Pfizer Logo

XTANDI® (enzalutamide) Approved by U.S. FDA for the Treatment of Metastatic Castration-Sensitive Prostate Cancer

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XTANDI is Now FDA-Approved for the Treatment of Metastatic Castration-Sensitive Prostate Cancer in Addition to Non-Metastatic and Metastatic Castration-Resistant Prostate Cancer

NEW YORK & TOKYO--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) and Astellas Pharma Inc. (TSE: 4503, President and CEO: Kenji Yasukawa, Ph.D., "Astellas") announced today that the U.S. Food and Drug Administration (FDA) has approved a supplemental New Drug Application (sNDA) for XTANDI® (enzalutamide) for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC). In 2019, it is estimated that just over 40,000 men in the United States are living with mCSPC, a form of prostate cancer that has spread to other parts of the body and still responds to a medical or surgical treatment that lowers testosterone.1,2,3

With this approval, XTANDI is now the first and only oral treatment approved by the FDA in three distinct types of advanced prostate cancer – non-metastatic and metastatic castration-resistant prostate cancer (CRPC) and mCSPC. The approval is based on results from ARCHES, a randomized Phase 3 study which evaluated 1,150 men with mCSPC and met its primary endpoint of radiographic progression-free survival (rPFS).

"Men with metastatic castration-sensitive prostate cancer face complex treatment decisions and it is critical for physicians and patients to have as much information as possible when deciding on all of the options available," said Andrew Armstrong, M.D., Professor of Medicine, Surgery, Pharmacology and Cancer Biology, Director of Research in the Duke Cancer Institute's Center for Prostate and Urologic Cancers and lead investigator of ARCHES. "The research supporting the FDA approval and updated treatment guidelines provide physicians and patients with compelling evidence to consider enzalutamide as a treatment option for men with this disease."

Data from the ARCHES trial demonstrated that the use of XTANDI plus androgen deprivation therapy (ADT) significantly reduced the risk of radiographic progression or death by 61 percent compared to placebo plus ADT (n=1,150; hazard ratio [HR]: 0.39 [95% confidence interval (CI): 0.30-0.50]; p<0.0001). Overall survival data were not mature at the time of final rPFS analysis.

The safety analysis of the ARCHES trial is generally consistent with the safety profile of XTANDI in previous clinical trials in CRPC. In ARCHES, common adverse reactions (Grade 1 to 4 ARs; occurring in at least 5% of patients) that were reported more frequently in patients treated with XTANDI plus ADT vs placebo plus ADT included hot flush (27% vs 22%), asthenic conditions (24% vs 20%), hypertension (8.0% vs 5.6%), fractures (6.5% vs 4.2%), and musculoskeletal pain (6.3% vs 4.0%).

"XTANDI has been established as a standard of care for men with castration-resistant prostate cancer and has been prescribed to more than 420,000 patients worldwide since it was first approved in 2012," said Andrew Krivoshik, M.D., Ph.D., Senior Vice President and Oncology Therapeutic Area Head at Astellas. "This approval

in metastatic castration-sensitive prostate cancer means physicians can now offer XTANDI to men earlier in their advanced prostate cancer treatment journey."

"Today's approval adds to over a decade of global clinical research aimed at better understanding the potential benefit of XTANDI for men with advanced prostate cancer," said Andy Schmeltz, Global President, Pfizer Oncology. "The FDA approval marks continued progress to help meet the needs of patients, including men living with metastatic castration-sensitive prostate cancer."

Pfizer and Astellas are committed to helping patients access XTANDI by providing them with access and reimbursement support resources, including information regarding patient healthcare coverage options and financial assistance options that may be available to help patients with financial needs. Patients can visit www.XTANDI.com or call XTANDI Support Solutions at 1-855-898-2634 to learn more.

About Metastatic Castration-Sensitive Prostate Cancer

Prostate cancer is considered metastatic once it has spread outside of the prostate gland to other parts of the body, such as the bones, lymph nodes, bladder, and rectum.2 Men are considered castration- (or hormone-) sensitive if their disease still responds to medical or surgical treatment to lower testosterone levels.1 The prevalence of mCSPC in the U.S. in 2019 is estimated to be just over 40,000.3

ARCHES Trial

The company-sponsored, Phase 3, randomized, double-blind, placebo-controlled, multi-national ARCHES trial (NCT02677896) enrolled 1,150 patients with mCSPC at sites in the U.S., Canada, Europe, South America, and the Asia-Pacific region. Patients in the trial were randomized to receive XTANDI 160 mg daily or placebo and continued on a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist or had a history of bilateral orchiectomy.

The primary endpoint of the trial was rPFS assessed by blinded independent central review. Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of two or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior cycles).

About XTANDI® (enzalutamide)

XTANDI (enzalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with castration-resistant prostate cancer (CRPC) and metastatic castration-sensitive prostate cancer (mCSPC).

Important Safety Information for XTANDI®

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in seven 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 seven 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 four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on XTANDI versus 0.7% 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 four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 10% of patients treated with XTANDI and in 4% 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 four randomized placebo-controlled trials, the most common ARs (? 10%) that occurred more frequently (? 2% over placebo) in XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. 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 adverse events (AEs) 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 AEs 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 AE as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of non-metastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AE 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 AEs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to AEs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

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 neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, and hypercalcemia.

Hypertension: In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of XTANDI patients and 5% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

Please see Full Prescribing Information for additional safety information.

About the Enzalutamide Development Program

As part of Pfizer and Astellas' ongoing commitment to the clinical development of enzalutamide, XTANDI is also being evaluated in the EMBARK trial, in men with high-risk non-metastatic CSPC. Details about EMBARK (NCT02319837) are available on www.clinicaltrials.gov.

The European Medicines Agency (EMA) and the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan are currently evaluating XTANDI for men with metastatic hormone-sensitive prostate cancer.

About Astellas

Astellas Pharma Inc., based in Tokyo, Japan, is a company dedicated to improving the health of people around the world through the provision of innovative and reliable pharmaceutical products. 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 patients. Today, Pfizer Oncology has an industry-leading portfolio of 22 approved

innovative cancer medicines and biosimilars across more than 30 indications, including breast, prostate, kidney and lung cancers, as well as leukemia and melanoma. Pfizer Oncology is striving to change the trajectory of cancer.

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 global agreement to jointly develop and commercialize enzalutamide. The companies jointly commercialize XTANDI in the United States and Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercializing XTANDI outside the United States.

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 December 16, 2019. 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 men with metastatic castration-sensitive prostate cancer, 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 our 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; 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 our clinical studies; whether and when drug applications for the new indication for XTANDI may be filed in any other jurisdictions and whether and when drug applications for any other potential indications for XTANDI may be filed in any jurisdictions; whether and when regulatory authorities in any jurisdictions may approve any such other applications that may be pending or filed (including the applications under review by the EMA and PMDA in Japan for the new indication), which will depend on myriad 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 such potential new indications 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; risks related to increasing competitive, reimbursement and economic challenges; dependence on the efforts and funding by Astellas Pharma Inc. for the development, manufacturing and commercialization of XTANDI; 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, 2018 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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1 Cancer.net. Prostate Cancer: Types of Treatment (03-2018). https://www.cancer.net/cancer-types/prostate-cancer/types-treatment. Accessed 912-2019.

2 American Society of Clinical Oncology. ASCO Answers: Prostate Cancer (2018). https://www.cancer.net/sites/cancer.net/files/asco_answers_guide_prostate.pdf. Accessed 10-07-2019.

3 Supplement to: Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. PLoS One 2015;10(10):e0139440.

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