patients. Discontinuations due to ARs were reported for 16% of XTANDI-treated patients. In PREVAIL, the placebo-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to ARs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AR as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of nonmetastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AR as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients.

In ARCHES, the placebo-controlled study of metastatic CSPC (mCSPC) patients, Grade 3 or higher ARs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to ARs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

In EMBARK, the placebo-controlled study of nonmetastatic CSPC (nmCSPC) with high-risk biochemical recurrence (BCR) patients, Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a

single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide.

Lab Abnormalities: Lab abnormalities that occurred in ? 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies are hemoglobin decrease, neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, hyperphosphatemia, and hypercalcemia.

Hypertension: In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14.2% of XTANDI patients and 7.4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions
Effect of Other Drugs on XTANDI Avoid coadministration with strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI.
Avoid coadministration with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs Avoid coadministration with certain CYP3A4, CYP2C9, and CYP2C19 substrates for which minimal decrease in concentration may lead to therapeutic failure of the substrate. If coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

Please see Full Prescribing Information for additional safety information.

About Astellas
Astellas Pharma Inc. is a pharmaceutical company conducting business in more than 70 countries around the world. We are promoting the Focus Area Approach that is designed to identify opportunities for the continuous creation of new drugs to address diseases with high unmet medical needs by focusing on Biology and Modality. Furthermore, we are also looking beyond our foundational Rx focus to create Rx+® healthcare solutions that combine our expertise and knowledge with cutting-edge technology in different fields of external partners. Through these efforts, Astellas stands on the forefront of healthcare change to turn innovative science into VALUE for patients. For more information, please visit our website at https://www.astellas.com/en.

About Pfizer Oncology
At Pfizer Oncology, we are committed to advancing medicines wherever we believe we can make a meaningful difference in the lives of people living with cancer. Today, we have an industry-leading portfolio of 24 approved innovative cancer medicines and biosimilars across more than 30 indications, including breast, genitourinary, colorectal, blood and lung cancers, as well as melanoma.

About the Pfizer/Astellas Collaboration
In October 2009, Medivation, Inc., which is now part of Pfizer (NYSE:PFE), and Astellas (TSE: 4503) entered into a commercial agreement to jointly develop and commercialize XTANDI® (enzalutamide) in the United States, while Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercializing the product outside the United States. Pfizer receives alliance revenues as a share of U.S. profits and receives royalties on sales outside the U.S.

Astellas Forward-Looking Statement
In this press release, statements made with respect to current plans, estimates, strategies and beliefs and other statements that are not historical facts are forward-looking statements about the future performance of Astellas. These statements are based on management's current assumptions and beliefs in light of the information currently available to it and involve known and unknown risks and uncertainties. A number of factors could cause actual results to differ materially from those discussed in the forward-looking statements. Such factors include, but are not limited to: (i) changes in general economic conditions and in laws and regulations, relating to pharmaceutical markets, (ii) currency exchange rate fluctuations, (iii) delays in new product launches, (iv) the inability of Astellas to market existing and new products effectively, (v) the inability of Astellas to continue to effectively research and develop products accepted by customers in highly competitive markets, and (vi) infringements of Astellas' intellectual property rights by third parties.

Information about pharmaceutical products (including products currently in development), which is included in this press release is not intended to constitute an advertisement or medical advice.

Pfizer Disclosure Notice
The information contained in this release is as of November 16, 2023. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about XTANDI® (enzalutamide) and a new indication in the U.S. for the treatment of patients with nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis (high-risk BCR), including their potential benefits, that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, uncertainties regarding the commercial success of XTANDI; the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as the possibility of unfavorable new clinical data and further analyses of existing clinical data; whether the EMBARK trial will meet the secondary endpoint of overall survival; the risk that clinical trial data are subject to differing interpretations and assessments by regulatory authorities; whether regulatory authorities will be satisfied with the design of and results from the clinical studies; whether and when drug applications for XTANDI may be filed in other jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such applications that may be pending or filed for XTANDI (including the application pending with the European Medicines Agency), which will depend on a myriad of factors, including making a determination as to whether the product's benefits outweigh its known risks and determination of the product's efficacy and, if approved, whether XTANDI for any potential indication will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety, and/or other matters that could affect the availability or commercial potential of XTANDI, including for the new indication; dependence on the efforts and funding by Astellas Pharma Inc. for the development, manufacturing and commercialization of XTANDI; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2022 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

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*leuprolide

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