NOW APPROVED

For the treatment of castration-resistant prostate cancer (CRPC), including nonmetastatic CRPC[1]

Xtandi® (enzalutamide) 40 mg capsules

XTANDI significantly extended metastasis-free survival* in patients with nonmetastatic CRPC[1]

Dear Customer,

Astellas Pharma US, Inc. and Pfizer Inc. are pleased to announce that XTANDI is now indicated for the treatment of patients with CRPC.[1]

PROSPER was a multinational, randomized, double-blind, placebo-controlled phase 3 study of XTANDI + LHRH therapy† in patients with nonmetastatic CRPC who had progressed on LHRH therapy.[†1,2] In PROSPER, 1401 patients with nonmetastatic CRPC were randomized 2:1 to receive XTANDI at a dose of 160 mg once daily (n = 933) or matching placebo once daily (n = 468).[1] Treatment randomization was stratified by PSA doubling time (< 6 months or ≥ 6 months) and baseline use of a bone-targeting agent (yes or no).[2] Patients in both arms continued to receive LHRH therapy† and had a PSA doubling time of 10 months or less.[1] The primary endpoint was metastasis-free survival.*[1] Eligibility criteria included: nonmetastatic CRPC (central review), 3 rising PSA values despite castrate testosterone levels (≤ 50 ng/dL),‡ baseline PSA at least 2 ng/mL, PSA doubling time 10 months or less, no prior chemotherapy and ECOG performance status of 0 or 1.[1,2]

Median metastasis-free survival* was **3 years** with XTANDI + LHRH therapy† vs 14.7 months with placebo + LHRH therapy†[1]

PROSPER TRIAL (N = 1401)

In the phase 3 PROSPER trial, XTANDI significantly extended metastasis-free survival* in patients with nonmetastatic CRPC. Median metastasis-free survival was **36.6 MONTHS** (95% CI, 33.1-NR) for patients receiving XTANDI + LHRH therapy† vs **14.7 MONTHS** (95% CI, 14.2-15.0) for patients receiving placebo + LHRH therapy† (HR = 0.29 [95% CI, 0.24-0.35]; *P* < 0.0001).[1]

71% reduction in the risk of metastasis or death with XTANDI + LHRH therapy† vs placebo + LHRH therapy† in patients with nonmetastatic CRPC (HR = 0.29 [95% CI, 0.24-0.35]; *P* < 0.0001).[1]

For additional details regarding the new XTANDI indication, please contact your XTANDI Account Manager.

CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LHRH, luteinizing hormone-releasing hormone; NR, not reached; PSA, prostate-specific antigen.

CRPC is defined as disease progression on androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy).[3]

*Metastasis-free survival was defined as the time from randomization to whichever of the following occurred first: 1) loco-regional and/or distant radiographic progression per blinded independent central review or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression.[1]

†**Or after bilateral orchiectomy.**[1]

‡Progression was defined as 3 rising PSA values (PSA1 < PSA2 < PSA3) taken at least 1 week apart despite castrate levels of testosterone (≤ 50 ng/dL) on LHRH therapy or after bilateral orchiectomy.[2]

Indication

XTANDI (enzalutamide) is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC).

Select Safety Information

Warnings and Precautions

Seizure occurred in 0.4% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. Patients in the study had one or more of the following pre-disposing factors: use of medications that may lower the seizure threshold; history of traumatic brain or head injury, cerebrovascular accident or transient ischemic attack, 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. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. 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) In post approval use, there have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder which 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.

Please see additional Important Safety Information on the next page and click here for Full Prescribing Information.

Important Safety Information (continued)

Warnings and Precautions (continued)

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in 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 placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.7% vs 1.2%). Grade 3-4 ischemic events occurred in 1.2% of patients on XTANDI versus 0.5% 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 In the placebo-controlled clinical studies, falls occurred in 10% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 8% of patients treated with XTANDI and in 3% of patients treated with placebo. 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.

Embryo-Fetal Toxicity 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. XTANDI should not be handled by females who are or may become pregnant.

Adverse Reactions

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI patients from the randomized placebo-controlled trials were asthenia/fatigue, decreased appetite, hot flush, arthralgia, dizziness/vertigo, hypertension, headache and weight decreased. In the bicalutamide-controlled study, the most common adverse reactions (≥ 10%) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In the placebo-controlled study of metastatic CRPC (mCRPC) patients taking XTANDI who previously received docetaxel, Grade 3 and higher adverse reactions were reported among 47% of XTANDI patients and 53% of placebo patients. Discontinuations due to adverse events were reported for 16% of XTANDI patients and 18% of placebo patients. In the placebo-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to adverse events were reported for 6% of both study groups. In the placebo-controlled study of non-metastatic CRPC (nmCRPC) patients, Grade 3 or higher adverse reactions were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an adverse event as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients. In the bicalutamide-controlled study of chemotherapy-naïve mCRPC patients, Grade 3-4 adverse reactions 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.

Lab Abnormalities: In the two placebo-controlled trials in patients with mCRPC, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). In the placebo-controlled trial in patients with nmCRPC, Grade 1-4 neutropenia occurred in 8% of patients receiving XTANDI (0.5% Grade 3-4) and in 5% of patients receiving placebo (0.2% Grade 3-4).

Hypertension: In the two placebo-controlled trials in patients with mCRPC, hypertension was reported in 11% of XTANDI patients and 4% of placebo patients. Hypertension led to study discontinuation in <1% of patients in each arm. In the placebo-controlled trial in patients with nmCRPC, hypertension was reported in 12% of patients receiving XTANDI and 5% of patients receiving placebo.

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 click here for Full Prescribing Information.

Kind regards,

XTANDI Account Management Team

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Pfizer. XTANDI. Data on File. **3.** Eisenberger MA, Saad F. Introduction—Castrate resistant prostate cancer: a rapidly expanding clinical state and a model for new therapeutic opportunities. In: Saad F, Eisenberger MA, eds. Management of Castration Resistant Prostate Cancer. 1st ed. New York, NY: Springer, 2014:3-8.

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