PUTTING PREDNISONE IN PERSPECTIVE

Understanding the role of prednisone in combination with ZYTIGA® (abiraterone acetate)

ZYTIGA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC).

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 blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

once-daily

Zytiga®
(abiraterone acetate)
250 mg tablets

Please see Important Safety Information on the last page.

Please see the full Prescribing Information

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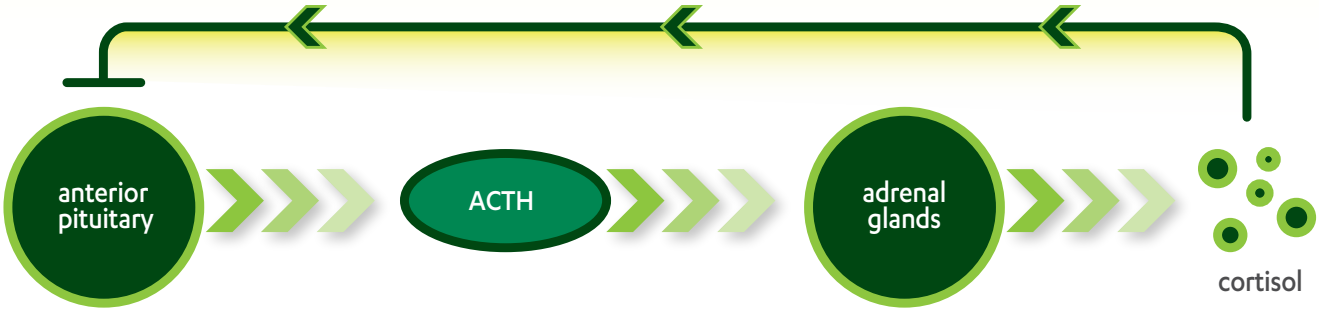
Prednisone reduces the incidence and severity of mineralocorticoid-related adverse reactions associated with ZYTIGA® (abiraterone acetate)

Mechanism of action

- ZYTIGA® is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17α-hydroxylase/C17,20 lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostate tumor tissues and is required for androgen biosynthesis
- This inhibition of the CYP17 enzyme complex can result in increased mineralocorticoid production and may cause hypertension, hypokalemia, and fluid retention
- Secretion of adrenocorticotropic hormone (ACTH) by the pituitary gland drives the production of mineralocorticoids, androgens, and glucocorticoids, such as cortisol, in the adrenal cortex[1]

Endogenous cortisol production under normal conditions[2]



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- Secreted levels of ACTH increase in response to decreased levels of cortisol due to CYP17 complex inhibition[1,3]
- Coadministration of prednisone suppresses the ACTH drive and reduces the incidence and severity of mineralocorticoid excess adverse reactions

Adrenocortical Insufficiency (AI)—AI was reported in patients receiving ZYTIGA® in combination with prednisone, 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, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

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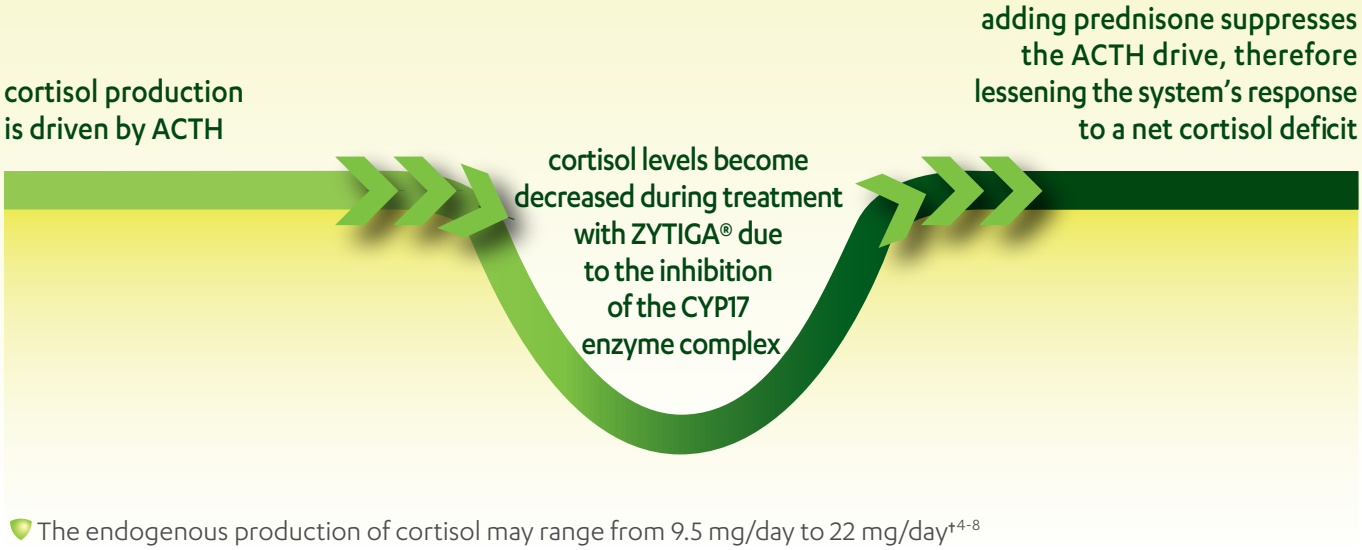
Coadministration of a corticosteroid suppresses the ACTH* drive, reducing the incidence and severity of mineralocorticoid adverse reactions



- The endogenous production of cortisol may range from 9.5 mg/day to 22 mg/day†[4-8]
- 7.5 mg/day to 10 mg/day of prednisone is approximately the physiologic equivalent of the amount of endogenous cortisol normally produced on a daily basis[4,9,10]

Recommended dosing

- ZYTIGA® 1,000 mg (four 250-mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily
- ZYTIGA® must be taken on an empty stomach. The tablets should be swallowed whole with water. Do not crush or chew tablets. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA® starting dose to 250 mg once daily. Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C)‡

*Adrenocorticotropic hormone.
†Endogenous cortisol levels vary per individual.
‡Please see full Prescribing Information, Dosage and Administration section, for dose modifications based on hepatic function and concomitant strong CYP3A4 inducers.

References: **1.** Auchus RJ. The genetics, pathophysiology, and management of human deficiencies of P450c17. *Endocrinol Metab Clin North Am*. 2001;30(1):101-119. **2.** Vassiliadi DA, Tsagarakis S. Endocrine incidentalomas—challenges imposed by incidentally discovered lesions. *Nat Rev Endocrinol*. 2011;7(11):668-680. **3.** Attard G, Reid AHM, Yap TA, et al. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571. **4.** Krasner AS. Glucocorticoid-induced adrenal insufficiency. *JAMA*. 1999;282(7):671-676. **5.** Kraan GPB, Dullaart RPF, Pratt JJ, Wolthers BG, Drayer NM, De Bruin R. The daily cortisol production reinvestigated in healthy men. The serum and urinary cortisol production rates are not significantly different. *J Clin Endocrinol Metab*. 1998;83(4):1247-1252. **6.** Debono M, Ross RJ, Newell-Price J. Inadequacies of glucocorticoid replacement and improvements by physiological circadian therapy. *Eur J Endocrinol*. 2009;160:719-729. **7.** U.S. Department of Health and Human Services. National Health Statistics Reports. Anthropometric reference data for children and adults: United States, 2003-2006. 2008;10:1-48. **8.** Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317(17):1098. **9.** Petri MA, Lahita RG, van Vollenhoven RF, et al. Effects of prasterone on corticosteroid requirements of women with systemic lupus erythematosus: a double-blind, randomized, placebo-controlled trial. *Arthritis & Rheumatism*. 2002;46(7):1820-1829. **10.** Prednisolone Tablets 5 mg Summary of Product Characteristics. Available at: http://www.medicines.org.uk/emc/medicine/10816/spc. Accessed January 08, 2015.

once-daily

Zytiga® (abiraterone acetate)

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IMPORTANT SAFETY INFORMATION

- **Contraindications**—ZYTIGA® (abiraterone acetate) is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.
- **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 blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.
- **Adrenocortical Insufficiency (AI)**—AI was reported in patients receiving ZYTIGA® in combination with prednisone, 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, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.
- **Hepatotoxicity**—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.
- **Increased ZYTIGA® Exposures with Food**—ZYTIGA® must be taken on an empty stomach. 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. Abiraterone C_{max} and $AUC_{0-\infty}$ (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.
- **Adverse Reactions**—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

  The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.
- **Drug Interactions**—Based on *in vitro* data, ZYTIGA® is a substrate of CYP3A4. In a drug interaction trial, co-administration of rifampin, a strong CYP3A4 inducer, decreased exposure of abiraterone by 55%. Avoid concomitant strong CYP3A4 inducers during ZYTIGA® treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA® dosing frequency only during the co-administration period [see Dosage and Administration (2.3)]. In a dedicated drug interaction trial, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

  ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzymes CYP2D6 and CYP2C8. Avoid co-administration with CYP2D6 substrates with a narrow therapeutic index. If alternative treatments cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate drug. In a CYP2C8 drug interaction trial in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% when administered with a single dose of ZYTIGA®. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.
- **Use in Specific Populations**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

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once-daily

Zytiga®

janssen

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use ZYTIGA safely and effectively. See full prescribing information for ZYTIGA.

ZYTIGA® (abiraterone acetate) Tablets
For Oral Administration
Initial U.S. Approval: 2011

RECENT MAJOR CHANGES

Dosage and Administration. (2.2) 05/2014

INDICATIONS AND USAGE

ZYTIGA is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. (1)

DOSAGE AND ADMINISTRATION

Recommended dose: ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily. ZYTIGA 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 at least one hour after the dose of ZYTIGA is taken. The tablets should be swallowed whole with water. Do not crush or chew tablets. (2.1)

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.2)
- For patients who develop hepatotoxicity during treatment, hold ZYTIGA until recovery. Retreatment may be initiated at a reduced dose. ZYTIGA should be discontinued if patients develop severe hepatotoxicity. (2.2)

DOSAGE FORMS AND STRENGTHS

Tablet 250 mg (3)

CONTRAINDICATIONS

- ZYTIGA is contraindicated in women who are or may become pregnant. (4.1, 8.1)

WARNINGS AND PRECAUTIONS

- Mineralocorticoid excess: Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with LVEF < 50% or NYHA Class III or IV heart failure in Study 1 or LVEF < 50% or NYHA Class II to IV heart failure in Study 2 was not established. Control hypertension and correct hypokalemia before treatment. Monitor blood pressure, serum potassium and symptoms of fluid retention at least monthly. (5.1)

- Adrenocortical insufficiency: Monitor for symptoms and signs of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations. (5.2)
- Hepatotoxicity: Increases in liver enzymes have led to drug interruption, dose modification and/or discontinuation. Monitor liver function and modify, interrupt, or discontinue ZYTIGA dosing as recommended. (5.3)

ADVERSE REACTIONS

The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities (>20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during ZYTIGA treatment. If a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency. (2.3, 7.1)
- CYP2D6 Substrates: Avoid co-administration of ZYTIGA with CYP2D6 substrates that have a narrow therapeutic index. If an alternative treatment cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate. (7.2)

USE IN SPECIFIC POPULATIONS

- Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). (8.6)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 5/2015

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

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