

## Enzalutamide (Xtandi®)

### National Drug Monograph

May 2013

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

*The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. These documents will be updated when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.*

### **Executive Summary:**

#### Clinical Efficacy

- Enzalutamide is a second generation androgen receptor inhibitor. It competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA.
- Enzalutamide was compared to placebo in an international, randomized, double-blinded clinical trial in patients with metastatic castration-resistant prostate cancer following 1 or 2 prior chemotherapy regimens of which one had to contain docetaxel.
- The enzalutamide dose was 160 mg orally daily (four 40mg capsules).
- The primary outcome was overall survival. The overall survival in the enzalutamide arm was 18.4 months versus 13.6 months in the placebo arm. The hazard ratio for death was 0.63 (95% CI 0.53-0.75).
- Secondary outcomes (radiographic Progression Free Survival, Time to PSA Progression, Time to 1<sup>st</sup> skeletal-related event, Functional Assessment of Cancer Treatment-Prostate, Best Soft Tissue Response, and PSA Response) were consistent and favored enzalutamide.

#### Clinical Safety

- The most common adverse events reported in the clinical trial were asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory tract infection, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension.
- Grade 3 or higher adverse reactions were reported in 47% of enzalutamide patients and in 53% of placebo patients. No one Grade 3 adverse reaction was reported in more than 9% of enzalutamide patients
- Discontinuation of therapy due to Grade 3 or higher adverse reactions occurred in 8% of enzalutamide patients and in 10% of placebo patients.
- There is a warning about seizures. Seizures occurred in 7 of 800 enzalutamide patients. Many of these patients had other factors that lowered seizure threshold. In earlier trials, seizures were seen primarily at higher doses.

#### Conclusion

Enzalutamide is a second generation androgen receptor inhibitor with clinically significant clinical activity in patients with metastatic castration-resistant prostate cancer following docetaxel based chemotherapy. While 47% of patients experienced a Grade 3 or 4 adverse reactions, no one event accounted for more than 9%. Patients with a history of seizures or predisposed to seizures should not receive enzalutamide at this time.

<b>Outcome in clinically significant area</b>	Overall Survival: 18.4 months versus 13.6 months
<b>Effect Size</b>	HR 0.63 (95% CI 0.53-0.75)
<b>Potential Harms</b>	No grade 3 or 4 Adverse Event in more than 9% of patients Grade 3 or 4 Adverse Event in 47%
<b>Net Clinical Benefit</b>	Moderate (high benefit with high risk)

## **Introduction**<sup>1,2,3,4</sup>

Normally, testosterone and its active metabolite dihydrotestosterone (DHT) are ligands for the androgen receptor (AR). Binding to the AR causes changes in the composition and conformation, leading to nuclear translocation from the cytoplasmic compartment. Once in the nucleus, the AR binds to androgen response elements on target genes (e.g. prostate specific antigen [PSA]) and leads to transcription of mRNA.

Traditional androgen deprivation therapy reduces intracellular concentrations of DHT and results in tumor regression in prostate cancer. However, androgen deprivation therapy does not completely inhibit intratumoral androgens or the expression of androgen receptor target genes.

The androgen receptor is central to the biology of metastatic castration resistant prostate cancer. The mechanisms that explain resistance to traditional androgen deprivation therapy include AR amplification or point mutations, ligand-independent activation of the AR, and alternative signaling pathways that no longer involve the AR. Androgen antagonists, including bicalutamide, have been shown to exhibit agonist activity when AR is overexpressed.

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating enzalutamide for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

## **Pharmacology/Pharmacokinetics**<sup>5,6</sup>

Enzalutamide is a second generation androgen receptor inhibitor. It competitively inhibits androgen binding to androgen receptors and inhibits androgen receptor nuclear translocation and interaction with DNA. Enzalutamide was developed through structure activity relationships and modifications using a scaffold with a higher binding capacity than bicalutamide for the AR in castration-resistant cells. In this castration-resistant prostate cancer cell line, enzalutamide did not show any agonist activity.

**Table #1            Pharmacokinetics**

<b>Parameter</b>	<b>Drug</b>
Metabolism	CYP2C8 to an active metabolite N-desmethyl enzalutamide and CYP3A4
Elimination	Primarily hepatic metabolism
Half-life	Mean enzalutamide terminal t <sub>1/2</sub> is 5.8 days (range 2.8 to 10.2 days); mean N-desmethyl enzalutamide terminal t <sub>1/2</sub> is 7.8-8.6 days.
Protein Binding	Enzalutamide 97-98% bound to plasma proteins, primarily albumin; N-desmethyl enzalutamide 95% bound to plasma proteins

## **FDA Approved Indication(s)**

Enzalutamide is indicated for the treatment of patients with metastatic castration-resistant prostate cancer who previously received docetaxel.

**Potential Off-label Uses**

This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's [Guidance on "Off-label" Prescribing](#) (available on the VA PBM Intranet site only).

Patients with metastatic castration-resistant prostate cancer who are chemotherapy naïve and who are asymptomatic or mildly symptomatic (on-going clinical trial).

**Current VA National Formulary Alternatives**

None

**Dosage and Administration**

Recommended dose: 160 mg (four 40 mg capsules) administered orally once daily. Enzalutamide can be taken with or without food. Capsules should be swallowed whole and not chewed. Do not dissolve or open capsules.

**Dose Modifications**

If a patient experiences a Grade 3 or greater toxicity or an intolerable side effect, withhold the dose for one week or until symptoms resolve to  $\leq$ Grade 2, then resume at the same or reduced dose (120 mg or 80mg) if warranted.

**Concomitant Strong CYP2C8 inhibitors**

Avoid the concomitant use of strong CYP2C8 inhibitors if possible. If a strong CYP2C8 inhibitor must be co-administered, reduce the enzalutamide dose to 80 mg once daily. If co-administration of the strong inhibitor is discontinued, the enzalutamide dose should be increased to the dose used prior to the initiation of the strong CYP2C8 inhibitor.

**Efficacy<sup>7,8</sup>****Efficacy Measures (see Appendix 1: Approval Endpoints)****Primary Endpoint**

Overall survival

**Secondary Endpoints**

- Radiographic Progression Free Survival (rPFS)
- Time to 1<sup>st</sup> Skeletal Related Event (SRE) [SRE=spinal cord compression, pathologic bone fracture, radiation therapy or surgery to bone, change in antineoplastic therapy to treat bone pain]
- Quality of Life (Functional Assessment of Cancer Therapy-Prostate [FACT-P])
- Time to PSA progression ( $\geq 25\%$  increase and an absolute increase of  $\geq 2$  ng/mL above the nadir at week 13 and confirmed by a second consecutive value 3 or more weeks later. If no PSA progression at week 13, the date that a  $\geq 25\%$  increase and an absolute increase of  $\geq 2$  ng/mL above the nadir was documented and confirmed by a second consecutive value 3 or more weeks later)
- Pain palliation
- Safety
- ECG changes compared to placebo
- Best Soft Tissue response by RECIST criteria

## Summary of efficacy findings

The AFFIRM trial (A Study Evaluating the Efficacy and Safety of the Investigational Drug MDV3100) was an international, phase 3, randomized, double-blind, placebo-controlled trial in patients with prostate cancer who had previously been treated with one or two chemotherapy regimens and at least one contained docetaxel. The trial compared enzalutamide 160mg once daily to placebo.

### Inclusion

- Adenocarcinoma of the prostate without small-cell features
- Ongoing androgen deprivation therapy with a serum testosterone < 50 ng/dL at screening
- If receiving a bisphosphonate, a stable dose for at least 4 weeks
- Progressive disease by PSA or imaging after docetaxel-based therapy. Progressive disease defined as one or more of the following: 1) three rising PSA levels with an interval  $\geq 1$  week between determinations. PSA at screening should be  $\geq 2$  ng/dL; 2) soft tissue disease progression defined by RECIST criteria; 3) Bone disease progression defined by 2 or more new lesions on bone scan
- No more than 2 prior chemotherapy regimens, with at least one regimen containing docetaxel
- ECOG Performance Status 0-2
- Life-expectancy of  $\geq 6$  months
- Able to swallow study drug and comply with study requirements.

### Exclusion

- Severe, concurrent disease, infection, or co-morbidity that would make patients inappropriate for enrollment
- Metastases in the brain or active epidural disease (patient with treated epidural disease allowed)
- ANC < 1500/microL, platelets < 100,000/microL, hemoglobin < 9 gm/dL at screening.
- Total bilirubin, alanine aminotransferase, or aspartate aminotransferase > 2 times the upper limit of normal at screening
- Creatinine > 2 mg/dL
- Albumin < 30 g/L
- History of other malignancy within the previous 5 years other than curatively treated non-melanomatous skin cancer
- Treatment with androgen receptor antagonists (bicalutamide, nilutamide, flutamide), 5- $\alpha$  reductase inhibitors (finasteride, dutasteride), estrogens, or chemotherapy within 4 weeks of enrollment.
- Treatment with therapeutic immunizations for prostate cancer (e.g. sipuleucel-T) or plans to initiate treatment.
- Use of herbal products that may decrease PSA (e.g. saw palmetto) or systemic corticosteroids greater than the equivalent of 10 mg of prednisone per day within 4 weeks of enrollment.
- History of prostate cancer progression on ketoconazole or plans to initiate ketoconazole during therapy
- Radiation therapy within 3 weeks and radionuclide therapy within 8 weeks of enrollment
- Planned palliative procedures for alleviation of bone pain
- Structurally unstable bone lesions suggesting impending fracture
- History of seizure, including febrile seizure, loss of consciousness, or transient ischemic attack within 12 months of enrollment, or any condition that may pre-dispose to seizure (e.g.

prior stroke, brain AV malformation, head trauma with loss of consciousness requiring hospitalization)

- Clinically significant cardiovascular disease including
  - Myocardial infarction within 6 months
  - Uncontrolled angina within 3 months
  - Congestive heart failure New York Heart Association (NYHA) Class 3 or 4 or patients with a history of congestive heart failure NYHA Class 3 or 3 in the past, unless a screening echocardiogram or multi-gated acquisition scan performed within 3 months results in a LVEF that is  $\geq 45\%$
  - Diagnosed or suspected congenital long QT Syndrome
  - History of clinically significant ventricular arrhythmias (e.g. ventricular tachycardia, ventricular fibrillation, torsade de pointes)
  - Prolonged corrected QT interval by Fridericia correction formula (QTcF) on screening ECK > 470 msec
  - History of Mobitz II second degree or third degree heart block without a permanent pacemaker
  - Hypotension (systolic blood pressure < 86 mm Hg or bradycardia with a heart rate < 50 beats per minute on any screening ECG)
  - Uncontrolled hypertension (resting systolic blood pressure >170 mmHG or diastolic blood pressure >105 mmHG) at screening
- Have used or plan to use from 30 days prior to enrollment through the end of the study the following medications which can lower seizure threshold or prolong the QT interval:
  - Aminophylline/theophylline
  - Atypical antipsychotics (e.g. clozapine, olanzapine, risperidone, ziprasidone)
  - Bupropion
  - Class IA and III antiarrhythmics (e.g. amiodarone, bretylium, disopyramide, ibutilide, procainamide, quinidine, sotalol)
  - Dolasetron
  - Droperidol
  - Gatafloxacin/moxifloxacin
  - Insulin
  - Lithium
  - Macrolide antibiotics (e.g. erythromycin, clarithromycin)
  - Pethidine
  - Phenothiazine antipsychotics (e.g. chlorpromazine, mesoridazine, thioridazine)
  - Pimozide
  - Tricyclic and tetracyclic antidepressants (e.g. amitriptyline, desipramine, doxepin, imipramine, maprotiline, mirtazapine)
  - Venlafaxine
- Gastrointestinal disorder affecting absorption (e.g. gastrectomy, active peptic ulcer within the last 3 months)
- Major surgery within 4 weeks of enrollment

**Table #2 Phase 3 Clinical Trial Results**

Outcome	Enzalutamide N=800	Placebo N=399
Overall Survival 95% CI	18.4 months 17.3- not yet reached	13.6 months 11.3-15.8
Hazard ratio for death 95%CI	0.63 0.53-0.75	- -
P value	<0.001	-
Time to PSA progression	8.3 months	3.0 months

95%CI	5.8-8.3	2.9-3.7
Hazard Ratio	0.25	-
95%CI	0.20-0.30	-
P value	<0.001	-
Radiographic PFS	8.3 months	2.9 months
95%CI	8.2-9.4	2.8-3.4
Hazard ratio	0.40	-
95%CI	0.35-0.47	-
P value	<0.001	-
Time to 1 <sup>st</sup> SRE	16.7 months	13.3 months
95%CI	14.6-19.1	9.9 to not yet reached
Hazard ratio	0.69	-
95%CI	0.57-0.84	-
P value	<0.001	-
FACT-P Quality of Life response	43%	18%
P value	<0.001	-
PSA Response		
Decline ≥50% from baseline	54%	2%
Decline ≥90% from baseline	25%	1%
P value	<0.001	-
Soft tissue objective response		
Patients with measurable disease-no. (%)	446 (56)	208 (52)
Complete or partial response	29%	4%

The subgroup analysis for overall survival showed all point estimates favoring the enzalutamide arm. The upper bound of the 95% confidence intervals crossed 1.0 in three smaller subgroups. The median duration of treatment was 8.3 months in the enzalutamide arm and 3.0 months on the placebo arm. At the interim analysis, the independent data and safety monitoring committee recommended stopping the trial, unblinding of the groups, and offering enzalutamide to eligible placebo patients. Subsequent therapy is seen in the table below.

**Table #3 Subsequent antineoplastic therapy**

Subsequent therapy	Enzalutamide	Placebo
Total	42%	61%
Abiraterone	21%	24%
Cabazitaxel	10%	14%
Docetaxel	9%	14%
Mitoxantrone	3%	11%

### Phase 1-2 trial

The primary objective was to assess pharmacokinetics, safety, and tolerability and to define a maximum tolerated dose. Secondary objectives were to assess antitumor effects.

Patients (N=140) had castration-resistant prostate cancer. The median age was 68 years old (range 44-93). The median time on study drug was 21 weeks. Waterfall plots of PSA decreases showed a fall that was dose dependent up to 150mg per day, but no obvious benefit above that dose. The most common adverse event was fatigue, requiring dose reductions at doses greater than or equal to 240mg per day. The most common mild (Grade 2) adverse events were fatigue, nausea, dyspnea, anorexia, and back pain. Two witnessed seizures occurred in patients receiving 600 mg and 360 mg per day, and one possible seizure at a dose of 480 mg per day. Patients with witnessed seizures were both on drugs that could lower seizure threshold and had complicated medical problems (including hypocalcemia requiring treatment, anemia requiring transfusion, and brain metastases). One patient discontinued due to a myocardial infarction after 15 weeks of therapy, but also had diabetes, hypertension, and hypercholesterolemia.

For further details on the efficacy results of the clinical trials, refer to *Appendix 2: Clinical Trials* (page 16).

### **Adverse Events (Safety Data)**

**Table #4 Adverse Reactions in trial**

Adverse Reaction	Enzalutamide N=800		Placebo N=399	
	Grade 1-4 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
General				
Asthenia	50.6	9.0	44.4	9.3
Peripheral Edema	15.4	1.0	13.3	0.8
Musculoskeletal/Connective Tissue				
Back pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal pain	15.0	1.3	11.5	0.3
Muscular weakness	9.8	1.5	6.8	1.8
Musculoskeletal stiffness	2.6	0.3	0.3	0.0
Gastrointestinal				
Diarrhea	21.8	1.1	17.5	0.3
Vascular				
Hot flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous system				
Headache	12.1	0.9	5.5	0.0
Dizziness	9.5	0.5	7.5	0.5
Spinal cord compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paresthesia	6.6	0.0	4.5	0.0
Mental impairment	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections				
Upper respiratory tract infection	10.9	0.0	6.5	0.3
Lower respiratory tract infection	8.5	2.4	4.8	1.3
Psychiatric				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal and Urinary				
Hematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury				
Fall	4.6	0.3	1.3	0.0
Non-pathologic fractures	4.0	1.4	0.8	0.3
Skin				
Pruritus	3.8	0.0	1.3	0.0
Dry skin	3.5	0.0	1.3	0.0
Respiratory				
Epistaxis	3.3	0.1	1.3	0.3

### **Deaths and Other Serious Adverse Events**

Deaths: Deaths occurred in 50% of the enzalutamide patients and in 62% of the placebo patients. Deaths due to reasons other than progression of disease occurred in 6.3% of enzalutamide

patients and 6.1% of placebo patients. Adverse Events leading to death occurred in 3.3% of enzalutamide patients and in 3.8% of placebo patients.

Non-fatal Serious Adverse Events (SAE): SAEs occurred in 34.9% of enzalutamide patients and 37.3% of placebo patients. Spinal cord compression and pathologic fractures were more common in the enzalutamide group despite an improvement in the time to development of a skeletal related event compared to the placebo group.

### **Common Adverse Events**

The most common adverse events were: asthenia/fatigue, back pain, diarrhea, arthralgia, hot flush, peripheral edema, musculoskeletal pain, headache, upper respiratory infection, muscular weakness, dizziness, insomnia, lower respiratory infections, spinal cord compression and cauda equina syndrome, hematuria, paresthesia, anxiety, and hypertension.

### **Other Adverse Events**

#### Laboratory Abnormalities

Grade 1-4 neutropenia: 15% enzalutamide vs 6% placebo

Grade 1-4 thrombocytopenia: 0.5% enzalutamide vs 1.0% placebo

Grade 1-4 elevations in ALT: 10% enzalutamide vs 18% placebo

Grade 1-4 elevations in bilirubin: 3% of enzalutamide vs 2% placebo

#### Infections

In the phase III trial, 1.0% of patients in the enzalutamide arm died from infections or sepsis versus 0.3% in the placebo arm.

#### Hallucinations

In the phase III trial 1.6% of patients in the enzalutamide arm reported Grade 1 or 2 hallucinations versus 0.3% in the placebo arm. The majority of patients reporting hallucinations were also on opioids. Hallucinations were visual, tactile, or undefined.

### **Tolerability**

Adverse events leading to discontinuation of therapy was reported in 7.6% of enzalutamide patients and 9.8% of placebo patients in the clinical trial. Adverse events leading to discontinuation in the enzalutamide group (in descending order of incidence): seizure (see Warnings and Precautions), fatigue, thrombocytopenia, colonic obstruction, diarrhea, and rash.

For further details on the safety results of the clinical trials, refer to *Appendix 2: Clinical Trials* (page 16).

### **Contraindications**

Pregnancy

### **Warnings and Precautions**

#### **Seizure**

In the phase III randomized trial, 7 patients (0.9%) of patients treated with 160 mg of enzalutamide experienced a seizure. Seizures occurred anywhere between 31 to 603 days after starting therapy with enzalutamide. All seizures resolved after permanent discontinuation of therapy. There is no clinical trial data for the readministration of enzalutamide to patients who experienced a seizure.



There is no data on the safety of enzalutamide in patients with predisposing factors to seizures as these patients were excluded from this clinical trial. Because of the risk for seizures, patients taking enzalutamide should be advised of the risk of participating in activities where sudden loss of consciousness could cause harm to themselves or others.

The proposed mechanism of seizures during enzalutamide therapy is off target effect mediated via inhibition of GABA (gamma aminobutyric acid) gated chloride channels. Animal studies suggest that the amount of inhibition is dependent on the concentrations of enzalutamide and its active metabolite in the brain. Early animal studies and the phase I dose escalation study in humans identified seizure as a potential dose-dependent adverse reaction.

## **Special Populations**

### **Pregnancy Category X**

Based on its mechanism of action, enzalutamide can cause fetal harm if administered to a pregnant female. There are no human or animal studies on use during pregnancy and it is not indicated for use in women. If used during pregnancy or if the patient becomes pregnant while taking the drug, advise the patient of the potential hazard to the fetus and risk for pregnancy loss. Advise females of reproductive age to avoid becoming pregnant during therapy with enzalutamide.

### **Nursing Mothers**

Enzalutamide is not indicated in women. It is not known if it is excreted in human breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made to either discontinue nursing or discontinue the drug therapy based on the importance of the drug to the mother.

### **Pediatric Use**

Safety and efficacy in pediatric patients has not been established.

### **Geriatric Use**

Seventy-one percent of the patients in the phase III clinical trial were 65 years old or older, and 25% were 75 and over. No overall differences in safety and efficacy were seen between these patients and younger patients. Other clinical experience with enzalutamide has not identified differences in response based on age, but greater sensitivity in some older patients cannot be ruled out.

### **Renal Impairment**

A clinical trial focused on renal impairment and enzalutamide has not been conducted. Based on population pharmacokinetics data from patients with metastatic castration-resistant prostate cancer and healthy volunteers, no significant difference in clearance was observed in patients with pre-existing mild to moderate renal impairment (creatinine clearance  $\geq 30$  mL/min and  $\leq 89$  mL/min) compared to patients and volunteers with normal renal function (creatinine clearance  $\geq 90$  mL/min). No initial dosage adjustment is needed for patients with mild to moderate renal impairment. Use in severe renal impairment (creatinine clearance  $< 30$  mL/min) and end-stage renal disease has not been assessed.

### **Hepatic Impairment**

A clinical trial focused on hepatic impairment compared systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild or moderate hepatic impairment

(Child-Pugh Class A and B, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild to moderate hepatic impairment compared to those with normal hepatic function. No initial dosage adjustment is needed for patients with baseline mild or moderate hepatic impairment. Use in severe hepatic impairment (Child-Pugh Class C) has not been assessed.

### **Sentinel Events**

No data

### **Look-alike / Sound-alike (LA / SA) Error Risk Potential**

As part of a JCAHO standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

LA/SA for generic name enzalutamide: bicalutamide, nilutamide, flutamide, encallantide, enfuvirtide, exenatide

LA/SA for trade name: Xtandi: Jevtana, Xgeva, Zometa, Zytiga, Exjade

### **Drug Interactions**

#### **Drug-Drug Interactions**

##### **Drugs that Inhibit or Induce CYP2C8**

Co-administration with a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide and N-desmethyl enzalutamide in healthy volunteers. Co-administration of enzalutamide with a strong CYP2C8 inhibitor should be avoided if possible. If co-administration cannot be avoided, reduce the dose of enzalutamide.

The effect of CYP2C8 inducers on enzalutamide pharmacokinetics has not been evaluated *in vivo*. Co-administration of enzalutamide and strong or moderate CYP2C8 inducers (e.g. rifampin) may change the plasma exposure of enzalutamide and should be avoided if possible. Selection of a concomitant drug with no or minimal CYP2C8 induction potential is recommended.

##### **Drugs that Inhibit or Induce CYP3A4**

Co-administration of a strong CYP3A4 inhibitor (itraconazole) increased the composite AUC of enzalutamide and N-desmethyl enzalutamide by 1.3 fold in volunteers.

The effect of CYP3A4 strong inducers on enzalutamide pharmacokinetics has not been evaluated *in vivo*. Co-administration of enzalutamide with strong CYP3A4 inducers (e.g. carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentin) may decrease the AUC of enzalutamide and should be avoided if possible. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) and St. John's Wort may also decrease the AUC of enzalutamide and should be avoided if possible.

##### **Effect of enzalutamide on Drug Metabolizing Enzymes**

In humans, enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. At steady state, enzalutamide reduced the plasma exposure of midazolam (CYP3A4

substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of enzalutamide with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, and tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), and CYP2C19 (e.g. S-mephenytoin) should be avoided as enzalutamide may decrease their plasma exposure. If co-administration with warfarin cannot be avoided, additional INR monitoring is required.

### **Acquisition Costs**

Please refer to the last page for VA drug acquisition costs. Prices shown in this internal, draft document may include additional discounts available to VA. This information is considered strictly confidential and must not be shared outside of VA. All cost information will be removed from the document when posted to the PBM website.

### **Pharmacoeconomic Analysis**

No published data.

### **Conclusions**

#### Clinical Efficacy

In a randomized, double-blinded, phase 3 clinical trial comparing enzalutamide, a second generation androgen receptor inhibitor, with placebo in men with metastatic castration-resistant prostate cancer who had progressed following chemotherapy containing docetaxel, enzalutamide prolonged overall survival by 4.8 months which is statistically and clinically significant. Subgroup analysis for survival was consistent and point estimates favored enzalutamide. Secondary outcomes such as Time to Progression, radiograph Progression Free Survival, Time to 1<sup>st</sup> skeletal related event, and improvement in quality of life were consistent and all favored the enzalutamide arm, supporting the findings for overall survival. What is unknown is the activity in patients who are chemotherapy naïve, although a trial in that setting has completed enrollment and results will be available by 2014, and the effectiveness of enzalutamide when given after abiraterone, although they are theoretically not cross-resistant based on their mechanism of action. Also, we don't currently have a biomarker to help guide who in the selection of patients likely to or not likely to respond to enzalutamide based on androgen receptor signaling.

#### Clinical Safety

In the phase 3 clinical trial, Grade 3 or higher adverse reactions were reported in 47% of enzalutamide patients and in 53% of placebo patients. No one Grade 3 adverse reaction was reported in more than 9% of enzalutamide patients. Discontinuation of therapy due to Grade 3 or higher adverse reactions occurred in 8% of enzalutamide patients and in 10% of placebo patients. The most common Grade 3-4 adverse event was fatigue. No significant QTc prolongation was seen at doses of 160 mg per day.

Seizures occurred in 7 out of 800 enzalutamide patients. The mechanism is unknown, but thought to be due to off target inhibition of GABA gated chloride channel as enzalutamide and its active metabolite cross the blood brain barrier. Earlier trials identified seizures as a possible dose-dependent adverse reaction. The FDA review found that in 6 of seven patients experiencing seizures there were other factors (medications, brain metastases) that may have lowered the

seizure threshold. Despite the exclusion criteria, there were approximately 18 patients with factors that predisposed them to seizures (prior stroke, history of head trauma, history of intracranial bleed, and prior seizure); none of these patients experienced a seizure during therapy. There is no data on the safety of retreatment with enzalutamide once a patient experiences a seizure.

**Conclusion:**

Enzalutamide is a second generation androgen receptor inhibitor with clinically significant clinical activity in patients with metastatic castration-resistant prostate cancer following docetaxel based chemotherapy. While 47% of patients experienced a Grade 3 or 4 adverse reactions, no one event accounted for more than 9%. Patients with a history of seizures or predisposed to seizures should not receive enzalutamide at this time.

<b>Outcome in clinically significant area</b>	Overall Survival: 18.4 months versus 13.6 months
<b>Effect Size</b>	HR 0.63 (95%CI 0.53-0.75)
<b>Potential Harms</b>	No grade 3 or 4 Adverse Event in more than 9% of patients Grade 3 or 4 Adverse Event in 47%
<b>Net Clinical Benefit</b>	Moderate (high benefit with high risk)

Definitions

**Outcome in clinically significant area:** morbidity, mortality, symptom relief, emotional/physical functioning, or health-related quality of life

**Effect Size:** odds ratio, relative risk, NNT, absolute risk reduction, relative risk reduction, difference in size of outcomes between groups, hazard ratio

**Potential Harms:** Low risk (Grade 3 or 4 toxicity in <20%) versus High risk (Grade 3 or 4 toxicity in ≥20%)

**Net Clinical Benefit:** Substantial (high benefit with low risk of harm), moderate (high benefit with high risk of harm), minimal (low benefit with low risk of harm), negative (low benefit with high risk of harm)

## **References**

- 
- <sup>1</sup> Kohli M, Qin R, Jiminez R, Dehm SM. Biomarker-based targeting of the androgen-androgen receptor axis in advanced prostate cancer. *Advances in Urology* 2012;2012:ID781459.
  - <sup>2</sup> Rathkopf D, Scher HI. Androgen receptor antagonists in castration-resistant prostate cancer. *The Cancer Journal* 2013;19:43-49.
  - <sup>3</sup> Chen CD, Welsbie DS, Tran C, Baek SH, Chen R, et al. Molecular determinants of resistance to antiandrogen therapy. *Nature Medicine* 2004;10:33-39.
  - <sup>4</sup> Culig Z, Hoffman J, Erdel M, Eder IE, Hobisch A, et al. Switch from antagonist to agonist of the androgen receptor blocker bicalutamide is associated with prostate tumor progression in a new model system. *Br J Canc* 1999;81:242-251.
  - <sup>5</sup> Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, et al. Development of a second-generation antiandrogen for the treatment of advanced prostate cancer. *Science* 2009;324:787-790.
  - <sup>6</sup> Xtandi (enzalutamide) product package insert; Astellas pharma US, Inc, Northbrook, IL and Medivation Inc., San Francisco, CA. August 2012.
  - <sup>7</sup> Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 367:1187-97.
  - <sup>8</sup> Scher HI, Beer TM, Higano C, Anand A, Taplin M-E, et al. Antitumor activity of MDV3100 in castration-resistant prostate cancer; a phase 1-2 study. *Lancet* 2010;375:1437-46.

**\*Note: Please point out information through the review that is especially significant in defining usage, safety, and application to VA patients.**

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**Prepared January 2013 Contact person: Mark C. Geraci, Pharm.D., BCOP**

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## Appendix 1: Approval Endpoints

**Table 1. A Comparison of Important Cancer Approval Endpoints**

Endpoint	Regulatory Evidence	Study Design	Advantages	Disadvantages
Overall Survival	Clinical benefit for regular approval	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding not essential</li> </ul>	<ul style="list-style-type: none"> <li>• Universally accepted direct measure of benefit</li> <li>• Easily measured</li> <li>• Precisely measured</li> </ul>	<ul style="list-style-type: none"> <li>• May involve larger studies</li> <li>• May be affected by crossover therapy and sequential therapy</li> <li>• Includes noncancer deaths</li> </ul>
Symptom Endpoints (patient-reported outcomes)	Clinical benefit for regular approval	<ul style="list-style-type: none"> <li>• Randomized blinded studies</li> </ul>	<ul style="list-style-type: none"> <li>• Patient perspective of direct clinical benefit</li> </ul>	<ul style="list-style-type: none"> <li>• Blinding is often difficult</li> <li>• Data are frequently missing or incomplete</li> <li>• Clinical significance of small changes is unknown</li> <li>• Multiple analyses</li> <li>• Lack of validated instruments</li> </ul>
Disease-Free Survival	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding preferred</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller sample size and shorter follow-up necessary compared with survival studies</li> </ul>	<ul style="list-style-type: none"> <li>• Not statistically validated as surrogate for survival in all settings</li> <li>• Not precisely measured; subject to assessment bias, particularly in open-label studies</li> <li>• Definitions vary among studies</li> </ul>
Objective Response Rate	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Can be assessed in single-arm studies</li> <li>• Assessed earlier and in smaller studies compared with survival studies</li> <li>• Effect attributable to drug, not natural history</li> </ul>	<ul style="list-style-type: none"> <li>• Not a direct measure of benefit in all cases</li> <li>• Not a comprehensive measure of drug activity</li> <li>• Only a subset of patients with benefit</li> </ul>
Complete Response	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Single-arm or randomized studies can be used</li> <li>• Blinding preferred in comparative studies</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Can be assessed in single-arm studies</li> <li>• Durable complete responses can represent clinical benefit</li> <li>• Assessed earlier and in smaller studies compared with survival studies</li> </ul>	<ul style="list-style-type: none"> <li>• Not a direct measure of benefit in all cases</li> <li>• Not a comprehensive measure of drug activity</li> <li>• Small subset of patients with benefit</li> </ul>
Progression-Free Survival (includes all deaths) or Time to Progression (deaths before progression censored)	Surrogate for accelerated approval or regular approval*	<ul style="list-style-type: none"> <li>• Randomized studies essential</li> <li>• Blinding preferred</li> <li>• Blinded review recommended</li> </ul>	<ul style="list-style-type: none"> <li>• Smaller sample size and shorter follow-up necessary compared with survival studies</li> <li>• Measurement of stable disease included</li> <li>• Not affected by crossover or subsequent therapies</li> <li>• Generally based on objective and quantitative assessment</li> </ul>	<ul style="list-style-type: none"> <li>• Not statistically validated as surrogate for survival in all settings</li> <li>• Not precisely measured; subject to assessment bias particularly in open-label studies</li> <li>• Definitions vary among studies</li> <li>• Frequent radiological or other assessments</li> <li>• Involves balanced timing of assessments among treatment arms</li> </ul>

\*Adequacy as a surrogate endpoint for accelerated approval or regular approval is highly dependent upon other factors such as effect size, effect duration, and benefits of other available therapy. See text for details.

**Guidance for Industry: Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.** U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), May 2007.

## **Appendix 2: Clinical Trials**

A literature search was performed on PubMed/Medline (1966 to January 2013) using the search terms enzalutamide and the Clinical Queries Therapy/Broad filter. The search was limited to studies performed in humans and published in English language. Reference lists of review articles and the manufacturer's AMCP dossier were searched for relevant clinical trials. All randomized controlled trials published in peer-reviewed journals were included.



**Enzalutamide Clinical Trials**

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results																																																																																													
<p>Scher et al. AFFIRM International, phase III, randomized, double-blind, placebo-controlled ITT analysis N=1199</p> <p>Support: Medivation and Astellas Pharma Global Development</p>	<p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>Histologically or cytologically confirmed prostate cancer (no small cell features)</li> <li>Castrate levels of testosterone (&lt; 50 ng/mL)</li> <li>No more than 2 previous chemotherapy treatments, one containing docetaxel</li> <li>Progressive disease defined by PCWG2 criteria including 3 increased values for PSA or soft tissue progression by RECIST criteria or bone disease progression defined by 2 or more new lesions on scan</li> <li>ECOG PS 0-2</li> <li>Not more than 2 previous chemotherapy regimens with at least 1 containing docetaxel</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Severe, concurrent disease, infection or co-morbidity</li> <li>Metastases in the brain or active epidural disease (pts with treated epidural disease allowed)</li> </ul>	<p>Rx1 Enzalutamide Orally 160 mg once daily as four 40 mg capsules</p> <p>Rx2 Placebo Orally Four capsules once daily</p> <p>Prednisone or glucocorticoids was permitted but not required.</p> <p>Therapy continued until radiographic evidence of disease progression requiring initiation of new antineoplastic therapy.</p>	<p>Age Median 69 % ≥ 75 years old: 25</p> <p>Median Yrs since diagnosis: 5.9</p> <p>ECOG PS: 0 or 1: 91.3% 2: 8.8%</p> <p>No. of prior chemo regimens: 1: 72.4% 2: 24.5% ≥3: 3.1%</p> <p>Prior docetaxel cycles (med): 8.5</p> <p>Baseline bisphosphonate use: Any: 43.1% Zoledronic acid: 37.9%</p> <p>Baseline testosterone: ≤35 ng/dL: 98.2% &gt;35 and &lt;50 ng/dL: 1.8%</p> <p>Baseline PSA: Median: 107.7 Range: 0.2 – 11794.1</p> <p>Extent of disease at baseline Bone: 92.2% &gt;20 lesions: 37.8% Soft tissue: 70.9% Lymph node: 55.8% Visceral liver: 11.6% Visceral lung: 15.3% Other: 18.6%</p>	<table border="1"> <thead> <tr> <th data-bbox="1312 492 1562 548">Outcome</th> <th data-bbox="1562 492 1766 548">Enzalutamide N = 800</th> <th data-bbox="1766 492 1927 548">Placebo N = 399</th> </tr> </thead> <tbody> <tr> <td data-bbox="1312 548 1562 597">Med OS- mos</td> <td data-bbox="1562 548 1766 597">18.4</td> <td data-bbox="1766 548 1927 597">13.6</td> </tr> <tr> <td data-bbox="1312 597 1562 646">95%CI</td> <td data-bbox="1562 597 1766 646">17.3 to not reached</td> <td data-bbox="1766 597 1927 646">11.3-15.8</td> </tr> <tr> <td data-bbox="1312 646 1562 695">Hazard ratio</td> <td data-bbox="1562 646 1766 695">0.63</td> <td data-bbox="1766 646 1927 695">-</td> </tr> <tr> <td data-bbox="1312 695 1562 743">95%CI</td> <td data-bbox="1562 695 1766 743">0.53-0.75</td> <td data-bbox="1766 695 1927 743">-</td> </tr> <tr> <td data-bbox="1312 743 1562 792">PSA response- %</td> <td data-bbox="1562 743 1766 792"></td> <td data-bbox="1766 743 1927 792"></td> </tr> <tr> <td data-bbox="1312 792 1562 841">≥50% from baseline</td> <td 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1117">95%CI</td> <td data-bbox="1562 1068 1766 1117">5.8-8.3</td> <td data-bbox="1766 1068 1927 1117">2.9-3.7</td> </tr> <tr> <td data-bbox="1312 1117 1562 1166">Hazard ratio</td> <td data-bbox="1562 1117 1766 1166">0.25</td> <td data-bbox="1766 1117 1927 1166"></td> </tr> <tr> <td data-bbox="1312 1166 1562 1214">95%CI</td> <td data-bbox="1562 1166 1766 1214">0.2-0.3</td> <td data-bbox="1766 1166 1927 1214"></td> </tr> <tr> <td data-bbox="1312 1214 1562 1263">P value</td> <td data-bbox="1562 1214 1766 1263">&lt;0.001</td> <td data-bbox="1766 1214 1927 1263"></td> </tr> <tr> <td data-bbox="1312 1149 1562 1198">Radiographic PFS mos</td> <td data-bbox="1562 1149 1766 1198">8.3</td> <td data-bbox="1766 1149 1927 1198">2.9</td> </tr> <tr> <td data-bbox="1312 1198 1562 1247">95%CI</td> <td data-bbox="1562 1198 1766 1247">8.2-9.4</td> <td data-bbox="1766 1198 1927 1247">2.8-3.4</td> </tr> <tr> <td data-bbox="1312 1247 1562 1295">Hazard ratio</td> <td data-bbox="1562 1247 1766 1295">0.4</td> 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	<ul style="list-style-type: none"> <li>• ANC&gt;1500, platelets &lt; 100K, Hgb &lt;9</li> <li>• T. bili, ALT, or AST &gt;2 times the upper limit of normal</li> <li>• Creatinine &gt; 2 mg/dL</li> <li>• Albumin &lt; 3.0 g/dL</li> <li>• Treatment with androgen receptor antagonist, 5-<math>\alpha</math> reductase inhibitors, estrogens, or chemotherapy within 4 weeks of enrollment</li> <li>• Treatment with sipuleucel-T or plans for treatment with sipuleucel-T or other therapeutic immunizations for prostate cancer</li> <li>• Herbal products that decrease PSA or systemic corticosteroids &gt; then equivalent of 10 mg of prednisone per day within 4 weeks of treatment</li> <li>• History of prostate cancer progression on ketoconazole</li> <li>• Planned palliative procedures to relieve bone pain</li> <li>• Structurally unstable bone lesions suggesting impending fracture</li> <li>• History of seizure,</li> </ul>		<p>Type of progression at baseline                      PSA only: 41%                      Radiographic: 59%                      Bone only: 25.6%                      Soft tissue only: 15.9%</p> <p><u>Subsequent chemotherapy</u></p> <table border="1" data-bbox="898 581 1289 743"> <thead> <tr> <th>Tx</th> <th>Enzalutamide</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Total</td> <td>42%</td> <td>61%</td> </tr> <tr> <td>Abiraterone</td> <td>21%</td> <td>24%</td> </tr> <tr> <td>Cabazitaxel</td> <td>10%</td> <td>14%</td> </tr> <tr> <td>Docetaxel</td> <td>9%</td> <td>14%</td> </tr> <tr> <td>Mitoxantrone</td> <td>3%</td> <td>11%</td> </tr> </tbody> </table>	Tx	Enzalutamide	Placebo	Total	42%	61%	Abiraterone	21%	24%	Cabazitaxel	10%	14%	Docetaxel	9%	14%	Mitoxantrone	3%	11%	<table border="1"> <tr> <td>95%CI</td> <td>0.57-0.84</td> </tr> <tr> <td>P value</td> <td>&lt;0.001</td> </tr> </table>	95%CI	0.57-0.84	P value	<0.001	<p>Median time on treatment: 8.3 months Enzalutamide                      3.0 months placebo</p>	<p>Median duration of follow-up: 14.4 months</p>
Tx	Enzalutamide	Placebo																										
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	<p>including febrile seizure, loss of consciousness or TIA within 12 months or any condition pre-disposing to seizure (prior stroke, brain AV malformation, head trauma with loss of consciousness requiring hospitalization)</p> <ul style="list-style-type: none"> <li>• Clinically significant heart disease (MI within 6 months, uncontrolled angina within 3 months, CHF NYHA class 3 or 4 or history of CHF NYHA class 3 or 4 unless screening echocardiogram or MUGA performed within 3 months with LVEF <math>\geq</math>45%)</li> <li>• Diagnosed/suspected long QT syndrome</li> <li>• History of clinical significant ventricular arrhythmias</li> <li>• Prolonged corrected QT interval by Fridericia correction formula (QTcF) on screening ECG <math>&gt;</math>470 msec</li> <li>• History of Mobitz II second degree heart block without a permanent pacemaker</li> <li>• Hypotension (systolic blood pressure <math>&lt;</math> 86</li> </ul>			

Citation Design Analysis type N Setting Funding source	Eligibility Criteria	Interventions/Endpoints	Patient Population Profile	Efficacy Results
	mmHg or bradycardia with heart rate < 50 beats per minute on ECG <ul style="list-style-type: none"> <li>• Uncontrolled hypertension (resting systolic pressure &gt;170 mmHg or diastolic pressure &gt;105 mmHg)</li> <li>• Have used or plan to use medications known to lower seizure threshold or prolong QTc</li> <li>• Gastrointestinal disorder affecting absorption (gastrectomy, active peptic ulcer within last 3 months)</li> <li>• Major surgery within 4 weeks of enrollment</li> </ul>			

ITT=Intention to Treat; PCWG2=Prostate Cancer Working Group; PSA=prostate-specific antigen; RECIST=Response Evaluation Criteria in Solid Tumors; ECOG PS=Eastern Cooperative Oncology Group Performance Status; CHF=congestive heart failure; NYHA=New York Heart Association; ANC=absolute neutrophil count; Hgb=hemoglobin; ALT=alanine aminotransferase; ALT=aspartate aminotransferase; TIA=transient ischemic attack; MUGA=multi-gated acquisition scan; LVEF=left ventricular ejection fraction ;ECG=electrocardiogram; OS=overall survival; CR=complete response; PR=partial response; FACT-P=Functional Assessment of Cancer Therapy-Prostate; QoL=quality of life; SRE=skeletal related event; NYR=not yet reached