

## Enzalutamide (Xtandi) Criteria for Use Updated March 2015

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. The clinician should utilize this guidance and interpret it in the clinical context of the individual patient. **Individual cases that are outside the recommendations should be adjudicated at the local facility according to the policy and procedures of its P&T Committee and Pharmacy Services.**

*The Product Information should be consulted for detailed prescribing information.*

*See the VA National PBM-MAP-VPE Monograph on this drug at [www.pbm.va.gov](http://www.pbm.va.gov) or <http://vawww.pbm.va.gov> for further information.*

**Exclusion Criteria** *If the answer to ANY item below is met, then the patient should NOT receive enzalutamide.*

- Brain metastases or active epidural disease
- Total bilirubin, ALT, or AST greater than 2 times the upper limit of normal or Child-Pugh Class C
- Severe renal impairment (creatinine clearance < 30 mL/min)
- History of seizure (including febrile seizure, loss of consciousness, or transient ischemic attack within the previous 12 months, any condition predisposing to seizure: prior stroke, brain AV malformation, head trauma with loss of consciousness requiring hospitalization)
- ECOG Performance Status greater than 2\*
- Inability to swallow capsules

**Inclusion Criteria** *The answers to all of the following must be fulfilled in order to meet criteria.*

- Patients with metastatic castration-resistant prostate cancer with objective evidence of progressive disease by laboratory or radiographic evidence while receiving androgen deprivation therapy (and **One** of the following):
  - o who progressed on or after docetaxel-based therapy
  - o who are asymptomatic or mildly symptomatic (does not require opioids for cancer related pain and average weekly cancer-related pain score is less than 4 on a 10 point visual analogue scale) in whom cytotoxic chemotherapy is not yet clinically indicated
  - o who are not a candidate for docetaxel chemotherapy because of Grade 2 or greater peripheral neuropathy, previous bone marrow irradiation, pre-existing cytopenias, poor bone-marrow reserve due to age or prior therapies, or patient declines chemotherapy

And ALL of the following:

- Goals of care and role of Palliative Care consult has been discussed and documented.
- On-going castrate testosterone levels (< 50 ng/dL) due to either medical or surgical castration
- ECOG Performance Status of 0-2<sup>†</sup>
- Patient is followed by a VA oncologist or designated VA expert in urologic oncology
- Counseling regarding sexual activity as indicated below is documented.

For men who are sexually active with a pregnant woman

- Use of a condom is required during therapy with enzalutamide and for 3 months after stopping enzalutamide therapy

For men whose sexual partner may become pregnant

- Use of a condom plus another form of birth control is required during therapy with enzalutamide and for 3 months after stopping enzalutamide therapy

### Dosage and Administration

Refer to Product Information.

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Updated versions may be found at <http://www.pbm.va.gov> or <http://vawww.pbm.va.gov>

**Monitoring**

- Blood pressure (monthly)

**Issues for Consideration**

- Enzalutamide is not indicated for use in women. Based on the mechanism of action, can cause fetal harm if used during pregnancy. Pregnancy Category X- use contraindicated during pregnancy. Exclude pregnancy before prescribing enzalutamide, discuss risks if pregnancy occurs, and provide contraceptive counseling.
- Use in patients taking concomitant medications which may lower the seizure threshold was not studied; caution patients about the risk of activities where the sudden loss of consciousness could cause serious harm if concomitant use cannot be avoided.
- Use in patients at risk for or with a strong history of falls: in the phase 3 clinical trial, falls or injuries from falls occurred in 4.6% of enzalutamide patients vs. 1.3% of placebo patients.
- Avoid strong inhibitors of CYP2C8 (e.g. gemfibrozil); if concomitant use cannot be avoided, reduce the dose of enzalutamide according to the package insert
- Co-administration with strong or moderate inducers of CYP3A4 (e.g. carbamazepine, phenobarbital, phenytoin, rifampin, bosentan, efavirenz, modafinil, nafcillin, St. John's Wort) or CYP2C8 (e.g. rifampin) should be avoided if possible.
- Drugs that are substrates of CYP3A4 (e.g. alfentanil, cyclosporine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), or CYP2C19 (e.g. S-mephenytoin) with a narrow therapeutic index should be avoided. If enzalutamide is co-administered with warfarin, additional INR testing should be conducted.
- Sequencing of enzalutamide and abiraterone has been evaluated in several small retrospective analyses; the majority of the analyses are in the post chemotherapy setting. From this limited observational data, it is unclear if there is a preferred sequencing of abiraterone and enzalutamide. There is some evidence for cross-resistance. There are ongoing investigations into mechanisms of resistance to enzalutamide and abiraterone.

**Discontinuation Criteria**

Asymptomatic or minimally symptomatic patient & evidence of progression of disease (when used **prior to cytotoxic chemotherapy**):

- **One** of the following criteria
  - Bone scan with  $\geq 2$  new lesions observed 12 or more weeks after starting enzalutamide therapy
  - Radiographic evidence of progression of soft tissue lesions by modified RECIST criteria.
  - Unequivocal clinical progression without radiographic evidence
    - Cancer-related pain requiring initiation of chronic opiate analgesia
    - Immediate need to start cytotoxic chemotherapy, radiation, or surgery due to complications from tumor progression
    - Deterioration of ECOG Performance Status to grade 3 or higher (i.e. Patient is capable of only limited self-care, confined to bed/chair > 50% of waking hours)
    -

Symptomatic patient with advanced disease & evidence of disease progression (when used **instead of docetaxel or after docetaxel**):

- **All three** of the following criteria
  - PSA progression of 25% over baseline and minimum increase of 5.0 ng/mL
  - Radiographic progression defined by **one** of the following:
    - Bone scan with  $\geq 2$  new lesions not due to tumor flare
    - Soft tissue disease progression as defined by modified RECIST criteria
  - Symptomatic or clinical progression as defined by **one** of the following:
    - Pain progression observed on 2 consecutive evaluations (>30% increase in bone pain scores on a visual analogue scale or >30% increase in analgesic use)
    - Skeletal related event (pathologic fracture, spinal cord compression, palliative radiation or surgery to bone)
    - Increase in prednisone dose or need to change to a more potent glucocorticoid to treat cancer-related symptoms
- New onset seizure

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**\*ECOG Performance Status**

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982