

## 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, Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity (2.2) 05/2014

Dosage and Administration, Dose Modification Guidelines for Strong CYP3A4 Inducers (2.3) 09/2013

### 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)
- Food effect: ZYTIGA must be taken on an empty stomach. Exposure (area under the curve) of abiraterone increases up to 10 fold when abiraterone acetate is taken with meals. (5.4)

### 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](http://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: 05/2014

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## **FULL PRESCRIBING INFORMATION**

### **1 INDICATIONS AND USAGE**

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

### **2 DOSAGE AND ADMINISTRATION**

#### **2.1 Recommended Dosage**

The recommended dose of ZYTIGA is 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 [see *Clinical Pharmacology (12.3)*]. The tablets should be swallowed whole with water. Do not crush or chew tablets.

#### **2.2 Dose Modification Guidelines in Hepatic Impairment and Hepatotoxicity**

##### **Hepatic Impairment**

In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. A once daily dose of 250 mg in patients with moderate hepatic impairment is predicted to result in an area under the concentration curve (AUC) similar to the AUC seen in patients with normal hepatic function receiving 1,000 mg once daily. However, there are no clinical data at the dose of 250 mg once daily in patients with moderate hepatic impairment and caution is advised. In patients with moderate hepatic impairment monitor ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. If elevations in ALT and/or AST greater than 5X upper limit of normal (ULN) or total bilirubin greater than 3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA and do not re-treat patients with ZYTIGA [see *Use in Specific Populations (8.6)* and *Clinical Pharmacology (12.3)*].

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

##### **Hepatotoxicity**

For patients who develop hepatotoxicity during treatment with ZYTIGA (ALT and/or AST greater than 5X ULN or total bilirubin greater than 3X ULN), interrupt treatment with ZYTIGA [see *Warnings and Precautions (5.3)*]. Treatment may be restarted at a reduced dose of 750 mg once daily following 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. For patients who resume treatment, monitor serum transaminases and bilirubin at a minimum of every two weeks for three months and monthly thereafter.

If hepatotoxicity recurs at the dose of 750 mg once daily, re-treatment may be restarted at a reduced dose of 500 mg once daily following 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.

If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA. The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

### **2.3 Dose Modification Guidelines for Strong CYP3A4 Inducers**

Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during ZYTIGA treatment. Although there are no clinical data with this dose adjustment in patients receiving strong CYP3A4 inducers, because of the potential for an interaction, if a strong CYP3A4 inducer must be co-administered, increase the ZYTIGA dosing frequency to twice a day only during the co-administration period (e.g., from 1,000 mg once daily to 1,000 mg twice a day). Reduce the dose back to the previous dose and frequency, if the concomitant strong CYP3A4 inducer is discontinued [see *Drug Interactions (7.1)* and *Clinical Pharmacology (12.3)*].

## **3 DOSAGE FORMS AND STRENGTHS**

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval-shaped tablets debossed with AA250 on one side.

## **4 CONTRAINDICATIONS**

### **4.1 Pregnancy**

ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss [see *Use in Specific Populations (8.1)*].

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess**

ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see *Clinical Pharmacology (12.1)*]. In the two randomized clinical trials, grade 3 to 4 hypertension occurred in 2% of patients, grade 3 to 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA. [see *Adverse Reactions (6)*].

Co-administration of a corticosteroid suppresses adrenocorticotrophic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <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) was not established because these patients were excluded from these randomized clinical trials [see *Clinical Studies (14)*]. Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

### **5.2 Adrenocortical Insufficiency**

Adrenal insufficiency occurred in the two randomized clinical studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations [see *Warnings and Precautions (5.1)*].

### **5.3 Hepatotoxicity**

In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months

after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those beginning with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

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. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 250 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two 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 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 [*see Dosage and Administration (2.2)*].

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

#### **5.4 Increased ZYTIGA Exposures with Food**

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. 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. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed [*see Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3)*].

## **6 ADVERSE REACTIONS**

The following are discussed in more detail in other sections of the labeling:

- Hypertension, Hypokalemia, and Fluid Retention due to Mineralocorticoid Excess [*see Warnings and Precautions (5.1)*].
- Adrenocortical Insufficiency [*see Warnings and Precautions (5.2)*].
- Hepatotoxicity [*see Warnings and Precautions (5.3)*].

- Increased ZYTIGA Exposures with Food [*see Warnings and Precautions (5.4)*].

## 6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchiectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions ( $\geq 10\%$ ) reported in the two randomized clinical trials that occurred more commonly ( $>2\%$ ) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and contusion.

The most common laboratory abnormalities ( $>20\%$ ) reported in the two randomized clinical trials that occurred more commonly ( $\geq 2\%$ ) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

### Study 1: Metastatic CRPC Following Chemotherapy

Study 1 enrolled 1195 patients with metastatic CRPC who had received prior docetaxel chemotherapy. Patients were not eligible if AST and/or ALT  $\geq 2.5$  XULN in the absence of liver metastases. Patients with liver metastases were excluded if AST and/or ALT  $>5$ X ULN.

Table 1 shows adverse reactions on the ZYTIGA arm in Study 1 that occurred with a  $\geq 2\%$  absolute increase in frequency compared to placebo or were events of special interest. The median duration of treatment with ZYTIGA was 8 months.

**Table 1: Adverse Reactions due to ZYTIGA in Study 1**

| System/Organ Class<br>Adverse reaction                 | ZYTIGA with Prednisone<br>(N=791) |                | Placebo with Prednisone<br>(N=394) |                |
|--|-----------------------------------|----------------|------------------------------------|----------------|
|  | All Grades <sup>1</sup><br>%      | Grade 3-4<br>% | All Grades<br>%                    | Grade 3-4<br>% |
| <b>Musculoskeletal and connective tissue disorders</b> |                                   |                |                                    |                |
| Joint swelling/discomfort <sup>2</sup>                 | 29.5                              | 4.2            | 23.4                               | 4.1            |
| Muscle discomfort <sup>3</sup>                         | 26.2                              | 3.0            | 23.1                               | 2.3            |
| <b>General disorders</b>                               |                                   |                |                                    |                |
| Edema <sup>4</sup>                                     | 26.7                              | 1.9            | 18.3                               | 0.8            |
| <b>Vascular disorders</b>                              |                                   |                |                                    |                |
| Hot flush  | 19.0                              | 0.3            | 16.8                               | 0.3            |
| Hypertension   | 8.5                               | 1.3            | 6.9                                | 0.3            |
| <b>Gastrointestinal disorders</b>                      |                                   |                |                                    |                |
| Diarrhea   | 17.6                              | 0.6            | 13.5                               | 1.3            |
| Dyspepsia  | 6.1                               | 0              | 3.3                                | 0              |
| <b>Infections and infestations</b>                     |                                   |                |                                    |                |
| Urinary tract infection                                | 11.5                              | 2.1            | 7.1                                | 0.5            |
| Upper respiratory tract infection                      | 5.4                               | 0              | 2.5                                | 0              |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                   |                |                                    |                |
| Cough  | 10.6                              | 0              | 7.6                                | 0              |
| <b>Renal and urinary disorders</b>                     |                                   |                |                                    |                |
| Urinary frequency                                      | 7.2                               | 0.3            | 5.1                                | 0.3            |
| Nocturia   | 6.2                               | 0              | 4.1                                | 0              |
| <b>Injury, poisoning and procedural complications</b>  |                                   |                |                                    |                |
| Fractures <sup>5</sup>                                 | 5.9                               | 1.4            | 2.3                                | 0              |
| <b>Cardiac disorders</b>                               |                                   |                |                                    |                |
| Arrhythmia <sup>6</sup>                                | 7.2                               | 1.1            | 4.6                                | 1.0            |
| Chest pain or chest discomfort <sup>7</sup>            | 3.8                               | 0.5            | 2.8                                | 0              |
| Cardiac failure <sup>8</sup>                           | 2.3                               | 1.9            | 1.0                                | 0.3            |

<sup>1</sup> Adverse events graded according to CTCAE version 3.0

<sup>2</sup> Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

<sup>3</sup> Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal stiffness

<sup>4</sup> Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema

<sup>5</sup> Includes all fractures with the exception of pathological fracture

<sup>6</sup> Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

<sup>7</sup> 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).

<sup>8</sup> Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased

Table 2 shows laboratory abnormalities of interest from Study 1. Grade 3-4 low serum phosphorus (7%) and low potassium (5%) occurred at a greater than or equal to 5% rate in the ZYTIGA arm.

**Table 2: Laboratory Abnormalities of Interest in Study 1**

| Laboratory Abnormality | Abiraterone (N=791) |               | Placebo (N=394) |               |
|------------------------|---------------------|---------------|-----------------|---------------|
|                        | All Grades (%)      | Grade 3-4 (%) | All Grades (%)  | Grade 3-4 (%) |
| Hypertriglyceridemia   | 62.5                | 0.4           | 53.0            | 0             |
| High AST               | 30.6                | 2.1           | 36.3            | 1.5           |
| Hypokalemia            | 28.3                | 5.3           | 19.8            | 1.0           |
| Hypophosphatemia       | 23.8                | 7.2           | 15.7            | 5.8           |
| High ALT               | 11.1                | 1.4           | 10.4            | 0.8           |
| High Total Bilirubin   | 6.6                 | 0.1           | 4.6             | 0             |

**Study 2: Metastatic CRPC Prior to Chemotherapy**

Study 2 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT  $\geq 2.5X$  ULN and patients were excluded if they had liver metastases.

Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a  $\geq 2\%$  absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

**Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2**

| System/Organ Class<br>Adverse reaction                 | ZYTIGA with Prednisone (N=542) |                | Placebo with Prednisone (N=540) |                |
|--|--------------------------------|----------------|---------------------------------|----------------|
|  | All Grades <sup>1</sup><br>%   | Grade 3-4<br>% | All Grades<br>%                 | Grade 3-4<br>% |
| <b>General disorders</b>                               |                                |                |                                 |                |
| Fatigue  | 39.1                           | 2.2            | 34.3                            | 1.7            |
| Edema <sup>2</sup>                                     | 25.1                           | 0.4            | 20.7                            | 1.1            |
| Pyrexia  | 8.7                            | 0.6            | 5.9                             | 0.2            |
| <b>Musculoskeletal and connective tissue disorders</b> |                                |                |                                 |                |
| Joint swelling/discomfort <sup>3</sup>                 | 30.3                           | 2.0            | 25.2                            | 2.0            |
| Groin pain   | 6.6                            | 0.4            | 4.1                             | 0.7            |
| <b>Gastrointestinal disorders</b>                      |                                |                |                                 |                |
| Constipation   | 23.1                           | 0.4            | 19.1                            | 0.6            |
| Diarrhea   | 21.6                           | 0.9            | 17.8                            | 0.9            |
| Dyspepsia  | 11.1                           | 0.0            | 5.0                             | 0.2            |
| <b>Vascular disorders</b>                              |                                |                |                                 |                |
| Hot flush  | 22.3                           | 0.2            | 18.1                            | 0.0            |
| Hypertension   | 21.6                           | 3.9            | 13.1                            | 3.0            |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                                |                |                                 |                |
| Cough  | 17.3                           | 0.0            | 13.5                            | 0.2            |
| Dyspnea  | 11.8                           | 2.4            | 9.6                             | 0.9            |
| <b>Psychiatric disorders</b>                           |                                |                |                                 |                |
| Insomnia   | 13.5                           | 0.2            | 11.3                            | 0.0            |
| <b>Injury, poisoning and procedural complications</b>  |                                |                |                                 |                |
| Contusion  | 13.3                           | 0.0            | 9.1                             | 0.0            |
| Falls  | 5.9                            | 0.0            | 3.3                             | 0.0            |
| <b>Infections and infestations</b>                     |                                |                |                                 |                |
| Upper respiratory tract infection                      | 12.7                           | 0.0            | 8.0                             | 0.0            |
| Nasopharyngitis  | 10.7                           | 0.0            | 8.1                             | 0.0            |
| <b>Renal and urinary disorders</b>                     |                                |                |                                 |                |
| Hematuria  | 10.3                           | 1.3            | 5.6                             | 0.6            |
| <b>Skin and subcutaneous tissue disorders</b>          |                                |                |                                 |                |
| Rash   | 8.1                            | 0.0            | 3.7                             | 0.0            |

<sup>1</sup> Adverse events graded according to CTCAE version 3.0

<sup>2</sup> Includes terms Edema peripheral, Pitting edema, and Generalized edema

<sup>3</sup> Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

Table 4 shows laboratory abnormalities that occurred in greater than 15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebo in Study 2. Grade 3-4 lymphopenia (9%), hyperglycemia (7%) and high alanine aminotransferase (6%) occurred at a greater than 5% rate in the ZYTIGA arm.

**Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of Study 2**

| Laboratory Abnormality     | Abiraterone (N=542) |                | Placebo (N=540) |                |
|----------------------------|---------------------|----------------|-----------------|----------------|
|                            | Grade 1-4<br>%      | Grade 3-4<br>% | Grade 1-4<br>%  | Grade 3-4<br>% |
| Hematology                 |                     |                |                 |                |
| Lymphopenia                | 38.2                | 8.7            | 31.7            | 7.4            |
| Chemistry                  |                     |                |                 |                |
| Hyperglycemia <sup>1</sup> | 56.6                | 6.5            | 50.9            | 5.2            |
| High ALT                   | 41.9                | 6.1            | 29.1            | 0.7            |
| High AST                   | 37.3                | 3.1            | 28.7            | 1.1            |
| Hypernatremia              | 32.8                | 0.4            | 25.0            | 0.2            |
| Hypokalemia                | 17.2                | 2.8            | 10.2            | 1.7            |

<sup>1</sup>Based on non-fasting blood draws

### Cardiovascular Adverse Reactions:

In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.6% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

## 6.2 Post Marketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

*Respiratory, Thoracic and Mediastinal Disorders:* non-infectious pneumonitis.

## 7 DRUG INTERACTIONS

### 7.1 Drugs that Inhibit or Induce CYP3A4 Enzymes

Based on *in vitro* data, ZYTIGA is a substrate of CYP3A4.

In a dedicated 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 [*see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)*].

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 [*see Clinical Pharmacology (12.3)*].

## **7.2 Effects of Abiraterone on Drug Metabolizing Enzymes**

ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. In a CYP2D6 drug-drug interaction trial, the  $C_{max}$  and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP2D6 with a narrow therapeutic index (e.g., thioridazine). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP2D6 substrate drug [*see Clinical Pharmacology (12.3)*].

*In vitro*, ZYTIGA inhibits CYP2C8. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP2C8. However, patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

## **8 USE IN SPECIFIC POPULATIONS**

### **8.1 Pregnancy**

**Pregnancy Category X** [*see Contraindications (4.1)*].

ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP17 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses  $\geq 10$  mg/kg/day, decreased fetal ano-genital distance at  $\geq 30$  mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses  $\geq 10$  mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

### **8.3 Nursing Mothers**

ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

### **8.4 Pediatric Use**

Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

### **8.5 Geriatric Use**

Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

### **8.6 Patients with Hepatic Impairment**

The pharmacokinetics of abiraterone were examined in subjects with baseline mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by

approximately 7-fold and the fraction of free drug increased 2-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function.

No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. Do not use ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C). If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see *Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3)*].

For patients who develop hepatotoxicity during treatment, interruption of treatment and dosage adjustment may be required [see *Dosage and Administration (2.2)*, *Warnings and Precautions (5.3)*, and *Clinical Pharmacology (12.3)*].

## **8.7 Patients with Renal Impairment**

In a dedicated renal impairment trial, the mean PK parameters were comparable between healthy subjects with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8) after a single oral 1,000 mg dose of ZYTIGA. No dosage adjustment is necessary for patients with renal impairment [see *Dosage and Administration (2.1)* and *Clinical Pharmacology (12.3)*].

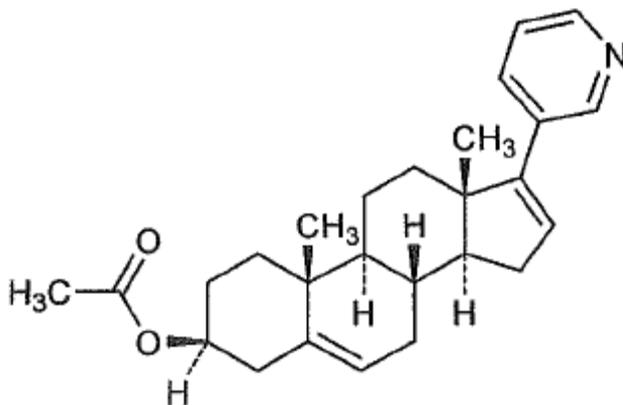
## **10 OVERDOSAGE**

Human experience of overdose with ZYTIGA is limited.

There is no specific antidote. In the event of an overdose, stop ZYTIGA, undertake general supportive measures, including monitoring for arrhythmias and cardiac failure and assess liver function.

## **11 DESCRIPTION**

Abiraterone acetate, the active ingredient of ZYTIGA is the acetyl ester of abiraterone. Abiraterone is an inhibitor of CYP17 (17 $\alpha$ -hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3 $\beta$ )-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is:



Abiraterone acetate is a white to off-white, non-hygroscopic, crystalline powder. Its molecular formula is  $C_{26}H_{33}NO_2$  and it has a molecular weight of 391.55. Abiraterone acetate is a lipophilic compound with an octanol-water partition coefficient of 5.12 (Log P) and is practically insoluble in water. The pKa of the aromatic nitrogen is 5.19.

Inactive ingredients in the tablets are colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits 17 $\alpha$ -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis.

CYP17 catalyzes two sequential reactions: 1) the conversion of pregnenolone and progesterone to their 17 $\alpha$ -hydroxy derivatives by 17 $\alpha$ -hydroxylase activity and 2) the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively, by C17, 20 lyase activity. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals [see *Warnings and Precautions (5.1)*].

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor.

ZYTIGA decreased serum testosterone and other androgens in patients in the placebo-controlled phase 3 clinical trial. It is not necessary to monitor the effect of ZYTIGA on serum testosterone levels.

Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

### 12.3 Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects and in patients with metastatic castration-resistant prostate cancer (CRPC). *In vivo*, abiraterone acetate is converted to abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (<0.2 ng/mL) in >99% of the analyzed samples.

#### Absorption

Following oral administration of abiraterone acetate to patients with metastatic CRPC, the median time to reach maximum plasma abiraterone concentrations is 2 hours. Abiraterone accumulation is observed at steady-state, with a 2-fold higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

At the dose of 1,000 mg daily in patients with metastatic CRPC, steady-state values (mean  $\pm$  SD) of  $C_{\max}$  were  $226 \pm 178$  ng/mL and of AUC were  $993 \pm 639$  ng.hr/mL. No major deviation from dose proportionality was observed in the dose range of 250 mg to 1,000 mg. However, the exposure was not significantly increased when the dose was doubled from 1,000 to 2,000 mg (8% increase in the mean AUC).

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone  $C_{\max}$  and  $AUC_{0-\infty}$  were approximately 7- and 5-fold higher, respectively, when abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in increased and highly variable exposures. Therefore, 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 [*see Dosage and Administration (2.1)*].

## **Distribution and Protein Binding**

Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean  $\pm$  SD) is  $19,669 \pm 13,358$  L. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp) and that abiraterone acetate is an inhibitor of P-gp. No studies have been conducted with other transporter proteins.

## **Metabolism**

Following oral administration of  $^{14}\text{C}$ -abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone (active metabolite). The conversion is likely through esterase activity (the esterases have not been identified) and is not CYP mediated. The two main circulating metabolites of abiraterone in human plasma are abiraterone sulphate (inactive) and N-oxide abiraterone sulphate (inactive), which account for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate.

## **Excretion**

In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean  $\pm$  SD) is  $12 \pm 5$  hours. Following oral administration of  $^{14}\text{C}$ -abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

## **Patients with Hepatic Impairment**

The pharmacokinetics of abiraterone was examined in subjects with baseline mild (n=8) or moderate (n=8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. Systemic exposure to abiraterone after a single oral 1,000 mg dose given under fasting conditions increased approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with baseline severe (n=8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone increased by approximately 7-fold in subjects with severe baseline hepatic impairment compared to subjects with normal hepatic function. In addition, the mean protein binding was found to be

lower in the severe hepatic impairment group compared to the normal hepatic function group, which resulted in a two-fold increase in the fraction of free drug in patients with severe hepatic impairment [see *Dosage and Administration (2.2)* and *Use in Specific Populations (8.6)*].

### **Patients with Renal Impairment**

The pharmacokinetics of abiraterone were examined in patients with end-stage renal disease (ESRD) on a stable hemodialysis schedule (N=8) and in matched control subjects with normal renal function (N=8). In the ESRD cohort of the trial, a single 1,000 mg ZYTIGA dose was given under fasting conditions 1 hour after dialysis, and samples for pharmacokinetic analysis were collected up to 96 hours post dose. Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis, compared to subjects with normal renal function [see *Use in Specific Populations (8.7)*].

### **Drug Interactions**

*In vitro* studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

In an *in vivo* drug-drug interaction trial, the  $C_{max}$  and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextromethorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold [see *Drug Interactions (7.2)*].

In a clinical study to determine the effects of abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) on a single 100 mg dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

Abiraterone is a substrate of CYP3A4, *in vitro*. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1,000 mg, the mean plasma  $AUC_{\infty}$  of abiraterone was decreased by 55% [see *Drug Interactions (7.1)*].

In a separate clinical pharmacokinetic interaction study of healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone [see *Drug Interactions (7.1)*].

## 12.6 QT Prolongation

In a multi-center, open-label, single-arm trial, 33 patients with metastatic CRPC received ZYTIGA orally at a dose of 1,000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline. However, small increases in the QTc interval (i.e., <10 ms) due to abiraterone acetate cannot be excluded due to study design limitations.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

A two-year carcinogenicity study was conducted in rats at oral abiraterone acetate doses of 5, 15, and 50 mg/kg/day for males and 15, 50, and 150 mg/kg/day for females. Abiraterone acetate increased the combined incidence of interstitial cell adenomas and carcinomas in the testes at all dose levels tested. This finding is considered to be related to the pharmacological activity of abiraterone. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Abiraterone acetate was not carcinogenic in female rats at exposure levels up to 0.8 times the human clinical exposure based on AUC. Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse.

Abiraterone acetate and abiraterone did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in both the *in vitro* cytogenetic assay using primary human lymphocytes and in the *in vivo* rat micronucleus assay.

ZYTIGA has the potential to impair reproductive function and fertility in humans based on findings in animals. In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at  $\geq 50$  mg/kg/day in rats and  $\geq 250$  mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone [see *Nonclinical Toxicology (13.2)*]. These effects were observed in rats at systemic exposures similar to humans and in monkeys at exposures approximately 0.6 times the AUC in humans.

In fertility studies in rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in males dosed for 4 weeks at  $\geq 30$  mg/kg/day. Mating of untreated females with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Effects on male rats were reversible after 16 weeks from the last abiraterone acetate administration.

Female rats dosed for 2 weeks until day 7 of pregnancy at  $\geq 30$  mg/kg/day had an increased incidence of irregular or extended estrous cycles and pre-implantation loss (300 mg/kg/day). There were no differences in mating, fertility, and litter parameters in female rats that received abiraterone acetate. Effects on female rats were reversible after 4 weeks from the last abiraterone acetate administration. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended dose of 1,000 mg/day based on body surface area.

### **13.2 Animal Toxicology and/or Pharmacology**

In 13- and 26-week studies in rats and 13- and 39-week studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone acetate at approximately one half the human clinical exposure based on AUC. As a result, decreases in organ weights and toxicities were observed in the male and female reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. The changes in the reproductive organs are consistent with the antiandrogenic pharmacological activity of abiraterone acetate. A dose-dependent increase in cataracts was observed in rats at 26 weeks starting at  $\geq 50$  mg/kg/day (similar to the human clinical exposure based on AUC). In the 39-week monkey study, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC). All other toxicities associated with abiraterone acetate reversed or were partially resolved after a 4-week recovery period.

## **14 CLINICAL STUDIES**

The efficacy and safety of ZYTIGA in patients with metastatic castration-resistant prostate cancer (CRPC) that has progressed on androgen deprivation therapy was demonstrated in two randomized, placebo-controlled, multicenter phase 3 clinical trials. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or pituitary disorders were excluded from these trials.

### **Study 1**

#### **Patients with metastatic CRPC who had received prior docetaxel chemotherapy:**

A total of 1195 patients were randomized 2:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily in combination with prednisone 5 mg orally twice daily (N=797) or placebo once daily plus prednisone 5 mg orally twice daily (N=398). Patients randomized to either arm were to continue treatment until disease progression (defined as a 25% increase in PSA over the patient's baseline/nadir together with protocol-defined radiographic progression and symptomatic or clinical progression), initiation of new treatment, unacceptable toxicity or withdrawal.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 39-95) and the racial distribution was 93.3% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status score of 0-1 and 45% had a Brief Pain Inventory-Short Form score of  $\geq 4$  (patient's reported worst pain over the previous 24 hours). Ninety percent of patients had metastases in bone and 30% had visceral involvement. Seventy percent of patients had radiographic evidence of disease progression and 30% had PSA-only progression. Seventy percent of patients had previously received one cytotoxic chemotherapy regimen and 30% received two regimens.

The protocol pre-specified interim analysis was conducted after 552 deaths and showed a statistically significant improvement in overall survival in patients treated with ZYTIGA compared to patients in the placebo arm (Table 5 and Figure 1). An updated survival analysis was conducted when 775 deaths (97% of the planned number of deaths for final analysis) were observed. Results from this analysis were consistent with those from the interim analysis (Table 5).

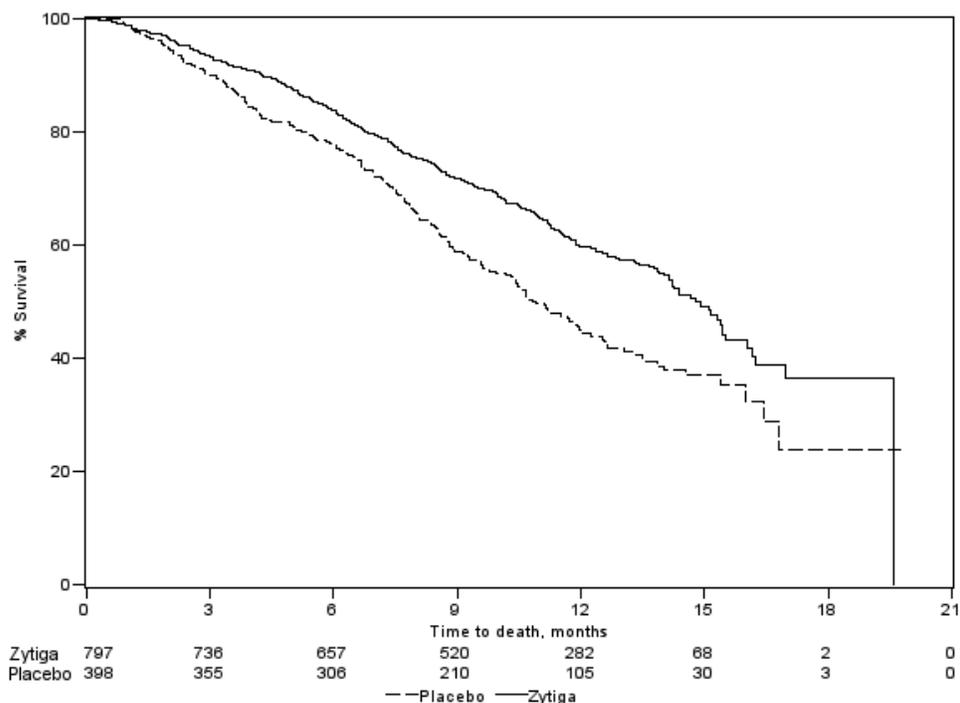
**Table 5: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)**

|                                      | <b>ZYTIGA<br/>(N=797)</b> | <b>Placebo<br/>(N=398)</b> |
|--------------------------------------|---------------------------|----------------------------|
| <b>Primary Survival Analysis</b>     |                           |                            |
| Deaths (%)                           | 333 (42%)                 | 219 (55%)                  |
| Median survival (months)<br>(95% CI) | 14.8 (14.1, 15.4)         | 10.9 (10.2, 12.0)          |
| p-value <sup>1</sup>                 | <0.0001                   |                            |
| Hazard ratio (95% CI) <sup>2</sup>   | 0.646 (0.543, 0.768)      |                            |
| <b>Updated Survival Analysis</b>     |                           |                            |
| Deaths (%)                           | 501 (63%)                 | 274 (69%)                  |
| Median survival (months)<br>(95% CI) | 15.8 (14.8, 17.0)         | 11.2 (10.4, 13.1)          |
| Hazard ratio (95% CI) <sup>2</sup>   | 0.740 (0.638, 0.859)      |                            |

<sup>1</sup> P-value is derived from a log-rank test stratified by ECOG performance status score (0-1 vs. 2), pain score (absent vs. present), number of prior chemotherapy regimens (1 vs. 2), and type of disease progression (PSA only vs. radiographic).

<sup>2</sup> Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

**Figure 1: Kaplan-Meier Overall Survival Curves in Study 1 (Intent-to-Treat Analysis)**



## Study 2

### **Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy**

In Study 2, 1088 patients were randomized 1:1 to receive either ZYTIGA at a dose of 1,000 mg once daily (N=546) or Placebo once daily (N=542). Both arms were given concomitant prednisone 5 mg twice daily. Patients continued treatment until radiographic or clinical (cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to 3 or more) disease progression, unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

Patient demographics were balanced between the treatment arms. The median age was 70 years. The racial distribution of patients treated with ZYTIGA was 95.4% Caucasian, 2.8% Black, 0.7% Asian and 1.1% Other. The ECOG performance status was 0 for 76% of patients, and 1 for 24% of patients. Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). Baseline pain assessment was 0-1 (asymptomatic) in 66% of patients and 2-3 (mildly symptomatic) in 26% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

Radiographic progression-free survival was assessed with the use of sequential imaging studies and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Working Group 2 criteria) and/or modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria for progression of soft tissue lesions. Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

At the protocol pre-specified third interim analysis for overall survival, 37% (200 of 546) of patients treated with ZYTIGA, compared with 43% (234 of 542) of patients treated with placebo, had died. Overall survival was longer for ZYTIGA than placebo with a hazard ratio of 0.792 (95% CI: 0.655 - 0.956). The p-value was 0.0151 which did not meet the pre-specified value for statistical significance (Table 6 and Figure 2).

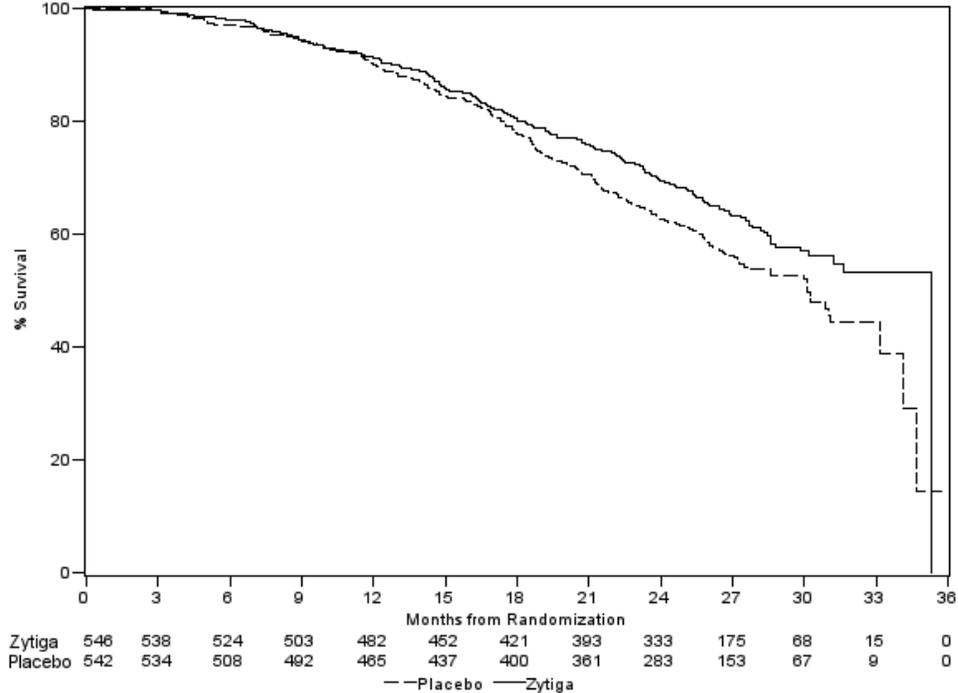
**Table 6: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)**

| Overall Survival                     | ZYTIGA<br>(N=546)      | Placebo<br>(N=542)     |
|--------------------------------------|------------------------|------------------------|
| Deaths                               | 200 (37%)              | 234 (43%)              |
| Median survival (months)<br>(95% CI) | 35.3<br>(31.24, 35.29) | 30.1<br>(27.30, 34.10) |
| p-value <sup>1</sup>                 | 0.0151                 |                        |
| Hazard ratio <sup>2</sup> (95% CI)   | 0.792 (0.655, 0.956)   |                        |

<sup>1</sup> P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

<sup>2</sup> Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

**Figure 2 – Kaplan Meier Overall Survival Curves in Study 2 (Intent-to-Treat analysis)**



At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA and 251 (46%) patients treated with placebo had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 7 and Figure 3).

**Table 7: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)**

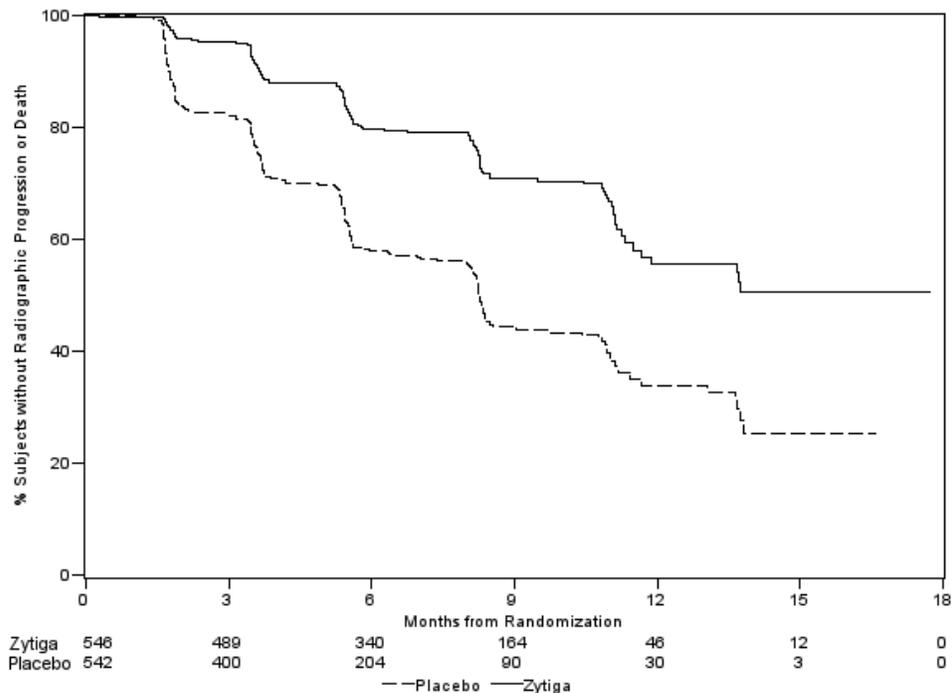
| Radiographic Progression-free Survival | ZYTIGA<br>(N=546)    | Placebo<br>(N=542)   |
|--|----------------------|----------------------|
| Progression or death                   | 150 (28%)            | 251 (46%)            |
| Median rPFS (months)<br>(95% CI)       | NR<br>(11.66, NR)    | 8.28<br>(8.12, 8.54) |
| p-value <sup>1</sup>                   | <0.0001              |                      |
| Hazard ratio <sup>2</sup> (95% CI)     | 0.425 (0.347, 0.522) |                      |

NR=Not reached

<sup>1</sup> P-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).

<sup>2</sup> Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA

**Figure 3 – Kaplan Meier Curves of Radiographic Progression-free Survival in Study 2 (Intent-to-Treat Analysis)**



The primary efficacy analyses are supported by the following prospectively defined endpoints. The median time to initiation of cytotoxic chemotherapy was 25.2 months for patients receiving ZYTIGA and 16.8 months for patients receiving placebo (HR=0.580; 95% CI: [0.487, 0.691], p<0.0001).

The median time to opiate use for prostate cancer pain was not reached for patients receiving ZYTIGA and was 23.7 months for patients receiving placebo (HR=0.686; 95% CI: [0.566, 0.833], p=0.0001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.

## 16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA (abiraterone acetate) 250 mg tablets are white to off-white, oval tablets debossed with AA250 on one side. ZYTIGA 250 mg tablets are available in high-density polyethylene bottles of 120 tablets.

NDC Number 57894-150-12

### Storage and Handling

Store at 20°C to 25°C (68°F to 77°F); excursions permitted in the range from 15°C to 30°C (59°F to 86°F) [see USP controlled room temperature].

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Therefore, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves [see Use in Specific Populations (8.1)].

## 17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling (Patient Information)

- Patients should be informed that ZYTIGA and prednisone are used together and that they should not interrupt or stop either of these medications without consulting their physician.
- Patients receiving GnRH agonists should be informed that they need to maintain this treatment during the course of treatment with ZYTIGA and prednisone.
- Patients should be informed that ZYTIGA must not be taken with food and that 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. They should be informed that the tablets should be swallowed whole with water without crushing or chewing. Patients should be informed that taking ZYTIGA with food causes increased exposure and this may result in adverse reactions.
- Patients should be informed that ZYTIGA is taken once daily and prednisone is taken twice daily according to their physician's instructions.
- Patients should be informed that in the event of a missed daily dose of ZYTIGA or prednisone, they should take their normal dose the following day. If more than one daily dose is skipped, patients should be told to inform their physician.

- Patients should be apprised of the common side effects associated with ZYTIGA, including peripheral edema, hypokalemia, hypertension, elevated liver function tests, and urinary tract infection. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.
- Patients should be advised that their liver function will be monitored using blood tests.
- Patients should be informed that ZYTIGA may harm a developing fetus; thus, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves. Patients should also be informed that it is not known whether abiraterone or its metabolites are present in semen and they should use a condom if having sex with a pregnant woman. The patient should use a condom and another effective method of birth control if he is having sex with a woman of child-bearing potential. These measures are required during and for one week after treatment with ZYTIGA.

**Manufactured by:**

Patheon Inc.

Mississauga, Canada

**Manufactured for:**

Janssen Biotech, Inc.

Horsham, PA 19044

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**PATIENT INFORMATION**  
**ZYTIGA® (Zye-tee-ga)**  
**(abiraterone acetate)**  
**Tablets**

Read this Patient Information that comes with ZYTIGA before you start taking it and each time you get a refill. There may be new information. This information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

**What is ZYTIGA?**

ZYTIGA is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has spread to other parts of the body.

ZYTIGA is not for use in women.

It is not known if ZYTIGA is safe or effective in children.

**Who should not take ZYTIGA?**

Do not take ZYTIGA if you are pregnant or may become pregnant. ZYTIGA may harm your unborn baby.

Women who are pregnant or who may become pregnant should not touch ZYTIGA without protection, such as gloves.

**What should I tell my healthcare provider before taking ZYTIGA?**

**Before you take ZYTIGA, tell your healthcare provider if you:**

- have heart problems
- have liver problems
- have a history of adrenal problems
- have a history of pituitary problems
- have any other medical conditions
- plan to become pregnant. See “Who should not take ZYTIGA?”
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breast milk. You and your healthcare provider should decide if you will take ZYTIGA or breastfeed. You should not do both. See “Who should not take ZYTIGA?”

**Tell your healthcare provider about all the medicines you take**, including prescription and non-prescription medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed ZYTIGA.

Know the medicines you take. Keep a list of them with you to show to your healthcare provider and pharmacist when you get a new medicine.

### **How should I take ZYTIGA?**

- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA one time a day.
- Your healthcare provider may change your dose if needed.
- Do not stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA on an empty stomach. **Do not take ZYTIGA with food.** Taking ZYTIGA with food may cause more of the medicine to be absorbed by the body than is needed and this may cause side effects.
- No food should be eaten 2 hours before and 1 hour after taking ZYTIGA.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- Men who are sexually active with a pregnant woman must use a condom during and for one week after treatment with ZYTIGA. If their sexual partner may become pregnant, a condom and another form of birth control must be used during and for one week after treatment with ZYTIGA. Talk with your healthcare provider if you have questions about birth control.
- If you miss a dose of ZYTIGA or prednisone, take your prescribed dose the following day. If you miss more than 1 dose, tell your healthcare provider right away.
- Your healthcare provider will do blood tests to check for side effects.

### **What are the possible side effects of ZYTIGA?**

**ZYTIGA may cause serious side effects including:**

- **High blood pressure (hypertension), low blood potassium levels (hypokalemia) and fluid retention (edema).** Tell your healthcare provider if you get any of the following symptoms:
  - dizziness
  - fast heartbeats
  - feel faint or lightheaded
  - headache
  - confusion
  - muscle weakness
  - pain in your legs
  - swelling in your legs or feet

- **Adrenal problems** may happen if you stop taking prednisone, get an infection, or are under stress.
- **Liver problems.** You may develop changes in liver function blood test. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA.

The most common side effects of ZYTIGA include:

- weakness
- joint swelling or pain
- swelling in your legs or feet
- hot flushes
- diarrhea
- vomiting
- cough
- high blood pressure
- shortness of breath
- urinary tract infection
- bruising
- low red blood cells (anemia) and low blood potassium levels
- high blood sugar levels, high blood cholesterol and triglycerides
- certain other abnormal blood tests

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ZYTIGA. For more information, ask your healthcare provider or pharmacist.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

### **How should I store ZYTIGA?**

- Store ZYTIGA at 59°F to 86°F (15°C to 30°C).

**Keep ZYTIGA and all medicines out of the reach of children.**

### **General information about ZYTIGA.**

Medicines are sometimes prescribed for purposes other than those listed in a patient information leaflet. Do not use ZYTIGA for a condition for which it was not prescribed. Do not give your ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

This leaflet summarizes the most important information about ZYTIGA. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for healthcare professionals.

For more information contact Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or [www.Zytiga.com](http://www.Zytiga.com).

**What are the ingredients of ZYTIGA?**

Active ingredient: abiraterone acetate

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

This Patient Information has been approved by the U.S. Food and Drug Administration.

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