

**Abiraterone (Zytiga)****Criteria for Use****Updated September 2014**

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. 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 EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA 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 abiraterone.*

- Baseline severe hepatic impairment defined as one of the following:
  - Baseline total bilirubin  $\geq$  1.5 times the upper limit of normal (except in documented Gilbert's disease)
  - AST or ALT  $\geq$  2.5 times the upper limit of normal (AST or ALT  $\leq$  5 times the upper limit of normal allowed in patients with known liver metastases)
  - Child-Pugh Class C\*
- Uncontrolled hypertension
- History of pituitary or adrenal dysfunction
- Clinically significant heart disease: myocardial infarction or arterial thrombotic event in the past 6 months, or severe or unstable angina or New York Heart Association Class III or IV heart failure or cardiac ejection fraction of  $<$ 50% at baseline.
- Inability or refusal or contraindication to taking prednisone
- History of non-compliance with oral medications or inability to swallow oral medications
- Refuses to transfer oncology care to VA oncologist or designated expert in urologic oncology

**Inclusion 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):
  - who progressed on or after docetaxel-based therapy
  - 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
  - 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 cytotoxic 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 abiraterone and for 1 week after stopping abiraterone therapy
  - For men whose sexual partner may become pregnant
    - Use of a condom plus another form of birth control is required during therapy with abiraterone and for 1 week after stopping abiraterone therapy

**Dosage and Administration**

The recommended dose of abiraterone is 1000 mg orally (4 X 250mg tablets) once daily in combination with prednisone 5 mg orally twice a day. Abiraterone must be taken on an empty stomach, at least one hour before or at least 2 hours after a meal. The tablets should be swallowed whole.

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## Dose Modifications

### Hepatic Impairment at baseline

In patients with baseline moderate hepatic impairment (Child-Pugh score B) reduce abiraterone dose to 250mg once daily. In patients with moderate hepatic impairment at baseline, measure AST, ALT, and bilirubin prior to starting therapy, every week for the first month, then every 2 weeks for the following 2 months, then monthly. If AST or ALT is elevated more than 5 times the upper limit of normal or total bilirubin is elevated more than 3 times the upper limit of normal in patients with baseline moderate hepatic impairment, discontinue abiraterone and do not re-treat.

### Hepatotoxicity during therapy

In patients who develop hepatotoxicity during treatment (AST and/or ALT elevations greater than 5 times the upper limit of normal or total bilirubin greater than 3 times the upper limit of normal), abiraterone therapy should be interrupted. Treatment may be restarted at 750 mg daily after the return of liver function tests to patient's baseline or to AST and ALT less than or equal to 2.5 times the upper limit of normal and total bilirubin less than or equal to 1.5 time the upper limit of normal. If restarted, monitor transaminases and bilirubin every 2 weeks for 3 months and monthly thereafter.

If hepatotoxicity recurs at the 750 mg dose, retreatment may be restarted at 500 mg daily following return of liver function tests to patient's baseline or to AST and ALT less than or equal to 2.5 times the upper limit of normal and total bilirubin less than or equal to 1.5 time the upper limit of normal.

If hepatotoxicity recurs at the 500 mg dose, discontinue abiraterone treatment.

## Monitoring

### Hepatic function

- AST, ALT, and total bilirubin at baseline, then every 2 weeks for the first three months, then monthly
- In patients with baseline hepatic impairment AST, ALT, and total bilirubin at baseline and weekly for the first month, every 2 weeks for 2 months, then monthly

### Hypokalemia, hypertension, and fluid retention due to mineralocorticoid excess

- Potassium, blood pressure, and signs of fluid retention monthly; control hypertension and correct potassium prior to starting therapy

### Adrenal insufficiency

- Monitor for signs and symptoms of adrenal insufficiency, especially in patients who stop prednisone, have a decrease in prednisone dose, or are under stress

### Response Evaluation

- PSA at 4 weeks: If <50% of baseline value, then measure every 3 months. If PSA not at least 50% of baseline value, then continue monthly PSAs
- Radiographic assessment of tumor size/burden every 3 months if patient has measurable disease

## Issues for Consideration

- Abiraterone must be taken on an empty stomach at least 2 hours after a meal; no food should be consumed for at least 1 hour after each dose. Following a single dose given with a meal compared to a fasted state, the C<sub>max</sub> and AUC were increased 17- and 10-fold higher, respectively.
- Strong inhibitors or inducers of CYP3A4 should be avoided or used with caution as abiraterone is a substrate for CYP3A4
- There is a potential for drug interactions with drugs that are substrates for CYP2D6 as abiraterone is a CYP2D6 inhibitor.

### For women of childbearing potential

- pregnancy must be excluded prior to receiving abiraterone and patient provided contraceptive counseling on potential risk vs. benefit of taking abiraterone if patient were to become pregnant

## 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 abiraterone 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

### \*Child-Pugh classification of severity of cirrhosis

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin	<2 mg/dL (<34.2 micromol/liter)	2-3 mg/dL (34.2 to 51.3 micromol/liter)	>3 mg/dL (>51.3 micromol/liter)
Albumin	>3.5 g/dL (35 g/liter)	2.8-3.5 g/dL (28 to 35 g/liter)	<2.8 g/dL (<28 g/liter)
Prothrombin time			
Seconds over control	<4	4-6	>6
INR	<1.7	1.7-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4

Modified Child-Pugh classification of the severity of liver disease according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy.

A total score of 5-6 is considered grade A (well-compensated disease); 7-9 is grade B (significant functional compromise); and 10-15 is grade C (decompensated disease).

#### References for Child-Pugh:

1. Pugh RN, Murray-Lyon IM, Dawson JL, et. al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg.* 1973; 60:646.
2. Child CG, Turcotte JG. The Liver and Portal Hypertension. *Philadelphia, WB Saunders Co.* 1964.
3. Trey C, Burns DG, Saunders SJ. Treatment of hepatic coma by exchange blood transfusion. *NEJM.* 1966; 274:473.

#### †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

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