Xtandi (enzalutamide)

NEW INDICATION REVIEW

MPR

Introduction

- **Brand name:** Xtandi
- **Generic name:** Enzalutamide
- **Pharmacological class:** Androgen receptor inhibitor
- **Strength and Formulation:** 40mg; soft gelatin caps
- **Manufacturer:** Astellas Pharma
- **How supplied:** Caps—120
- **Legal Classification:** Rx

Xtandi


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(enzalutamide)
capsules
40 mg
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Indications

- **New indication**
  - Treatment of patients with castration-resistant prostate cancer (CRPC)

- Previous indication
  - Treatment of patients with metastatic CRPC

Dosage & Administration

- Swallow whole
- 160mg once daily
- Patients receiving Xtandi should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy

Dosage & Administration

- **≥Grade 3 toxicity or intolerable side effect:** withhold dosing for 1 week or until symptoms improve to ≤Grade 2, then resume at same or reduced dose (120mg or 80mg), if warranted
- **Concomitant strong CYP2C8 inhibitors:** avoid if possible; if co-administration necessary, reduce enzalutamide dose to 80mg once daily

Dosage & Administration

- **Concomitant strong CYP3A4 inducers:** avoid if possible; if co-administration necessary, increase enzalutamide dose to 240mg once daily.
- When CYP2C8 inhibitor or CYP3A4 inducer is **discontinued**, return enzalutamide dose to that prior to initiation of the inhibitor or inducer

Considerations for Special Populations

- **Pediatric:** Not established
- **Pregnancy:** Can cause fetal harm and loss of pregnancy; do not handle if pregnant or may become pregnant
- **Nursing mothers:** Not established
- **Elderly:** No overall differences in safety or efficacy
- **Renal impairment:** Severe (CrCl <30mL/min) and ESRD: not assessed

Warnings/Precautions

- Risk of **seizure**; permanently discontinue if occurs
- Discontinue if **posterior reversible encephalopathy syndrome** (PRES) develops
- Permanently discontinue for serious hypersensitivity reactions

Warnings/Precautions

- Monitor for **ischemic heart disease**; discontinue for Grade 3-4 ischemic heart disease
- Evaluate for **fracture and fall risk**
- Males with female partners of reproductive potential: use **effective contraception** during and for 3 months after final dose

Interactions

- **Avoid** concomitant CYP2C8 inhibitors (eg, gemfibrozil) if possible; if co-administration unavoidable, reduce dose (see Dosing)
- **Avoid** concomitant CYP3A4 inducers (eg, carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St. John's Wort); if unavoidable, increase dose (see Dosing)

Interactions

- **Antagonizes** midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate)
- May antagonize concomitant drugs with **narrow therapeutic indexes** metabolized by CYP3A4 (eg, alfentanil, cyclosporine dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (eg, phenytoin, warfarin), CYP2C19 (eg, S-mephenytoin, clopidogrel); avoid

Interactions

- Conduct more **INR monitoring** if concomitant warfarin cannot be avoided
- Caution with concomitant drugs that may lower the seizure threshold

Adverse Reactions

- Asthenia/fatigue
- Decreased appetite
- Hot flush
- Arthralgia
- Dizziness/vertigo
- Hypertension
- Headache
- Decreased weight
- Seizure
- PRES
- Ischemic heart disease
- Falls and fractures

Mechanism of Action

- **Enzalutamide** competitively inhibits androgen binding to androgen receptors, inhibiting nuclear translocation of androgen receptors and their interaction with DNA

Clinical Studies

- The safety and efficacy Xtandi for non-metastatic CRPC was evaluated in a randomized, multicenter study (**PROSPER**) in 1401 patients
- Data from the PROSPER trial supported the approval of an expanded indication for Xtandi in CRPC

Clinical Studies

- Patients received Xtandi 160mg once daily or placebo once daily
- All received a GnRH analog or had a prior bilateral orchiectomy
- Patients were allowed to continue or start glucocorticoids

Clinical Studies

- The major efficacy outcome of the study was metastasis-free survival (MFS), defined as time from randomization to whichever of the following occurred first:
  - Loco-regional and/or distant radiographic progression per BICR
  - Death up to 112 days after treatment discontinuation without evidence of radiographic progression

Clinical Studies

- MFS:
  - Number of events: **23.5%** (Xtandi) vs **48.7%** (placebo)
  - Median, months: 36.6 (95% CI, 33.1–NR) vs 14.7 (95% CI, 14.2–15.0)
  - HR 0.29 (95% CI, 0.24–0.35; *P* <.0001)

Clinical Studies

- A **statistically significant delay** in time to first use of antineoplastic therapy (TTA) was seen with Xtandi vs placebo
  - 39.6 months vs. 17.7 months (HR 0.21, 95% CI, 0.17–0.26; *P* <.0001)

Clinical Studies

- Overall survival (OS) data were not mature at time of final MFS analysis

- For more clinical data, see full labeling

New Product Monograph

- For more information view the product monograph available at:

  https://www.empr.com/xtandi/drug/8023/