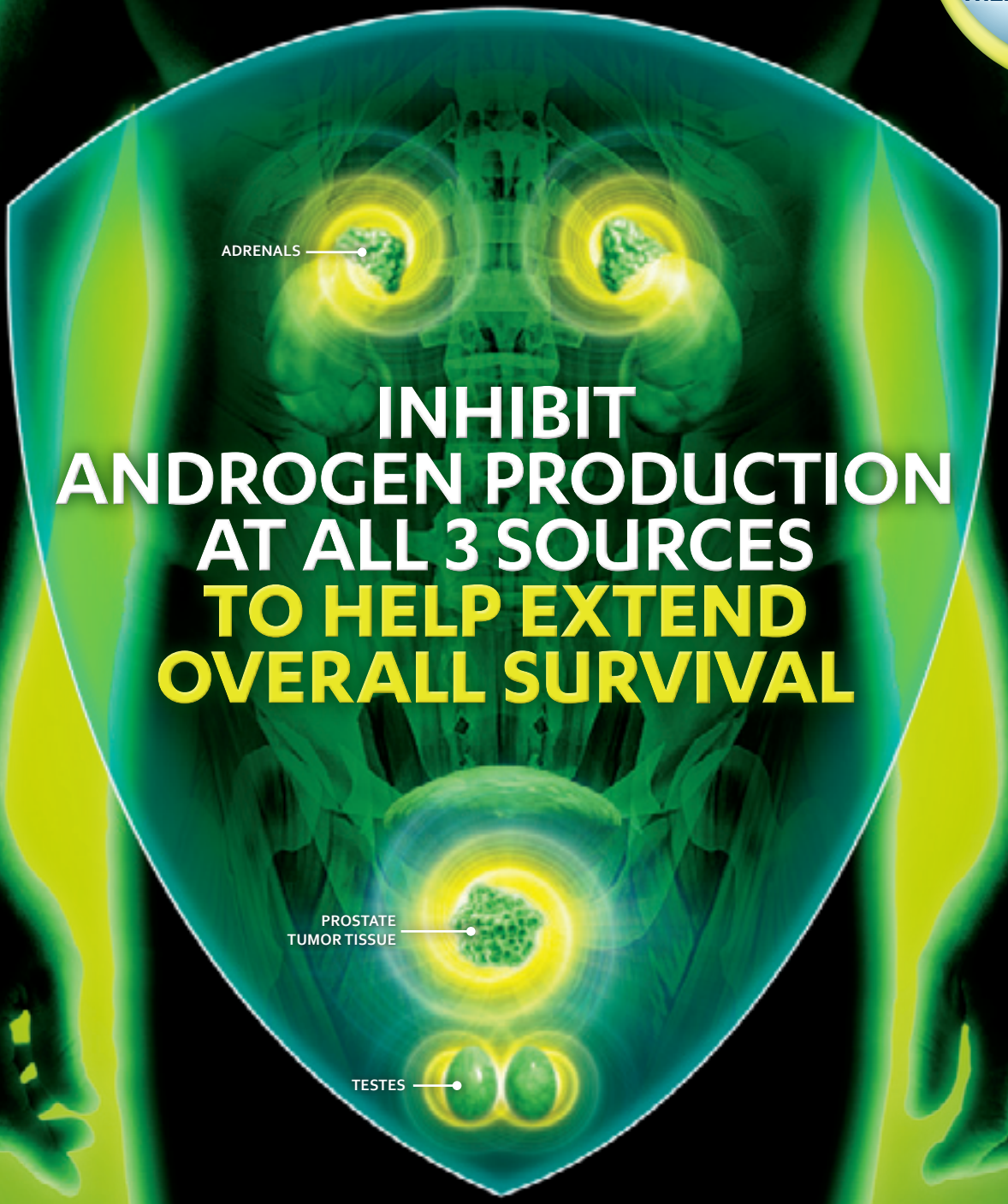
FOR YOUR UROLOGY PRACTICE

FOR PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER...

NEW ORAL THERAPY



INHIBIT ANDROGEN PRODUCTION AT ALL 3 SOURCES TO HELP EXTEND OVERALL SURVIVAL

ZYTIGA™ in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

Please see Important Safety Information on the following pages.
Please see accompanying full Prescribing Information.

NEW
once-daily tablets
Zytiga™
abiraterone acetate

CASTRATION-RESISTANT PROSTATE CANCER IS AN ANDROGEN-SENSITIVE DISEASE

In castration-resistant prostate cancer, the tumor continues to be androgen-sensitive[1,2]

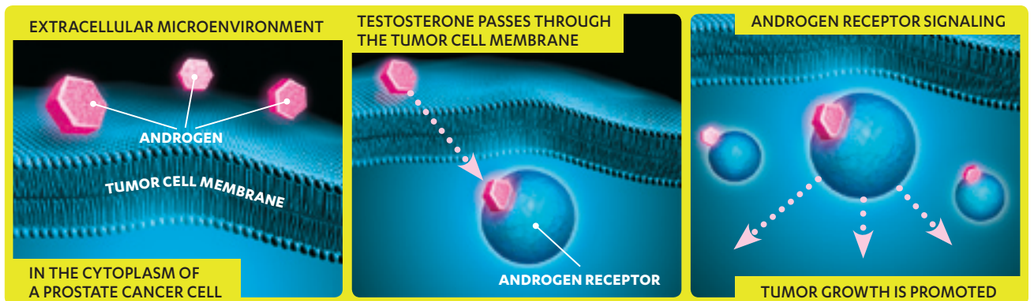
- The androgen signaling pathway remains important throughout the course of castration-resistant prostate cancer[1,2]
- Hormone-refractory (or hormone-resistant) prostate cancer does not adequately describe advanced disease[1,2]
- Clinical evidence suggests that the tumor growth remains primarily hormone driven[1,2]

Prostate cancer tumor cells produce androgen to fuel their own growth[3,4]

- Prostate cancer tumor cells have enzymatic pathways that produce androgen to fuel their own growth
- Tissue levels of androgen in castration-resistant prostate cancer remain at levels sufficient to activate the androgen receptor[5,6]

In castration-resistant prostate cancer, even a small amount of androgen can fuel tumor growth[7,8]

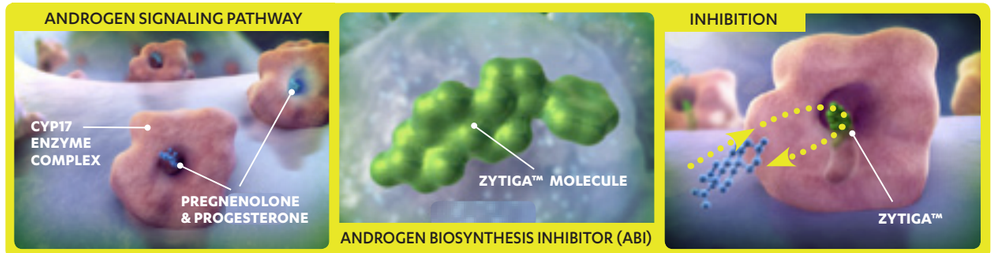
- The androgen receptor remains sensitive to low levels of androgen, increasing the growth-promoting effects of dihydrotestosterone (DHT)[9]



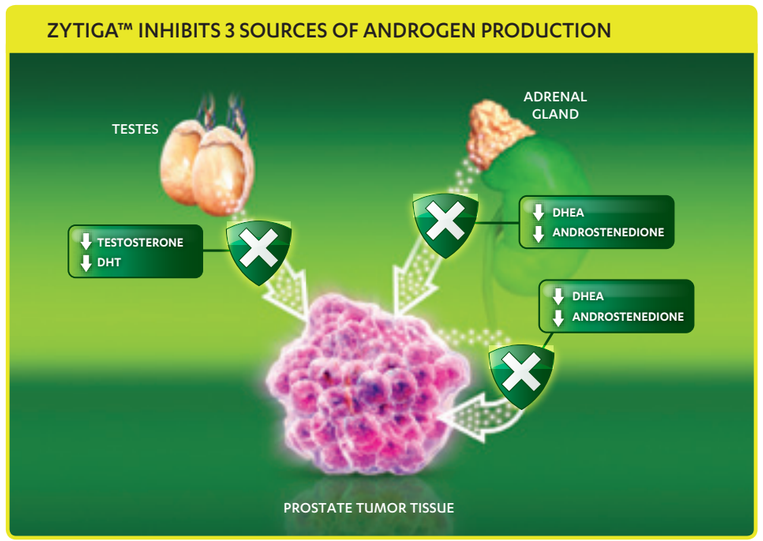
MOA: INHIBIT ANDROGEN PRODUCTION AT ALL 3 SOURCES WITH ZYTIGA™

Androgen biosynthesis inhibition: a different way to target androgen production

- Abiraterone is an androgen biosynthesis inhibitor (ABI) that directly affects the androgen signaling pathway by inhibiting CYP17 (17α-hydroxylase/C17,20-lyase), an enzyme complex needed for androgen biosynthesis
  - — Consequently, androgen biosynthesis is inhibited at all 3 sources: the testes, adrenal glands, and prostate tumor tissue

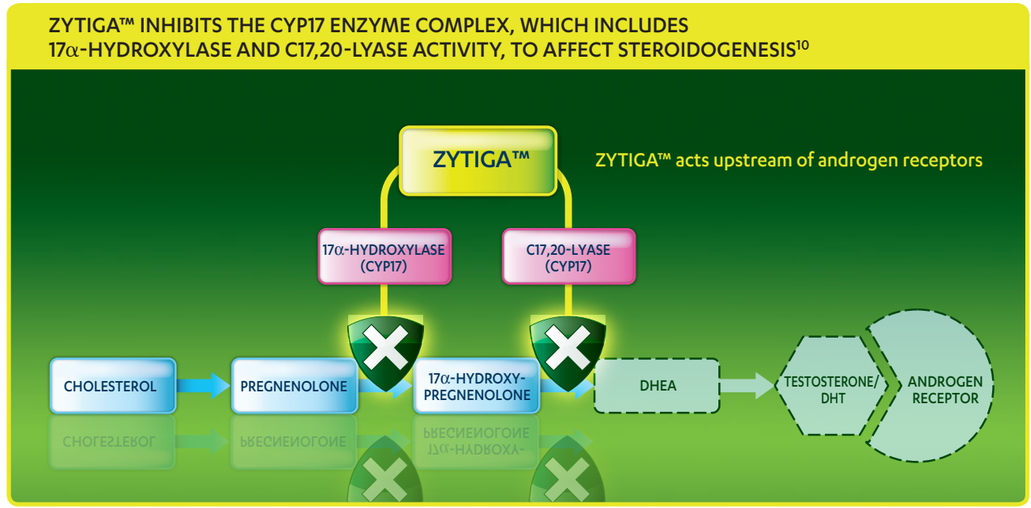


- In contrast, androgen-deprivation therapies—such as GnRH agonists or orchiectomy—decrease androgen production in the testes, but do not affect androgen production by the adrenal glands or in the tumor



Androgens include DHEA, androstenedione, DHT, and testosterone. Testosterone is the primary androgen.

Abbreviation: GnRH = gonadotropin-releasing hormone.



- Androgen biosynthesis inhibition with ZYTIGA™ results in decreased levels of serum testosterone and other androgens

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in hypertension, hypokalemia and fluid retention. Safety has not been established in patients with LVEF < 50% or NYHA Class III or IV heart failure. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

Contraindications

ZYTIGA™ may cause fetal harm (Pregnancy Category X) and is contraindicated in women who are or may become pregnant.

Please see accompanying full Prescribing Information.

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NEW once-daily tablets Zytiga™ abiraterone acetate

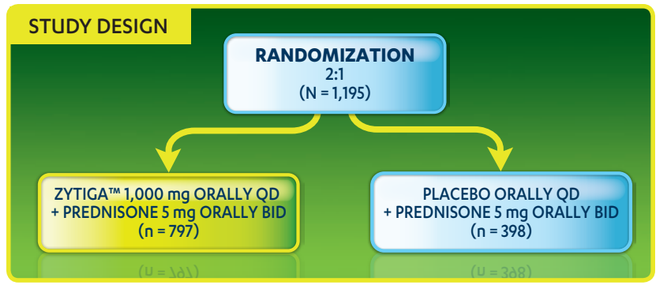
ZYTIGA™ ACHIEVED A STATISTICALLY SIGNIFICANT MEDIAN OVERALL SURVIVAL DIFFERENCE

Efficacy proven in a phase 3, randomized, double-blind, placebo-controlled, multicenter study

Efficacy and safety evaluated for ZYTIGA™ + prednisone vs placebo + prednisone for the treatment of patients with metastatic castration-resistant prostate cancer

Primary end point: Overall survival

Patient population: Patients were using a GnRH agonist or were previously treated with orchiectomy



Criteria for discontinuation of treatment due to progression

In the phase 3 clinical study, *all* of the following criteria were required for discontinuation of study[11]

1. PSA progression as defined by PSAWG eligibility criteria (25% increase over baseline/nadir) with minimum PSA increase of 5 ng/mL
2. Radiographic progression defined by progression on bone scans or soft-tissue disease progression
3. Symptomatic or clinical progression defined by pain progression, development of an SRE, or any increase in prednisone or prednisolone dose

- Other reasons for discontinuation of study included initiation of new treatment, unacceptable toxicity, or withdrawal

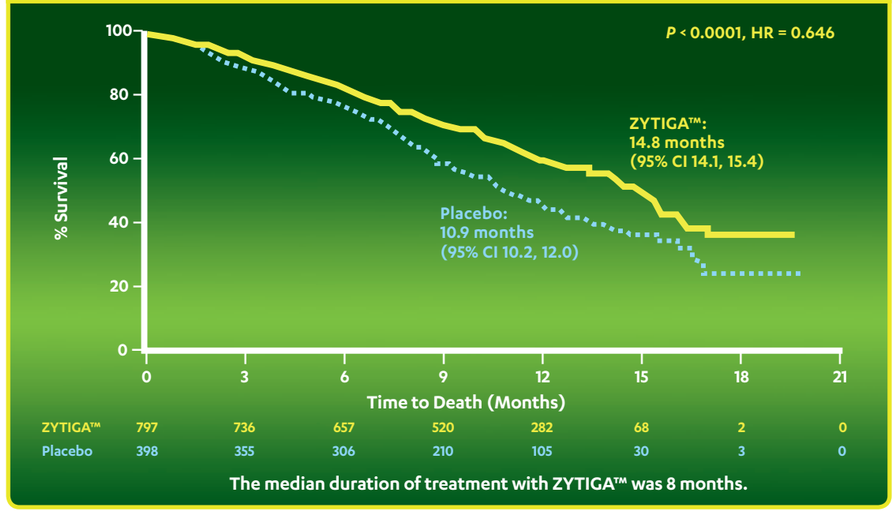
Baseline Patient Demographics and Disease Characteristics

- Median age: 69 years (range, 39-95 years)
- ECOG performance score of 0 to 1 = 89%
- Bone metastases = 90%; visceral involvement = 30%
- Radiographic evidence of disease progression = 70%; PSA-only progression = 30%
- Prior chemotherapy: one cytotoxic chemotherapy regimen, 70%; two cytotoxic chemotherapy regimens, 30%

Abbreviations: PSAWG = PSA Working Group; SRE = skeletal-related event.

ZYTIGA™ in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.

KAPLAN-MEIER SURVIVAL CURVES OF PATIENTS TREATED WITH EITHER ZYTIGA™ + PREDNISONE OR PLACEBO + PREDNISONE (INTERIM ANALYSIS)



The median duration of treatment with ZYTIGA™ was 8 months.

- The interim analysis showed a 3.9-month difference in median overall survival compared with placebo + prednisone ($P < 0.0001$)
- In an updated analysis, results were consistent with those from the interim analysis, with a 4.6-month difference between the two arms in median overall survival (15.8 months vs 11.2 months [HR = 0.74])
  - 41% improvement in median overall survival compared with placebo + prednisone

Adverse Reactions

The most common adverse reactions (≥ 5%) reported in clinical trials were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia and upper respiratory tract infection.

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NEW
once-daily tablets
Zytiga™
abiraterone acetate

ZYTIGA™ HAS AN ESTABLISHED SAFETY PROFILE

ADVERSE REACTIONS (≥ 2%*) DUE TO ZYTIGA™ IN A PLACEBO-CONTROLLED PHASE 3 TRIAL

System/Organ Class Adverse Reaction	ZYTIGA™ With Prednisone (n = 791)		Placebo With Prednisone (n = 394)	
	All Grades† %	Grade 3-4 %	All Grades %	Grade 3-4 %
Musculoskeletal and Connective Tissue Disorders				
Joint swelling/discomfort‡	29.5	4.2	23.4	4.1
Muscle discomfort§	26.2	3.0	23.1	2.3
General Disorders				
Edema‖	26.7	1.9	18.3	0.8
Vascular Disorders				
Hot flush	19.0	0.3	16.8	0.3
Hypertension	8.5	1.3	6.9	0.3
Gastrointestinal Disorders				
Diarrhea	17.6	0.6	13.5	1.3
Dyspepsia	6.1	0	3.3	0
Infections and Infestations				
Urinary tract infection	11.5	2.1	7.1	0.5
Upper respiratory tract infection	5.4	0	2.5	0
Respiratory, Thoracic, and Mediastinal Disorders				
Cough	10.6	0	7.6	0
Renal and Urinary Disorders				
Urinary frequency	7.2	0.3	5.1	0.3
Nocturia	6.2	0	4.1	0
Cardiac Disorders				
Arrhythmia¶	7.2	1.1	4.6	1.0
Chest pain or chest discomfort#	3.8	0.5	2.8	0
Cardiac failure**	2.3	1.9	1.0	0.3

* Table shows adverse reactions due to ZYTIGA™ that occurred with either a ≥ 2% absolute increase in frequency compared to placebo or were events of special interest (mineralocorticoid excess, cardiac adverse reactions, and liver toxicities).
† Adverse events graded according to CTCAE version 3.0.
‡ Includes terms arthritis, arthralgia, joint swelling, and joint stiffness.
§ Includes terms muscle spasms, musculoskeletal pain, myalgia, musculoskeletal discomfort, and musculoskeletal stiffness.
‖ Includes terms edema, edema peripheral, pitting edema, and generalized edema.
¶ Includes terms arrhythmia, tachycardia, atrial fibrillation, supraventricular tachycardia, atrial tachycardia, ventricular tachycardia, atrial flutter, bradycardia, atrioventricular block complete, conduction disorder, and bradyarrhythmia.
# Includes terms angina pectoris, chest pain, and angina unstable. Myocardial infarction or ischemia occurred more commonly in the placebo arm than in the ZYTIGA™ arm (1.3% vs 1.1%, respectively).
** Includes terms cardiac failure, cardiac failure congestive, left ventricular dysfunction, cardiogenic shock, cardiomegaly, cardiomyopathy, and ejection fraction decreased.

- In a phase 3 clinical study, abnormalities related to mineralocorticoid effects (all grades) were seen more commonly in patients treated with ZYTIGA™ + prednisone vs placebo + prednisone: hypokalemia, 28% vs 20%; hypertension, 9% vs 7%; and fluid retention (edema), 27% vs 18%, respectively

Coadministration of prednisone reduces the incidence and severity of these mineralocorticoid-related adverse reactions (hypokalemia, hypertension, fluid retention)

- Secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland drives the production of mineralocorticoids, androgens, and glucocorticoids such as cortisol[12]
- Treatment with ZYTIGA™ inhibits the production of cortisol and androgens as a result of CYP17 inhibition[12]
- Secreted levels of ACTH increase in response to a decrease in circulating cortisol levels (loss of a negative feedback mechanism)[12]
- There is a corresponding increase in mineralocorticoid levels that may lead to these adverse reactions[12]
- Prednisone (5 mg orally twice daily) in combination with ZYTIGA™ preempts the activation of this negative feedback mechanism because the system no longer perceives a net cortisol deficit[10]

Adrenocortical Insufficiency (AI) has been reported in clinical trials after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn or if the patient experiences unusual stress. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during and after stressful situations.

Hepatotoxicity—Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, withhold or discontinue ZYTIGA™ dosing as recommended (see Prescribing Information for more information).

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ZYTIGA™ HAS ORAL, ONCE-DAILY DOSING

Recommended dosing

- 1,000 mg administered orally once daily that must be taken on an empty stomach
  - — No food should be consumed for at least two hours before the dose of ZYTIGA™ is taken and for one hour after the dose of ZYTIGA™ is taken
  - — Tablets should be swallowed whole with water

Food Effect—ZYTIGA™ must be taken on an empty stomach. Exposure of abiraterone increases up to 10-fold when abiraterone acetate is taken with meals. No food should be eaten for at least two hours before the dose of ZYTIGA™ is taken and for at least one hour after the dose of ZYTIGA™ is taken.

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- ZYTIGA™ is used in combination with prednisone
  - — The recommended dose of prednisone is 5 mg administered orally twice daily
  - — 7.5 mg/day to 10 mg/day of prednisone is the physiologic equivalent of the amount of endogenous cortisol normally produced on a daily basis[13]
- Avoid ZYTIGA™ in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA™ has not been studied in this population, and no dose adjustment can be predicted
- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA™ starting dose to 250 mg once daily
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA™ until recovery. Re-treatment may be initiated at a reduced dose. ZYTIGA™ should be discontinued if patients develop severe hepatotoxicity

Dose adjustments for patients with renal impairment

- No dosage adjustment is necessary for patients with renal impairment

Patient monitoring recommendations with ZYTIGA™

- Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA™, every two weeks for the first three months of treatment, and monthly thereafter
- Control hypertension and correct hypokalemia before and during treatment with ZYTIGA™

Drug Interactions

ZYTIGA™ is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. Additionally, abiraterone is a substrate of CYP3A4 *in vitro*. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

References: 1. Chen Y, Clegg NJ, Scher HI. Anti-androgens and androgen-depleting therapies in prostate cancer: new agents for an established target. *Lancet Oncol*. 2009;10:981-991. **2.** Scher HI, Steineck G, Kelly WK. Hormone-refractory (D3) prostate cancer: refining the concept. *Urology*. 1995;46(2):142-148. **3.** Montgomery RB, Mostaghel EA, Vessella R, et al. Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res*. 2008;68(11):4447-4454. **4.** Stanbrough M, Bubley GJ, Ross K, et al. Increased expression of genes converting adrenal androgens to testosterone in androgen-independent prostate cancer. *Cancer Res*. 2006;66(5):2815-2825. **5.** Mohler JL, Gregory CW, Ford OH III, et al. The androgen axis in recurrent prostate cancer. *Clin Cancer Res*. 2004;10:440-448. **6.** Titus MA, Schell MJ, Lih FB, Tomer KB, Mohler JL. Testosterone and dihydrotestosterone tissue levels in recurrent prostate cancer. *Clin Cancer Res*. 2005;11(13):4653-4657. **7.** Chen CD, Welsbie DS, Tran C, et al. Molecular determinants of resistance to antiandrogen therapy. *Nat Med*. 2004;10(1):33-39. **8.** Pienta KJ, Bradley D. Mechanisms underlying the development of androgen-independent prostate cancer. *Clin Cancer Res*. 2006;12(6):1665-1671. **9.** Locke JA, Guns ES, Lubik AA, et al. Androgen levels increase by intratumoral de novo steroidogenesis during progression of castration-resistant prostate cancer. *Cancer Res*. 2008;68(15):6407-6415. **10.** Attard G, Belldegrun AS, de Bono JS. Selective blockade of androgenic steroid synthesis by novel lyase inhibitors as a therapeutic strategy for treating metastatic prostate cancer. *BJU Int*. 2005;96:1241-1246. **11.** Data on file, Centocor Ortho Biotech Inc. **12.** Auchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. *Endocrinol Metab Clin North Am*. 2001;30(1):101-119. **13.** Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA*. 1999;282(7):671-676.

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NEW ORAL THERAPY

INTRODUCING ZYTIGA™ (abiraterone acetate): ORAL, ONCE-DAILY DOSING

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ORAL, ONCE-DAILY DOSING

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MOA

- Abiraterone is an androgen biosynthesis inhibitor (ABI) that directly affects the androgen signaling pathway by inhibiting CYP17 (17α-hydroxylase/C17,20-lyase), an enzyme complex needed for androgen biosynthesis

EFFICACY

- At a prespecified interim analysis, ZYTIGA™ + prednisone showed a statistically significant improvement in overall survival compared with the control arm ($P < 0.0001$)

SAFETY

- Proven safety profile; the most common adverse reactions (≥ 5%) reported in clinical trials were joint swelling or discomfort, hypokalemia, edema, muscle discomfort, hot flush, diarrhea, urinary tract infection, cough, hypertension, arrhythmia, urinary frequency, nocturia, dyspepsia, and upper respiratory tract infection
- Prednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions

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