

# Abiraterone (Zytiga), a Novel Agent for the Management of Castration-Resistant Prostate Cancer



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## INTRODUCTION

Prostate cancer is the second most common cancer diagnosed in men living in the U.S. The disease was expected to account for more than 28,000 deaths in 2012,<sup>1</sup> and more than 241,700 new cases were expected to be diagnosed that year.<sup>2</sup> Prostate cancer usually affects men after the age of 40. Besides age, other risk factors include ethnicity, dietary practices, and genetic predisposition.<sup>3</sup> The highest incidence is seen in African-American patients, followed by Caucasian and Hispanic patients, respectively (Table 1).<sup>4</sup>

Prostate cancer is highly dependent on androgen levels. The testes secrete 95% of testosterone, and the remaining 5% is produced by the adrenal glands.<sup>5</sup> The diagnosis is made by prostate-specific antigen (PSA) screening, a digital rectal examination, and genitourinary symptoms. A small percentage of men may present with symptoms of metastatic disease such as bone pain. PSA is a marker that is specific to the prostate.

PSA levels may also be elevated in benign conditions such as benign prostatic hyperplasia (BPH). Cancerous tissue produces more PSA, thus making it a good diagnostic and prognostic biomarker.

After an initial elevation in PSA levels, a biopsy is recommended to confirm the diagnosis. As a result of the

implementation of PSA screening in the U.S., almost 90% of cases are diagnosed at an early stage; however, up to 40% of men will develop metastasis.<sup>6</sup> For most patients with metastasis, progression of the disease occurs despite treatment.<sup>6</sup>

The tumor-node-metastasis (TNM) staging system guides clinicians with initial therapy. Androgen-deprivation therapy (ADT) remains the mainstay of treatment.<sup>7</sup> In metastatic disease, ADT is used alone or in combination with radiation therapy.<sup>8</sup>

Castration-resistant prostate cancer (CRPC) may develop regardless of surgical or pharmacological castration therapies.<sup>8,9</sup> CRPC is currently managed with cytotoxic chemotherapy, with docetaxel (Taxotere, Sanofi) remaining as the therapy of choice.<sup>10,11</sup> Mitoxantrone (Novantrone, Sero/O/SI) is an option for men who are not candidates for docetaxel-based regimens.<sup>10</sup>

Abiraterone acetate (Zytiga, Janssen Biotech) is a new cytochrome P450 (CYP) 17 inhibitor that was approved by the FDA in 2011 in combination with prednisone for CRPC in patients who have received prior docetaxel chemotherapy. It is also being studied in patients with earlier-stage prostate cancer and in women with metastatic breast cancer.<sup>12</sup>

In December 2012, Janssen received the FDA's approval to market abiraterone preceding chemotherapy in men with CRPC.<sup>13</sup>

## CLINICAL PHARMACOLOGY

Abiraterone acetate is converted to abiraterone *in vivo*. Abiraterone inhibits 17 $\alpha$ -hydroxylase CYP17, which is required for androgen biosynthesis and is expressed in testicular, adrenal, and prostatic tumor tissues. CYP17 serves as a catalyst for the conversion of pregnenolone and progesterone to their 17 $\alpha$ -hydroxy derivatives and the formation of dehydroepiandrosterone (DHEA) and androstenedione. DHEA and androstenedione are precursors of testosterone. Inhibition of CYP17 at the sites outside of the testes provides advantages over traditional ADT.<sup>14</sup>

The administration of abiraterone may potentiate mineralocorticoid production by the adrenal glands via inhibition of CYP17. Increased mineralocorticoid synthesis occurs as a result of enhanced deoxycorticosterone conversion from pregnenolone. This may potentially lead to fluid retention, hypertension, and hypokalemia.<sup>15</sup>

## Pharmacokinetics

The pharmacokinetic properties of abiraterone acetate have been studied in healthy subjects and in patients with CRPC.<sup>16,17</sup> In plasma, abiraterone acetate is converted to abiraterone (the active metabolite) via hydrolysis.<sup>16,17</sup> Abiraterone is then transformed into two inactive metabolites—abiraterone sulfate and *N*-oxide abiraterone sulfate.

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**Table 1 Diagnosis of Prostate Cancer by Race**

Race/Ethnicity	Incidence per 100,000 Men (%)
All races	154.8
Caucasian	146.9
African-American	236.0
Asian/Pacific Islander	85.4
American Indian/Alaskan Native	78.4
Hispanic	125.9
Data from the National Cancer Institute. <sup>4</sup>	

In dose-ranging studies, the median time to reach maximum plasma concentrations ( $C_{max}$ ) of abiraterone was 2 hours. The  $C_{max}$  after a 1,000-mg daily dose were  $226 \pm 178$  ng/mL at steady state, with resulting area-under-the-curve (AUC) concentrations of  $1,173 \pm 690$  ng • hour/mL.<sup>16,17</sup> The volume of distribution was  $19,669$  (mean)  $\pm 13,358$  L (standard deviation). Abiraterone was found to be more than 99% bound to albumin and  $\alpha_1$ -acid glycoprotein.

The mean half-life of abiraterone in CRPC patients is  $12 \pm 5$  hours. After an oral dose, 88% of the administered drug is recovered in feces, mostly as unchanged abiraterone acetate. Another 5% is excreted in the urine.<sup>16,17</sup>

## Effect of Dietary Intake

There is significant variability in the absorption of abiraterone acetate, depending on whether it is administered with or without food. In clinical trials, patients taking abiraterone with high-fat meals had a 4.4-fold higher overall drug exposure (as evident by higher  $C_{max}$  and AUC), compared with patients who took the drug with low-fat meals. Across the dosing range in the first study, the  $C_{max}$  ranged from 283 to 510 nM/L in fasting patients and from 421 to 2,194 nM/L in nonfasting patients. Across the dosing range in the second study, the AUC concentration ranged from 1,411 to 3,478 nM/L/hour in fasting patients and from 1,387 to 14,404 nM/L/hour in nonfasting patients.<sup>16,17</sup>

Based on the extent of variability in exposure when abiraterone is taken with a high-fat food content, and given the normal variations in the content and composition of meals that cannot be controlled outside of the clinical trial setting, the FDA has requested that the product labeling reflect that abiraterone has to be administered 2 hours before meals.<sup>15</sup> The label also states that no food should be consumed for an additional 1 hour after the administration of abiraterone.

## CLINICAL TRIALS

Abiraterone acetate has been studied in phase 2 and phase 3 clinical trials.<sup>18–20</sup> The first phase 2 trial evaluated abiraterone acetate in 47 patients with CRPC who were previously treated with docetaxel. The primary objective was to attain a decline in PSA of 50% or more from baseline.

Median patient age was 67 years with a PSA of 403 ng/mL. Patients also had to have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 2<sup>21</sup> (i.e., indicating the ability to ambulate, perform at least light work, and stay awake for more than 50% of waking hours) and progressive disease (two consecutive increases in PSA), as defined by PSA Working Group criteria.<sup>22</sup>

Of 47 patients, 45 had bone metastases at trial initiation. All patients in the study previously received luteinizing hormone-releasing hormone (LHRH) agonists and experienced disease progression. Patients received abiraterone acetate 1,000 mg (four capsules of 250 mg each) in 28-day cycles. Because of an accumulation of mineralocorticoids, some patients experienced hypertension, hypokalemia, and fluid retention. These patients were managed with eplerenone (Inspra, Pfizer) 50 to 200 mg or with low-dose glucocorticoids.

Bone scans and computed tomography (CT) were performed at baseline and at 3 and 6 months. PSA, albumin, liver and renal function tests, and alkaline phosphatase levels were monitored at baseline and then every 4 weeks. Twenty-four patients (51%) responded to treatment, as shown by a decline in PSA of 50% or more from the start of the trial. Sixty-eight percent of patients had a decline of 30% or more in PSA values, and 15% of patients demonstrated a PSA decline of 90% or more.

The median time to PSA progression was 24 weeks. Most of the patients received the study drug for 12 to 48 weeks. Three patients died during the study, but these deaths were not attributed to the medication. The promising results of this trial led to the development of a phase 3 clinical study.

The second phase 2 trial was a multicenter, open-label, single-arm study of abiraterone plus prednisone in patients with docetaxel-treated CRPC. Fifty-eight men with progressive metastatic CRPC were evaluated for a PSA decline of 50% or more. The investigators anticipated phase 3 progression of abiraterone acetate and designed the trial to address the outcome of the number and type of prior hormone treatments, mainly ketoconazole (Nizoral, Janssen). Eligibility criteria included a serum testosterone level of less than 50 ng/dL, an ECOG PS score of 2 or less,

normal serum potassium levels, and normal renal and hepatic function.

Patients received abiraterone acetate 1,000 mg (four 250-mg tablets) in the morning on an empty stomach plus prednisone 5 mg by mouth twice daily for 28-day cycles (a minimum of 12 cycles). Complete blood count, basic metabolic panel, and PSA and androgen levels were evaluated monthly.

The trial also assessed time to PSA progression, changes in ECOG PS scores, and pre- and post-therapy circulating tumor cell counts. The trial was powered at 86% with a required enrollment of 50 patients. At least 25% of enrollees had to have a decline in PSA of 50% or more to reject the study's null hypothesis of no difference.

Men were enrolled in seven study centers from June 2007 to November 2007. Median PSA and testosterone levels at enrollment were 190 ng/mL and 4.8 ng/dL, respectively. Fifty-two patients (91%) had received prior antiandrogens, nine (16%) received estrogens, 98% had received previous treatment with LHRH, and 27 (47%) had prior ketoconazole treatment. All enrolled patients had received docetaxel, whereas only 24% had also received a second-line chemotherapeutic agent.

Of the 58 patients enrolled, 53% had an ECOG PS score of 1 and 45% had a history of bone and soft-tissue metastases. Twenty-five patients (43%) achieved the primary outcome of at least a 50% decrease in PSA levels (95% confidence interval [CI], 30–55); this included eight of the 27 patients who had received ketoconazole (95% CI, 13–47). The median time to PSA progression was approximately 24 weeks in all patients (95% CI, 12–29). In the ketoconazole subgroup, the median time to PSA progression was approximately 14.1 weeks (95% CI, 8–24).

No deaths or major adverse reactions were reported throughout the study period. As with the previous phase 2 study, it was concluded that there was enough evidence to progress to a phase 3 trial. The investigators also determined that coadministration of prednisone 5 mg twice daily with abiraterone acetate decreased mineralocorticoid-related adverse events.

The phase 3 trial was a randomized, double-blind, placebo-controlled study of abiraterone acetate plus prednisone or placebo that evaluated prolongation

**Table 2 Results of a Phase 3 Clinical Trial of Abiraterone/Prednisone and Placebo/Prednisone\***

	Treatment (n = 797)	Placebo (n = 398)	Hazard Ratio	95% Confidence Interval
Median survival time (months)	14.8	10.9	0.66	0.56–0.79
Deaths during study follow-up (%)	42	55	0.65	0.54–0.77
Survival in patients with baseline ECOG PS score of 2	7.3	7.0	0.81	0.53–1.24 (NS)
Time to PSA progression (months)	10.2	6.6	0.58	0.46–0.73
Radiographic evidence of disease progression-free survival (months)	5.6	3.6	0.67	0.59–0.78

ECOG PS = Eastern Cooperative Oncology Group performance status; NS = not significant; PSA = prostate-specific antigen.  
 \*All data are statistically significant unless otherwise noted by NS.  
 Adapted from De Bono JS, Logothetis CJ, Molina A, et al. *N Engl J Med* 2011;364:1995–2005.<sup>20</sup>

of overall survival among patients with metastatic CRPC.

Patients were assigned to therapy according to their ECOG PS scores, level of pain, number of previous chemotherapeutic regimens, and evidence of disease progression in a 2:1 ratio (abiraterone/prednisone to placebo/prednisone).

Enrollees received abiraterone acetate for 28-day cycles until the PSA level, radiography, or clinical findings showed disease progression. The median age of the patients was 69 years.

ECOG PS scores were 90% (0 or 1) in the treatment group and 89% (0 or 1) in the placebo group.

Patients received treatment for a median time of 8 months and 4 months in the abiraterone acetate and placebo groups, respectively. Forty-two percent of treated patients and 55% of the placebo patients did not survive until study follow-up (median survival time, 14.8 vs. 10.9 months, respectively) (Table 2).

Abiraterone acetate therapy resulted in increased survival in all treatment groups, compared with placebo, and was associated with a low frequency of treatment-related adverse events.

**ADVERSE EFFECTS AND PRECAUTIONS**

More urinary tract infections occurred with abiraterone than with placebo (12% vs. 7%, respectively;  $P = 0.02$ ). Fluid retention and edema were observed more frequently in the abiraterone acetate arm (31%) than in the placebo arm (22%) ( $P = 0.04$ ). Hypokalemia also affected more abiraterone patients than placebo participants (17% vs. 8%, respectively;  $P < 0.001$ ). There were no significant differences in fatal cardiac events between the two groups. The other events were considered not to be attributable to abiraterone acetate and occurred with a frequency similar to that of placebo (Table 3).

Abiraterone acetate is contraindicated in pregnancy and should be used with caution in patients with cardiac disease.<sup>15</sup> Because of the potential increase in blood pressure and fluid retention, abiraterone acetate should be used with caution in patients with heart failure and ventricular arrhythmias.<sup>15</sup>

**DOSAGE AND ADMINISTRATION**

The dosage for abiraterone acetate is 1,000 mg once daily administered as four 250-mg tablets. Abiraterone should be taken with 5 mg of prednisone administered twice daily, and it should be taken on an empty stomach with no food for at least 2 hours before meals and 1 hour after meals. The tablets should be swallowed whole with water.<sup>15</sup>

According to the manufacturer’s recommendation, therapy should be interrupted if liver transaminases (ALT/AST) increase more than five times the upper limit of normal (ULN). When liver func-

**Table 3 Most Common Adverse Events in Placebo-Controlled Trials**

	Abiraterone Acetate			Placebo		
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Fatigue	44%	2%	<1%	43%	3%	1%
Back pain	30%	6%	<1%	33%	9%	<1%
Nausea	30%	2%	<1%	32%	3%	0
Urinary tract infection*	12%	2%	0%	7%	<1%	0%
Bone pain	25%	5%	<1%	28%	6%	1%
Fluid retention, edema*	31%	2%	<1%	22%	1%	0%
Hypokalemia*	17%	3%	<1%	8%	1%	0%

\*Denotes statistical significance.

Grade 1 = mild adverse event; grade 2 = moderate adverse event; grade 3 = severe adverse event; grade 4 = life-threatening or disabling adverse event; grade 5 = death related to adverse event.

Adapted from De Bono JS, Logothetis CJ, Molina A, et al. *N Engl J Med* 2011;364:1995–2005.<sup>20</sup>

tion test results return to baseline or 2.5 times or less the ULN, abiraterone acetate may be restarted at a lower dose of 750 mg. Transaminases and bilirubin levels should be monitored every 2 weeks for 3 months and monthly thereafter. For patients experiencing hepatotoxicity with a 750-mg dose, abiraterone acetate may be restarted at 500 mg. It is advisable not to rechallenge patients if hepatotoxicity develops with the 500-mg dose.

## DRUG INTERACTIONS

Abiraterone is an inhibitor of CYP2D6 and CYP1A2, and it moderately inhibits CYP2C9, CYP2C19, and CYP3A4/5.1 Abiraterone is also a CYP3A4 substrate. Coadministration of abiraterone acetate and dextromethorphan (e.g., Robitussin, Nyquil) should be avoided because of an increased AUC and  $C_{max}$  of dextromethorphan.<sup>15</sup> Interactions with CYP3A4 inducers and inhibitors have not been evaluated.

## COST AND FORMULARY CONSIDERATIONS

Abiraterone acetate (Zytiga) is available as 250-mg white to off-white, oval tablets. They are marked with AA250 on one side. The average wholesale price (AWP) for a month's supply (a package of 120 tablets) is \$6,983.05 (\$58.19 per tablet). The wholesale acquisition cost (WAC) is \$5,819.21.<sup>23</sup> With a median expected treatment duration of about 8 months, abiraterone carries a significant financial burden on patients and institutions.

The current guidelines recommend using abiraterone acetate as a second-line agent based on the published data. Because abiraterone has shown a significant survival benefit for patients with docetaxel-resistant CRPC, we recommend adding this agent to outpatient formularies with appropriate restrictions.

For patients who are admitted to an inpatient facility, therapy with abiraterone should be continued. To date, no published pharmaco-economic analyses have confirmed the value of using abiraterone as a cost-effective treatment option. These analyses would be valuable to help guide P&T committees in making formulary decisions.

## CONCLUSION

Abiraterone acetate is approved by the FDA as an oral treatment option

for CRPC. It has been shown to be efficacious in patients who did not respond to docetaxel-based regimens. The drug increased survival in patients with castration-resistant disease. By blocking androgen synthesis via CYP17 inhibition, abiraterone acetate produces tumor responses in patients who no longer respond to standard hormonal therapies.

Adverse events are driven mainly by the mechanism of action of the medication and may be minimized by the administration of prednisone 5 mg twice daily. Studies investigating abiraterone acetate in metastatic breast cancer and earlier stages of prostate cancer are under way.

## REFERENCES

1. Siegel R, Naishadham D, Hemal A. Cancer statistics, 2012. *Ca Cancer J Clin* 2012;62(1):10–29.
2. National Cancer Institute. Clinical trials search results. Available at: [www.cancer.gov/cancertopics/types/prostate](http://www.cancer.gov/cancertopics/types/prostate). Accessed June 18, 2012.
3. Platz EA, Rimm EB, Willett WC, et al. Racial variation in prostate cancer incidence and in hormonal system markers among male health professionals. *J Natl Cancer Inst* 2000;92(24):2009–2017.
4. Howlader N, Noone AM, Krapcho M, et al. (eds.). SEER Cancer Statistics Review, 1975–2009 (Vintage 2009 Populations). Bethesda, Md.: National Cancer Institute. Based on November 2011 SEER data submission. Updated August 20, 2012. Available at: [http://seer.cancer.gov/csr/1975\\_2009\\_pops09](http://seer.cancer.gov/csr/1975_2009_pops09). Accessed December 12, 2012.
5. Mohler JL, Gregory CW, Ford OH III, et al. The androgen axis in recurrent prostate cancer. *Clin Cancer Res* 2004;10(2):440–448.
6. DeVita VT, Lawrence TS, Rosenberg SA. *DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology*, 9th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2011.
7. Chen Y, Sawyers CL, Scher HI. Targeting the androgen receptor pathway in prostate cancer. *Curr Opin Pharmacol* 2008;8(4):440–448.
8. Mohler JL, Armstrong AJ, Bahnson RR, et al. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: Prostate cancer. Available at: [www.nccn.org/professionals/physician\\_gls/pdf/prostate.pdf](http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf). Accessed June 18, 2012.
9. Antonarakis ES, Eisneberger MA. Expanding treatment options for metastatic prostate cancer. *N Engl J Med* 2011;364(21):2055–2058.
10. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced pros-

11. National Comprehensive Cancer Network. *Clinical Practice Guidelines: Prostate Cancer*, version 3.2012.
12. Mohler JL, Gregory CW, Ford OH III, et al. The androgen axis in recurrent prostate cancer. *Clin Cancer Res* 2004;10(2):440–448.
13. FDA expands Zytiga use for late-stage prostate cancer. December 10, 2012. Available at: [www.fda.gov](http://www.fda.gov). Accessed December 12, 2012.
14. Mostaghel EA, Marck BT, Plymate SR, et al. Resistance to CYP17A1 inhibition with abiraterone in castration-resistant prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. *Clin Cancer Res* 2011;17:5913–5925.
15. Zytiga (abiraterone acetate), product information. Horsham, Pa.: Janssen Biotech Inc.; April 2011.
16. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol* 2010;28(9):1481–1488.
17. Acharya M, Bernard A, Gonzalez M, et al. Open-label, phase I, pharmacokinetic studies of abiraterone acetate in healthy men. *Cancer Chemother Pharmacol* 2012;69(6):1583–1590.
18. Reid AHM, Attard G, Danila DC, et al. Significant and sustained antitumor activity in post-docetaxel, castration-resistant prostate cancer with the CYP17 inhibitor abiraterone acetate. *J Clin Oncol* 2010;28:1489–1495.
19. Danila DC, Morris MJ, de Bono JS, et al. Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel treated castration-resistant prostate cancer. *J Clin Oncol* 2010;28:1496–1501.
20. De Bono JS, Logothetis CJ, Molin A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011;364:1995–2005.
21. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982;5:649–655.
22. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: Recommendations from the Prostate-Specific Antigen Working Group. *J Clin Oncol* 1999;17:3461–3467.
23. Red Book online®. Available at: [www.thomsonhc.com](http://www.thomsonhc.com). Accessed June 29, 2012. ■