

XTANDI® (enzalutamide) Capsules: A Treatment Option for Metastatic Castration-Resistant Prostate Cancer (CRPC)



XTANDI® (enzalutamide) was approved by the Food and Drug Administration (FDA) for the treatment of a type of prostate cancer that: no longer responds to a medical or surgical treatment that lowers testosterone, and has spread, or metastasized, beyond the prostate to other parts of the body.¹

HELPFUL INFORMATION ABOUT XTANDI DOSING



The recommended dose of XTANDI is four 40 mg capsules (160 mg) taken once a day, at the same time each day¹



XTANDI can be taken with or without food¹



Steroids, for example oral prednisone, can be taken but are not required with XTANDI^{2*}



XTANDI is taken with hormone therapy injections^{3**}

HOW XTANDI WORKS



Metastatic CRPC refers to when the cancer spreads outside the prostate and progresses despite treatment.⁴ That's why a doctor may recommend an additional medication like XTANDI to help treat metastatic CRPC.

In prostate cancer, the androgen receptor (AR) is a key driver of progression.⁵ XTANDI is an AR-binding inhibitor, which works by preventing testosterone from binding to prostate cancer cells.² XTANDI is thought to act on multiple steps of the AR-signaling pathway within the tumor cells in vitro.¹

SELECT SAFETY INFORMATION

Contraindications: XTANDI is not indicated for use in women. XTANDI can cause fetal harm and potential loss of pregnancy.

Effect of XTANDI on Other Drugs: XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. 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.

*In the PREVAIL trial, 27% of patients in the XTANDI arm and 30% of patients in the placebo arm received glucocorticoids for varying reasons. In the AFFIRM trial, 48% of patients in the XTANDI arm and 46% of patients in the placebo arm received glucocorticoids.

**Or after surgical castration.

XTANDI® (enzalutamide) Capsules: A Treatment Option for Metastatic Castration-Resistant Prostate Cancer (CRPC)



AFFIRM

The AFFIRM trial was an international, randomized, double-blind, placebo-controlled study in 1,199 men with prostate cancer who had previously undergone medical or surgical castration and had been treated with one or two chemotherapy regimens, at least one of which contained the chemotherapy docetaxel.⁶

Results of the study demonstrated XTANDI:

- **Extended median Overall Survival (OS)** post-docetaxel in patients with metastatic CRPC by **18.4 months** compared to **13.6 months** with placebo, (hazard ratio [HR]* = 0.63 [95% Confidence Interval (CI), 0.53-0.75]; P < 0.0001).⁶

PREVAIL

The FDA approval expanding XTANDI's indication to include chemotherapy-naïve men with metastatic CRPC was based on results of the PREVAIL trial, a randomized, double-blind, placebo-controlled trial in 1,717 men with metastatic CRPC who had previously undergone medical or surgical castration and had no symptoms or had mild symptoms.³

XTANDI, in combination with the hormone therapy, gonadotropin-releasing hormone (GnRH), was shown to:

- Significantly extended OS with a **23% reduction in risk of death** compared with placebo (HR = 0.77 [95% CI, 0.67-0.88]).¹
- Significantly **reduced the risk of radiographic progression** (when the disease progresses) or death, by **83%** compared with placebo (HR = 0.17 [95% CI, 0.14-0.21]; P < 0.0001).¹

TERRAIN

The TERRAIN trial was a randomized study comparing XTANDI to bicalutamide in 375 chemotherapy-naïve patients with metastatic CRPC who had previously undergone medical or surgical castration.⁵ Results of the study demonstrated XTANDI:

- XTANDI, in combination with (GnRH) **reduced the risk of radiographic progression or death by 40%** in patients with metastatic CRPC compared with bicalutamide (HR = 0.60 [95% CI, 0.43-0.83]).¹

ABOUT THE ASTELLAS/PFIZER COLLABORATION

Astellas and Pfizer jointly commercialize XTANDI in the United States. Astellas has responsibility for manufacturing and all additional regulatory filings globally, as well as commercializing XTANDI outside the United States.

SELECT SAFETY INFORMATION

Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

There have been post approval reports of posterior reversible encephalopathy syndrome (PRES), a neurological disorder that can present with rapidly evolving symptoms and requires confirmation by brain imaging. Discontinue XTANDI in patients who develop PRES.

*Hazard ratio (HR) indicates the relative risk of a complication based on comparison of event rates between treatment and control.

XTANDI® (enzalutamide) Capsules: A Treatment Option for Metastatic Castration-Resistant Prostate Cancer (CRPC)



Important Safety Information

Contraindications XTANDI is not indicated for women. XTANDI can cause fetal harm and potential loss of pregnancy.

Warnings and Precautions Seizure occurred in 0.5% of patients receiving XTANDI in clinical studies. In a study of patients with predisposing factors, seizures were reported in 2.2% of patients. See section 5.1 of the Prescribing Information for the list of predisposing factors. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. 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.

Adverse Reactions The most common adverse reactions ($\geq 10\%$) that occurred more commonly ($\geq 2\%$ over placebo) in the XTANDI patients from the two placebo-controlled clinical trials were asthenia/fatigue, back pain, decreased appetite, constipation, arthralgia, diarrhea, hot flush, upper respiratory tract infection, peripheral edema, dyspnea, musculoskeletal pain, weight decreased, headache, hypertension, and dizziness/vertigo. In the bicalutamide-controlled study of chemotherapy-naïve patients, the most common adverse reactions ($\geq 10\%$) reported in XTANDI patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, upper respiratory tract infection, diarrhea, and weight loss.

In the placebo-controlled study of 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 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 bicalutamide-controlled study of chemotherapy-naïve patients, Grade 3-4 adverse reactions were reported in 38.8% of XTANDI patients and 37.6% of bicalutamide patients. Discontinuations due to adverse events were reported for 7.6% of XTANDI patients and 6.3% of bicalutamide patients.

Lab Abnormalities In the two placebo-controlled trials, Grade 1-4 neutropenia occurred in 15% of XTANDI patients (1% Grade 3-4) and 6% of placebo patients (0.5% Grade 3-4). Grade 1-4 thrombocytopenia occurred in 6% of XTANDI patients (0.3% Grade 3-4) and 5% of placebo patients (0.5% Grade 3-4). Grade 1-4 elevations in ALT occurred in 10% of XTANDI patients (0.2% Grade 3-4) and 16% of placebo patients (0.2% Grade 3-4). Grade 1-4 elevations in bilirubin occurred in 3% of XTANDI patients (0.1% Grade 3-4) and 2% of placebo patients (no Grade 3-4).

Infections In the study of patients taking XTANDI who previously received docetaxel, 1% of XTANDI patients compared to 0.3% of placebo patients died from infections or sepsis. In the study of chemotherapy-naïve patients, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Falls (including fall-related injuries) occurred in 9% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in XTANDI patients, and included non-pathologic fractures, joint injuries, and hematomas.

Hypertension occurred in 11% of XTANDI patients and 4% of placebo patients in the two placebo-controlled trials. No patients experienced hypertensive crisis. Medical history of hypertension was balanced between arms. 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.

XTANDI® (enzalutamide) Capsules: A Treatment Option for Metastatic Castration-Resistant Prostate Cancer (CRPC)



References

1. XTANDI [package insert]. Northbrook, IL: Astellas, Inc.
2. Urology Care Foundation. Advanced Prostate Cancer Patient Guide. www.urologyhealth.org/educational-materials. Accessed 02-16-2017.
3. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. *N Engl J Med*. 2014;371(5):424-33.
4. Cancer.Net. Treatment of Metastatic Castration-Resistant Prostate Cancer (09-08-2014). www.cancer.net/research-and-advocacy/asco-care-and-treatment-recommendations-patients/treatment-metastatic-castration-resistant-prostate-cancer. Accessed 02-16-2017.
5. Shore ND, Chowdhury S, Villers A, et al. Efficacy and safety of enzalutamide versus bicalutamide for patients with metastatic prostate cancer (TERRAIN): a randomized, double-blind, phase 2 study. *Lancet Oncol* 2016;17(2):153-63.
6. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012;367(13):1187-97.