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.

Please see Important Safety Information on the last page.
Please see the full Prescribing Information.
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/17,20 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.

**Endogenous cortisol production under normal conditions**

- Secreted levels of ACTH increase in response to decreased levels of cortisol due to CYP17 complex inhibition.
- 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

adding prednisone suppresses the ACTH drive, therefore lessening the system’s response to a net cortisol deficit

cortisol production is driven by ACTH
cortisol levels become decreased during treatment with ZYTIGA® due to the inhibition of the CYP17 enzyme complex

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 basis4-6

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)*

*Adrenocorticotrophic 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.

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.

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**Hepatotoxicity**—In postmarketing experience, there have been ZYTIGA®-associated severe hepatic toxicities, including fulminant hepatitis, acute liver failure and deaths. 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. Re-treatment with ZYTIGA® at a reduced dose level may take place only after return of liver function tests to the patient’s baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN.

Permanently discontinue ZYTIGA® for patients who develop a concurrent elevation of ALT greater than 3X ULN and total bilirubin greater than 2X ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

**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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Please see the full Prescribing Information.