ZYTIGA® (abiraterone acetate) Tablets

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 (CRPC), (1)
- Metastatic high-risk castration-sensitive prostate cancer (CSPC). (1)

2 DOSAGE AND ADMINISTRATION

- Metastatic castration-resistant prostate cancer:
  - ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally twice daily. (2.1)
  - ZYTIGA 1,000 mg orally once daily with prednisone 5 mg orally once daily. (2.2)

Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

- ZYTIGA tablets must be taken as a single dose once daily on an empty stomach. Do not eat food 2 hours before and 1 hour after taking ZYTIGA. The tablets must be swallowed whole with water. Do not crush or chew tablets. (2.3)

Dose Modification:

- For patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the ZYTIGA starting dose to 250 mg once daily. (2.4)
- 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. (2.4)

3 DOSAGE FORMS AND STRENGTHS

- Film-Coated Tablet 500 mg (3)
- Uncoated Tablet 250 mg (3)

4 CONTRAINDICATIONS


5 WARNINGS AND PRECAUTIONS

- Embryo-Fetal Toxicity: ZYTIGA can cause fetal harm. Advise males with female partners of reproductive potential to use effective contraception. (5.5, 8.1, 8.3)
- Hypoglycemia: Severe hypoglycemia has been reported in patients with pre-existing diabetes who are taking medications containing thiazolidinediones (including pioglitazone) or repaglinide. Monitor blood glucose in patients with diabetes and assess if antidiabetic agent dose modifications are required. (5.6)

6 ADVERSE REACTIONS

The most common adverse reactions (≥10%) are fatigue, arthralgia, hypertension, nausea, edema, hypokalemia, hot flush, diarrhea, vomiting, upper respiratory infection, cough, and headache. (6.1)

7 DRUG INTERACTIONS

- 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)

8 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: 8/2021
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE
ZYTGIA® (abiraterone acetate) Tablets are indicated in combination with prednisone for the treatment of patients with:
- Metastatic castration-resistant prostate cancer (CRPC)
- Metastatic high-risk castration-sensitive prostate cancer (CSPC)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage for Metastatic CRPC
The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg orally twice daily.

2.2 Recommended Dose for Metastatic High-risk CSPC
The recommended dose of ZYTIGA is 1,000 mg (two 500 mg tablets or four 250 mg tablets) orally once daily with prednisone 5 mg administered orally once daily.

2.3 Important Administration Instructions
Patients receiving ZYTIGA should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchietomy.

ZYTGIA tablets must be taken as a single dose once daily on an empty stomach. Do not eat food 2 hours before and 1 hour after taking ZYTIGA. The tablets must be swallowed whole with water. Do not crush or chew tablets.

2.4 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. 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 5 x upper limit of normal (ULN) or total bilirubin greater than 3 x 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 5 x ULN or total bilirubin greater than 3 x 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 ALT and AST less than or equal to 2.5 x ULN and total bilirubin less than or equal to 1.5 x 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 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN. If hepatotoxicity recurs at the reduced dose of 500 mg once daily, discontinue treatment with ZYTIGA.

Permanently discontinue ZYTIGA for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation [see Warnings and Precautions (5.3)].

2.5 Dose Modification Guidelines for Strong CYP3A4 Inducers
Avoid concomitant strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) during ZYTIGA treatment. 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
Tablets (500 mg): purple, oval-shaped, film-coated tablets debossed with “AA” one side and “500” on the other side.
Tablets (250 mg): white to off-white, oval-shaped tablets debossed with “AA250” on one side.

4 CONTRAINDICATIONS
None.

5 WARNINGS AND PRECAUTIONS
5.1 Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions due to Mineralocorticoid Excess
ZYTGIA may cause hypokalemia, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition [see Clinical Pharmacology (12.1)]. 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
Adrenocortical insufficiency occurred in 0.3% of 2230 patients taking ZYTIGA and in 0.1% of 1763 patients taking placebo in the combined data of the 5 randomized, placebo-controlled, clinical trials. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone, following interruption of daily steroids and/or with concurrent infection or stress.

Monitor patients for symptoms and signs of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience stress, unusual stress, or inpatients treated with ZYTIGA. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosages of corticosteroids may be indicated before, during and after stressful situations [see Warnings and Precautions (5.1)].

5.3 Hepatotoxicity
In postmarketing experience, there have been ZYTIGA-associated severe hepatic toxicities, including fulminant hepatitis, acute liver failure and deaths [see Adverse Reactions (6.2)].

In the combined data of 5 randomized clinical trials, grade 3-4 ALT or AST increases (at least 5 x ULN) were reported in 6% of 2220 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 ALT and AST increases or abnormal hepatic function occurred in 1.1% of 2220 patients taking ZYTIGA. In these clinical trials, 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 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. Promptly measure serum total bilirubin, ALT, and AST 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 2.5 x ULN and total bilirubin less than or equal to 1.5 x ULN [see Dosage and Administration (2.4)].

Continually DISCONTINUE ZYTIGA for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation [see Dosage and Administration (2.4)].

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

5.4 Increased Fractures and Mortality in Combination with Radium Ra 223 Dichloride
ZYTGIA plus prednisone/prednisolone is not recommended for use in combination with radium Ra 223 dichloride outside of clinical trials.

The clinical efficacy and safety of concurrent initiation of ZYTIGA plus prednisone/prednisolone and radium Ra 223 dichloride was assessed in a randomized, placebo-controlled multicenter study (ERA-223 trial) in 806 patients with asymptomatic or mildly symptomatic castration-resistant prostate cancer with bone metastases. The study was unblinded early based on an Independent Data Monitoring Committee recommendation.
5.5 Embryo-Fetal Toxicity

The safety and efficacy of ZYTIGA have not been established in females. Based on animal reproduction studies and mechanism of action, ZYTIGA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose. Advise male partners of reproductive potential to use effective contraception during treatment with ZYTIGA and for 3 weeks after the last dose of ZYTIGA [see Use in Specific Populations (8.1, 8.3)]. ZYTIGA should not be handled by females who are or may become pregnant [see How Supplied/Storage and Handling (16)].

5.6 Hypoglycemia

Severe hypoglycemia has been reported when ZYTIGA was administered to patients with pre-existing diabetes receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide [see Drug Interactions (7.2)]. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with ZYTIGA. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

6 ADVERSE REACTIONS

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

- Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions 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 Fractures and Mortality in Combination with Radium Ra 223 Dichloride [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 (COU-AA-301 and COU-AA-302) enrolled patients who had metastatic CRPC in which ZYTIGA was administered orally 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 patients on the control arm. A third randomized placebo-controlled, multicenter clinical trial (LATITUDE) enrolled patients who had metastatic high-risk CRPC in which ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg once daily. Placebos were administered to patients in the control arm. Additionally, two other randomized, placebo-controlled trials were conducted in patients with metastatic CRPC. The safety data pooled from 2320 patients in the 5 randomized, controlled trials constitute the basis for the data presented in the Warnings and Precautions, Grade 1-4 adverse reactions, and Grade 1-4 laboratory abnormalities. In all trials, a gonadotropin-releasing hormone (GnRH) analog or prior orchietomy was required in both arms.

In the pooled data, median treatment duration was 11 months (0.1, 43) for ZYTIGA-treated patients and 7.2 months (0.1, 43) for placebo-treated patients. The most common adverse reactions (>1%) observed in clinical trials of ZYTIGA included:

- Fatigue
- Asthenia
- Depression
- Insomnia
- Anorexia
- Cough
- Diarrhea
- Vomiting
- Upper respiratory infection
- Headache

6.2 Laboratory Abnormalities

The most common laboratory abnormalities (>20%) that occurred more commonly in ZYTIGA-treated patients and >2% in placebo-treated patients were:

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYTIGA arm (1.3% vs. 1.1% respectively).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>8.5% (1.3% vs 6.9%)</td>
</tr>
<tr>
<td>Hypophysostasia</td>
<td>24% (7.2% vs 16%)</td>
</tr>
</tbody>
</table>
| Metastatic CRPC Prior to Chemotherapy

COU-AA-302 enrolled 1088 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT >2.5 x ULN and patients were excluded if they had liver metastases. Table 3 shows adverse reactions on the ZYTIGA arm in COU-AA-302 that occurred in ≥5% of patients with a ≥2% absolute increase in frequency compared to placebo. The median duration of treatment with ZYTIGA with prednisone was 13.8 months.

Table 1: Adverse Reactions due to ZYTIGA in COU-AA-301

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ZYTIGA with Prednisone (N=791)</th>
<th>Placebo with Prednisone (N=394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>30% (4.2) vs 23% (4.1)</td>
<td>26% (3.0) vs 23% (2.3)</td>
</tr>
<tr>
<td>General disorders</td>
<td>27% (1.9) vs 18% (0.8)</td>
<td>12% (2.1) vs 7% (0.5)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>19% (0.3) vs 17% (0.3)</td>
<td>8.5% (1.3) vs 6.9% (0.3)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>18% (0.6) vs 14% (1.3)</td>
<td>6.1% (0.3) vs 3.3% (0)</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>5.9% (1.4) vs 2.3% (0)</td>
<td>7.2% (1.1) vs 4.6% (1)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>3.8% (0.5) vs 2.8% (0)</td>
<td>2.3% (1.9) vs 1.0% (0.3)</td>
</tr>
<tr>
<td>Fractures</td>
<td>7 3.8 0.5 2.8 0</td>
<td>11 7.2 1.1 4.6 1.0</td>
</tr>
<tr>
<td>Chest pain or chest discomfort</td>
<td>3.8% (0.5) vs 2.8% (0)</td>
<td>2.3% (1.9) vs 1.0% (0.3)</td>
</tr>
</tbody>
</table>

1 Includes terms Arrhythmia, Atrial fibrillation, Supraventricular tachycardia, and Atrial flutter.
2 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema.
3 Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness.
4 Includes terms Edema, Edema peripheral, Pitting edema, and Generalized edema.
5 Includes all fractures with the exception of pathological fracture.
6 Includes terms Arrhythmia, Tachycardia, Atrial fibrillation, Supraventricular tachycardia, Atrial tachycardia, Ventricular tachycardia, Atrial flutter, Bradyca, Bradyarrhythmia.
7 Includes terms Angina pectoris, Chest pain, and Angina unstable.
8 Includes terms Cardiac failure, Cardiac failure congestive, Left ventricular dysfunction, Cardiogenic shock, Cardiomegaly, Cardiomyopathy, and Ejection fraction decreased.
ZYTIGA® (abiraterone acetate) Tablets

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in COU-AA-302

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Placebo with Prednisone (N=542)</th>
<th>ZYTIGA with Prednisone (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades¹</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>General disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>29</td>
<td>2.2</td>
</tr>
<tr>
<td>Edema</td>
<td>25</td>
<td>0.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8.7</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joint swelling/discomfort²</td>
<td>30</td>
<td>2.0</td>
</tr>
<tr>
<td>Grain pain</td>
<td>6.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>23</td>
<td>0.4</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22</td>
<td>0.9</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>11</td>
<td>0.0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>22</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22</td>
<td>3.9</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>17</td>
<td>0.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12</td>
<td>2.4</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>14</td>
<td>0.2</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contusion</td>
<td>13</td>
<td>0.0</td>
</tr>
<tr>
<td>Falls</td>
<td>5.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>13</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>11</td>
<td>0.0</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>10</td>
<td>1.3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8.1</td>
<td>0.0</td>
</tr>
</tbody>
</table>

¹Adverse events graded according to CTCAE version 3.0.
²Includes terms Edema peripheral, Pitting edema, and Generalized edema.
³Includes 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 placebos.

Table 4: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of COU-AA-302

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ZYTIGA with Prednisone (N=542)</th>
<th>Placebo with Prednisone (N=540)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>38</td>
<td>8.7</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia¹</td>
<td>57</td>
<td>6.5</td>
</tr>
<tr>
<td>High ALT</td>
<td>42</td>
<td>6.1</td>
</tr>
<tr>
<td>High AST</td>
<td>37</td>
<td>3.1</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>33</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>17</td>
<td>2.8</td>
</tr>
</tbody>
</table>

¹Based on non-fasting blood draws

LATITUDE: Patients with Metastatic High-risk CSPC

LATITUDE enrolled 1198 patients with newly-diagnosed metastatic, high-risk CSPC who had not received prior cytotoxic chemotherapy. Patients were ineligible if AST and/or ALT >2.5 x ULN or if they had liver metastases. All the patients received GnRH analogs or had prior bilateral orchiectomy during the trial. The median duration of treatment with ZYTIGA and prednisone was 24 months.

Table 5 shows adverse reactions on the ZYTIGA arm that occurred in ≥5% of patients with a ≥2% absolute increase in frequency compared to those on the placebo arm.

Table 5: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in LATITUDE

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Placebos (N=597)</th>
<th>ZYTIGA with Prednisone (N=597)</th>
<th>Placebos (N=602)</th>
<th>ZYTIGA with Prednisone (N=602)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades²</td>
<td>Grade 3-4</td>
<td>All Grades²</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>37</td>
<td>20</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Hot flush</td>
<td>15</td>
<td>0.0</td>
<td>13</td>
<td>0.2</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>20</td>
<td>10</td>
<td>3.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alanine aminotransferase increased²</td>
<td>16</td>
<td>5.5</td>
<td>13</td>
<td>1.3</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>15</td>
<td>4.4</td>
<td>11</td>
<td>1.5</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7.0</td>
<td>1.0</td>
<td>3.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>6.7</td>
<td>0.2</td>
<td>4.7</td>
<td>0.2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>7.5</td>
<td>0.3</td>
<td>5.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>6.5</td>
<td>0.0</td>
<td>3.2</td>
<td>0.0</td>
</tr>
</tbody>
</table>

²All patients were receiving an GnRH agonist or had undergone orchietomy.
²Adverse events graded according to CTCAE version 4.0
²Reported as an adverse event or reaction
⁴Including cough, productive cough, upper airway cough syndrome

Table 6 shows laboratory abnormalities that occurred in >15% of patients, and more frequently (>5%) in the ZYTIGA arm compared to placebos.

Table 6: Laboratory Abnormalities in >15% of Patients in the ZYTIGA Arm of LATITUDE

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>Placebos (N=602)</th>
<th>ZYTIGA with Prednisone (N=597)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>20</td>
<td>4.1</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>30</td>
<td>9.6</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>46</td>
<td>6.4</td>
</tr>
<tr>
<td>Elevated total bilirubin</td>
<td>16</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Cardiovascular Adverse Reactions

In the combined data of 5 randomized, placebo-controlled clinical studies, cardiac failure occurred more commonly in patients on the ZYTIGA arm compared to patients on the placebo arm (2.6% versus 0.9%). Grade 3-4 cardiac failure occurred in 1.3% of patients taking ZYTIGA and led to 5 treatment discontinuations and 4 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and two deaths due to cardiac failure in the placebo group.

In the same combined data, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and three patients with sudden death in the ZYTIGA arms and five deaths in the placebo arms. There were 7 (0.3%) deaths due to cardiorespiratory arrest in the ZYTIGA arms and 10 (1.7) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 3 deaths in the ZYTIGA arms.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of ZYTIGA with prednisone. 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.
Musculoskeletal and Connective Tissue Disorders: myopathy, including rhabdomyolysis.
Hepatobiliary Disorders: fulminant hepatitis, including acute hepatic failure and death.
Cardiac Disorders: QT prolongation and Torsades de Pointes (observed in patients who developed hypokalemia or had underlying cardiovascular conditions).
Immune System Disorders – Hypersensitivity: anaphylactic reactions (severe allergic reactions that include, but are not limited to difficulty swallowing or breathing, swollen face, lips, tongue or throat, or an itchy rash (urticaria)).
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 (2.5) 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 enzymes CYP2D6 and CYP2C8. In a CYP2D6 drug-drug interaction trial, the Cmax 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, consider a dose reduction of the concomitant CYP2D6 substrate drug [see Clinical Pharmacology (12.3)].

In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given together with a single dose of 1,000 mg abiraterone acetate. Therefore, patients should be monitored closely for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA [see Clinical Pharmacology (12.3) and Warnings and Precautions (5.6)].

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
The safety and efficacy of ZYTIGA have not been established in females. Based on findings from animal studies and the mechanism of action, ZYTIGA can cause fetal harm and potential loss of pregnancy.

There are no human data on the use of ZYTIGA in pregnant women. In animal reproduction studies, oral administration of abiraterone acetate to pregnant rats during organogenesis caused adverse developmental effects at maternal exposures approximately ≥ 0.03 times the human exposure (AUC) at the recommended dose (see Data).

Data
Animal Data
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 ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥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.

8.2 Lactation
Risk Summary
The safety and efficacy of ZYTIGA have not been established in females. There is no information available on the presence of abiraterone in human milk, or on the effects on the breastfed child or milk production.

8.3 Females and Males of Reproductive Potential
Contraception
Males
Based on findings in animal reproduction studies and its mechanism of action, 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 ≥10 mg/kg/day, decreased fetal ano-genital distance at ≥30 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day. Doses ≥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.

Female
Based on animal studies, ZYTIGA may impair reproductive function and fertility in males of reproductive potential [see Nonclinical Toxicology (13.1)].

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 randomized clinical trials, 70% of patients were 65 years and over and 27% 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 >5 x ULN or total bilirubin >3 x ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see Dosage and Administration (2.4) 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 (2.4), Warnings and Precautions (5.3), and Clinical Pharmacology (12.3)].

8.7 Patients with Renal Impairment
No dosage adjustment is necessary for patients with renal impairment [see 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 (17α-hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains either 250 mg or 500 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3β)-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 C22H27NO5 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.

ZYTIGA tablets are available in 500 mg film-coated tablets and 250 mg uncoated tablets with the following inactive ingredients:

- 500 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, silicified microcrystalline cellulose, and sodium lauryl sulfate. The coating, Opadry® II Purple, contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
- 250 mg uncoated tablets: 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 17α-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 17α-hydroxy derivatives by 17α-hydroxylase/C17,20-lyase 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 orchectomy, 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 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.

12.2 Pharmacodynamics
Cardiac Electrophysiology
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.

12.3 Pharmacokinetics
Following administration of abiraterone acetate, the pharmacokinetics of abiraterone have been studied in healthy subjects and in patients with metastatic 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 trough concentrations (mean ± SD) of Cmax were 226 ± 178 ng/mL and of AUC were 993 ± 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).

Effect of Food
Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. In healthy subjects abiraterone C max  and AUC 0- ∞  were higher exposure (steady-state AUC) compared to a single 1,000 mg dose of abiraterone acetate.

The C max  and AUC of dextromethorphan (CYP2D6 substrate) were increased 7- to 5-fold higher, respectively, when a single dose of abiraterone acetate was administered with a low-fat meal (7% fat, 300 calories) and approximately 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a high-fat (57% fat, 825 calories) meal compared to overnight fasting. Abiraterone AUC∞ was approximately 7-fold or 1.6-fold higher, respectively, when a single dose of abiraterone acetate was administered 2 hours after or 1 hour before a medium fat meal (25% fat, 493 calories) compared to overnight fasting.

Systemic exposures of abiraterone in patients with metastatic CRPC, after repeated dosing of abiraterone acetate were similar when abiraterone acetate was taken with low-fat meals for 7 days and increased approximately 2-fold when taken with high-fat meals for 7 days compared to when taken at least 2 hours after a meal and at least 1 hour before a meal for 7 days.

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.

Distribution
Abiraterone is highly bound (>99%) to the human plasma proteins, albumin and alpha-1 acid glycoprotein. The apparent steady-state volume of distribution (mean ± SD) is 13,669 ± 12,238 L.

Elimination
In patients with metastatic CRPC, the mean terminal half-life of abiraterone in plasma (mean ± SD) is 12 ± 5 hours.

Metabolism
Following oral administration of 14C-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 45% 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
Following oral administration of 14C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major components present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

ZYTIGA® (abiraterone acetate) Tablets
Specific Populations
Patients with Hepatic Impairment
The pharmacokinetics of abiraterone was examined in subjects with baseline severe (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 1.6-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.

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.

Drug Interaction Studies
Clinical Studies
Effect of Other Drugs on ZYTIGA
Strong CYP3A4 inducers: 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∞ of abiraterone was decreased by 55%.

Strong CYP3A4 inhibitors: Co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Effect of ZYTIGA on Other Drugs
CYP2D6 substrates: The Cmax 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). For dextromethorphan, the active metabolite of dextromethorphan, increased approximately 1.3 fold.

CYP1A2 substrates: When abiraterone acetate 1,000 mg daily (plus prednisone 5 mg twice daily) was given with a single dose of 100 mg theophylline (CYP1A2 substrate), no increase in systemic exposure of theophylline was observed.

CYP2C8 substrates: The AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given to healthy subjects with a single dose of 1,000 mg abiraterone acetate.

In Vitro Studies
Cytochrome P450 (CYP) Enzymes: Abiraterone is a substrate of CYP3A4 and has the potential to inhibit CYP1A2, CYP2D6, CYP2C8 and to a lesser extent CYP2C9, CYP2C19 and CYP3A4/5.

Transporter Systems: 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. In vitro, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter DAT1P1B1. There are no clinical data available to confirm transporter based interaction.

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 and mice were dosed for a longer period than humans to develop 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 were not mutagenic in an in vitro microbial mutagenesis (Ames) assay or clastogenic in an in vitro cytokentic assay using primary human lymphocytes or an in vivo rat micronucleus assay.
ZYTIGA® (abiraterone acetate) Tablets

In repeat-dose toxicity studies in male rats (13- and 26-weeks) and monkeys (39-weeks), atrophy, aspermatogenesis, and hyperplasia in the reproductive system were observed at ≥50 mg/kg/day in rats and ≥250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. 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 a fertility study in male rats, reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility were observed in animals dosed for 4 weeks at ≥30 mg/kg/day orally. Mating of untreated females with males that received 30 mg/kg/day oral 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.

In a fertility study in female rats, animals dosed orally for 2 weeks until day 7 of pregnancy at ≥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.

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.

13.2 Animal Toxicology and/or Pharmacology

A dose-dependent increase in cataracts was observed in rats after daily oral abiraterone acetate administration for 26 weeks starting at ≥50 mg/kg/day (similar to the human clinical exposure based on AUC). In a 39-week monkey study with daily oral abiraterone acetate administration, no cataracts were observed at higher doses (2 times greater than the clinical exposure based on AUC).

14 CLINICAL STUDIES

The efficacy and safety of ZYTIGA with prednisone was established in three randomized placebo-controlled international clinical studies. All patients in these studies received a GnRH analog or had prior bilateral orchiectomy. Patients with prior ketoconazole treatment for prostate cancer and a history of adrenal gland or systemic therapy were excluded. Patients with moderate or severe pain, or visceral organ metastases were excluded. Unacceptable toxicity or withdrawal. Patients with moderate or severe pain, opiate use for cancer pain, or visceral organ metastases were excluded.

COU-AA-301: Patients with metastatic CRPC who had received prior docetaxel chemotherapy

In COU-AA-301 (NCT00638690), 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% Caucasian, 3.6% Black, 1.7% Asian, and 1.6% Other. Eighty-nine percent of patients enrolled had an ECOG performance status of 0-1 and 45% had a Brief Pain Inventory-Short Form score of ≤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 352 deaths and showed a statistically significant improvement in overall survival (OS) in patients treated with ZYTIGA with prednisone compared to patients in the placebo with prednisone arm (Table 9 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 7).

<table>
<thead>
<tr>
<th>Primary Survival Analysis</th>
<th>ZYTIGA with Prednisone (N=797)</th>
<th>Placebo with Prednisone (N=398)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths (%)</td>
<td>333 (42%)</td>
<td>219 (55%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>14.8 (14.1, 15.4)</td>
<td>10.9 (10.2, 12.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.646 (0.543, 0.768)</td>
<td>0.740 (0.638, 0.859)</td>
</tr>
</tbody>
</table>

1 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).

2 Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

COU-AA-302: Patients with metastatic CRPC who had not received prior cytotoxic chemotherapy

In COU-AA-302 (NCT00887198), 1088 patients were randomized 1:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily (N=546) or Placebo orally 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% 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.
The planned final analysis for OS, conducted after 741 deaths (median follow up of 49 months) demonstrated a statistically significant OS improvement in patients treated with ZYTIGA with prednisone compared to those treated with placebo with prednisone (Table 8 and Figure 2). Sixty-five percent of patients on the ZYTIGA arm and 78% of patients on the placebo arm used subsequent therapies that may prolong OS in metastatic CRPC. ZYTIGA was used as a subsequent therapy in 13% of patients on the ZYTIGA arm and 44% of patients on the placebo arm.

Table 8: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th></th>
<th>ZYTIGA with Prednisone</th>
<th>Placebo with Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=546)</td>
<td>(N=542)</td>
<td></td>
</tr>
<tr>
<td>Deaths</td>
<td>354 (65%)</td>
<td>387 (71%)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>34.7 (32.7, 36.8)</td>
<td>30.3 (28.7, 33.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value¹</td>
<td>0.0033</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio²  (95% CI)</td>
<td>0.81 (0.70, 0.93)</td>
<td></td>
</tr>
</tbody>
</table>

¹ p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
² Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

Figure 2: Kaplan Meier Overall Survival Curves in COU-AA-302

At the pre-specified rPFS analysis, 150 (28%) patients treated with ZYTIGA with prednisone and 251 (46%) patients treated with placebo with prednisone had radiographic progression. A significant difference in rPFS between treatment groups was observed (Table 9 and Figure 3). Sixty-five percent of patients on the ZYTIGA arm and 44% of patients on the placebo arm used subsequent therapies that may prolong OS in metastatic CRPC. ZYTIGA was used as a subsequent therapy in 13% of patients on the ZYTIGA arm and 41% of patients on the placebo arm.

Table 9: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in COU-AA-302 (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th></th>
<th>ZYTIGA with Prednisone</th>
<th>Placebo with Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=546)</td>
<td>(N=542)</td>
<td></td>
</tr>
<tr>
<td>Progression or death</td>
<td>150 (28%)</td>
<td>251 (46%)</td>
</tr>
<tr>
<td>Median rPFS (months)</td>
<td>NR (NR)</td>
<td>28.2 (28.2, 33.3)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>p-value¹</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Hazard ratio²  (95% CI)</td>
<td>0.425 (0.347, 0.522)</td>
<td></td>
</tr>
</tbody>
</table>

¹ p-value is derived from a log-rank test stratified by ECOG performance status score (0 vs. 1).
² Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

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 in the ZYTIGA arm and 16.8 months for patients in the placebo arm (HR=0.590; 95% CI: [0.467, 0.681], 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=0.001). The time to opiate use result was supported by a delay in patient reported pain progression favoring the ZYTIGA arm.

LATITUDE: Patients with metastatic high-risk CSPC
In LATITUDE (NCT01715285), 1199 patients with metastatic high-risk CSPC were randomized 1:1 to receive either ZYTIGA orally at a dose of 1,000 mg once daily with prednisone 5 mg once daily (N=597) or placebo orally once daily (N=602). High-risk disease was defined as having at least two of three risk factors at baseline: a total Gleason score of ≥8, presence of ≥3 lesions on bone scan, and evidence of measurable visceral metastases. Patients with significant cardiac, adrenal, or hepatic dysfunction were excluded. Patients continued treatment until radiographic or clinical disease progression, unacceptable toxicity, withdrawal or death. Clinical progression was defined as the need for cytotoxic chemotherapy, radiation or surgical treatment for cancer, pain requiring chronic opioids, or ECOG performance status decline to ≥3.

Patient demographics were balanced between the treatment arms. The median age was 67 years among all randomized subjects. The racial distribution of patients treated with ZYTIGA was 69% Caucasian, 2.5% Black, 21% Asian, and 8.1% Other. The ECOG performance status was 0 for 55%, 1 for 42%, and 2 for 3.5% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 50% of patients, 2-3 (mildly symptomatic) in 23% of patients, and ≥4 in 28% of patients as defined by the Brief Pain Inventory-Short Form (worst pain over the last 24 hours).

A major efficacy outcome was overall survival. The pre-specified interim analysis after 406 deaths showed a statistically significant improvement in OS in patients on ZYTIGA with prednisone compared to those on placebo. Twenty-one percent of patients on the ZYTIGA arm and 41% of patients on the placebo arm received subsequent therapies that may prolong OS in metastatic CRPC. An updated survival analysis was conducted when 618 deaths were observed. The median follow-up time was 52 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 10 and Figure 4). At the updated analysis, 29% of patients on the ZYTIGA arm and 45% of patients on the placebo arm received subsequent therapies that may prolong OS in metastatic CRPC.
Table 10: Overall Survival of Patients Treated with Either ZYTIGA or Placebos in LATITUDE (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th></th>
<th>ZYTIGA with Prednisone (N=597)</th>
<th>Placebos (N=602)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>169 (28%)</td>
<td>237 (39%)</td>
</tr>
<tr>
<td>Median survival (months) (95% CI)</td>
<td>NE (NE, NE)</td>
<td>34.7 (33.1, NE)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;0.0001</td>
<td>0.62 (0.51, 0.76)</td>
</tr>
<tr>
<td>Updated Overall Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths (%)</td>
<td>275 (46%)</td>
<td>343 (57%)</td>
</tr>
<tr>
<td>Median survival (months) (95% CI)</td>
<td>53.3 (42.9, 55.7)</td>
<td>36.5 (33.5, 40.0)</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)&lt;sup&gt;2&lt;/sup&gt;</td>
<td>0.66 (0.56, 0.78)</td>
<td></td>
</tr>
</tbody>
</table>

NE = Not estimable

<sup>1</sup> This is based on the pre-specified interim analysis
<sup>2</sup> p-value is from log-rank test stratified by ECOG PS score (0/1 or 2) and visceral (absent or present).
<sup>3</sup> Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA with prednisone.

The major efficacy outcome was supported by a statistically significant delay in time to initiation of chemotherapy for patients in the ZYTIGA arm compared to those in the placebo arm. The median time to initiation of chemotherapy was not reached for patients on ZYTIGA with prednisone and was 38.9 months for patients on placebos (HR = 0.44; 95% CI: [0.35, 0.56], p < 0.0001).

16 HOW SUPPLIED/STORAGE AND HANDLING

ZYTIGA<sup>(r)</sup> (abiraterone acetate) Tablets are available in the strengths and packages listed below:

- **ZYTIGA**<sup>(r)</sup> 500 mg film-coated Tablets
  - Purple, oval-shaped tablets debossed with “AA” one side and “500” on the other side.
  - NDC 57894-195-06
  - 60 tablets available in high-density polyethylene bottles

- **ZYTIGA**<sup>(r)</sup> 250 mg uncoated Tablets
  - White to off-white, oval-shaped tablets debossed with “AA250” on one side.
  - NDC 57894-150-12
  - 120 tablets available in high-density polyethylene bottles

**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].

Keep out of reach of children.

Based on its mechanism of action, ZYTIGA may harm a developing fetus. Women who are pregnant or women who may be pregnant should not handle ZYTIGA 250 mg uncoated tablets or other ZYTIGA tablets if broken, crushed, or damaged without protection, e.g., gloves [see Use in Specific Populations (8.1)].

17 PATIENT COUNSELING INFORMATION

Advises the patient to read the FDA-approved patient labeling (Patient Information)

**Hypokalemia, Fluid Retention, and Cardiovascular Adverse Reactions**
- Inform patients that ZYTIGA is associated with hypertension, hypokalemia, and peripheral edema that may lead to QT prolongation and Torsades de Pointes in patients who develop hypokalemia while taking ZYTIGA. Advise patients that their blood pressure, serum potassium and signs and symptoms of fluid retention will be monitored clinically at least monthly. Advise patients to adhere to corticosteroids and to report symptoms of hypertension, hypokalemia, or edema to their healthcare provider [see Warnings and Precautions (5.1)].
What is ZYTIGA?
ZYTIGA® is a prescription medicine that is used along with prednisone. ZYTIGA is used to treat men with prostate cancer that has spread to other parts of the body.

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

Before taking ZYTIGA, tell your healthcare provider about all of your medical conditions, including if you:
- have heart problems
- have liver problems
- have diabetes
- have a history of adrenal problems
- have a history of pituitary problems
- are receiving any other treatment for prostate cancer
- are pregnant or plan to become pregnant. ZYTIGA can cause harm to your unborn baby and loss of pregnancy (miscarriage).
  Females who are or may become pregnant should not handle ZYTIGA uncoated tablets or other ZYTIGA tablets if broken, crushed, or damaged without protection, such as gloves.
- have a partner who is pregnant or may become pregnant.
  ° Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with ZYTIGA and for 3 weeks after the last dose of ZYTIGA.
- are breastfeeding or plan to breastfeed. It is not known if ZYTIGA passes into your breastmilk.

Tell your healthcare provider about all the medicines you take or treatments you receive, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ZYTIGA can interact with many other medicines.

How should I take ZYTIGA?
- Take ZYTIGA and prednisone exactly as your healthcare provider tells you.
- Take your prescribed dose of ZYTIGA 1 time a day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of ZYTIGA or prednisone without talking with your healthcare provider first.
- Take ZYTIGA tablets as a single dose one time a day on an empty stomach. Do not eat food 2 hours before and 1 hour after taking ZYTIGA.
- 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.
- Swallow ZYTIGA tablets whole. Do not crush or chew tablets.
- Take ZYTIGA tablets with water.
- 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), fluid retention (edema), and irregular heartbeats can happen during treatment with ZYTIGA. This can be life threatening. To decrease the chance of this happening, you must take prednisone with ZYTIGA exactly as your healthcare provider tells you. Your healthcare provider will check your blood pressure, do blood tests to check your potassium levels, and check for any signs and symptoms of fluid retention every month during treatment with ZYTIGA.

Tell your healthcare provider if you get any of the following symptoms:
- dizziness
- fast or irregular heartbeats
- feel faint or lightheaded
- headache
- confusion
- muscle weakness
- pain in your legs
- swelling in your legs or feet
What are the possible side effects of ZYTIGA? (continued)

- **Adrenal problems.** May happen if you stop taking prednisone, get an infection, or are under stress.

- **Severe liver problems.** You may develop changes in liver function blood tests. Your healthcare provider will do blood tests to check your liver before treatment with ZYTIGA and during treatment with ZYTIGA. Liver failure may occur, which can lead to death. Tell your healthcare provider right away if you notice any of the following changes:
  - yellowing of the skin or eyes
  - darkening of the urine
  - severe nausea or vomiting

- **Increased risk of bone fracture and death.** When ZYTIGA and prednisone or prednisolone, is used in combination with a type of radiation called radium Ra 223 dichloride. Tell your healthcare provider about any other treatments you are taking for prostate cancer.

- **Severe low blood sugar (hypoglycemia).** Severe low blood sugar with ZYTIGA can happen in people who have diabetes and take certain antidiabetic medicines. You and your healthcare provider should check your blood sugar levels regularly during treatment with ZYTIGA and after you stop treatment. Your healthcare provider may also need to change the dose of your antidiabetic medicines. Signs and symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness
  - dizziness
  - confusion
  - irritability
  - hunger
  - fast heartbeat
  - sweating
  - feeling jittery

The most common side effects of ZYTIGA include:

- feeling very tired
- joint pain
- high blood pressure
- nausea
- swelling in your legs or feet
- low blood potassium levels
- hot flushes
- diarrhea
- vomiting
- infected nose, sinuses, or throat (cold)
- cough
- headache
- low red blood cells (anemia)
- high blood cholesterol and triglycerides
- high blood sugar levels
- certain other abnormal blood tests

ZYTIGA may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all the possible side effects of ZYTIGA. Call your healthcare provider 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 room temperature between 68°F to 77°F (20°C to 25°C).

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

General information about the safe and effective use of 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 ZYTIGA to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your healthcare provider or pharmacist for information about ZYTIGA that is written for health professionals.

What are the ingredients of ZYTIGA?

**Active ingredient:** abiraterone acetate

**Inactive ingredients:**

- 500 mg film-coated tablets: colloidal silicon dioxide, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, silicon dioxide microcrystalline cellulose, and sodium lauryl sulfate. The film-coating contains iron oxide black, iron oxide red, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
- 250 mg uncoated tablets: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

Product of Belgium

**500 mg Tablets**

Manufactured by: Patheon France S.A.S., Bourgoin Jallieu, France

**250 mg Tablets**

Manufactured by: Patheon Inc., Mississauga, Canada

Manufactured for: Janssen Biotech, Inc., Horsham, PA 19044

For more information, call Janssen Biotech, Inc. at 1-800-526-7736 (1-800-JANSSEN) or go to www.Zytiga.com.

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This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: August 2021

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