

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

202379Orig1s007

Trade Name: Zytiga

Generic or Proper Name: Abiraterone acetate

Sponsor: Janssen Research & Development, LLC.

Approval Date: September 12, 2013

Indication: in combination with predisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CENTER FOR DRUG EVALUATION AND RESEARCH

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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APPROVAL LETTER



NDA 202379/S-007

**SUPPLEMENT APPROVAL
FULLFILLMENT OF POSTMARKETING
REQUIREMENT**

Janssen Research & Development, LLC
Attention: Kelly Reid Johnson, MS, RAC
Associate Director, Regulatory Affairs
920 Route 202,
Raritan, NJ 08869

Dear Ms. Reid Johnson:

Please refer to your Supplemental New Drug Application (sNDA) dated March 12, 2013, received March 12, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Zytiga[®] (abiraterone acetate) Tablets, 250 mg.

We acknowledge receipt of your amendments dated April 5, August 2, August 30, and September 9, 2013.

This “Prior Approval” supplemental new drug application provides for the following changes:

- Updates to the United States Prescribing Information (USPI) that recommend avoiding strong inducers of CYP3A4 based on data from the final study reports for drug-drug interaction trials evaluating the effect of a CYP3A4 inhibitor and a CYP3A4 inducer on the pharmacokinetics of Zytiga[®] (abiraterone acetate)
- Updates to the Overdosage section of the USPI to reflect limited human experience of overdose with Zytiga[®] (abiraterone acetate)

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and text for the patient package insert), with the addition of any labeling changes in pending “Changes Being

Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

FULFILLMENT OF POSTMARKETING REQUIREMENT(S)/COMMITMENT(S)

We have received your submission dated March 12, 2013, containing the final reports for the following postmarketing requirements listed in the April 28, 2011, approval letter.

1748-3 Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (*e.g.*, rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed trial protocol must be submitted for review prior to trial initiation.

Final Protocol Submission:	October 2011
Trial Completion:	April 2013
Final Report Submission:	November 2013

1748-4 Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (*e.g.*, ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed trial protocol must be submitted for review prior to trial initiation.

Final Protocol Submission:	October 2011
Trial Completion:	April 2013
Final Report Submission:	November 2013

We have reviewed your submission and conclude that the above requirements are fulfilled.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Rajesh Venugopal, Regulatory Project Manager, at (301) 796-4730.

Sincerely,

{See appended electronic signature page}

Amna Ibrahim, MD
Deputy Division Director
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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LABELING

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

Indications and usage (1)	12/2012
Dosage and Administration, Dose Modification Guidelines (2.3)	09/2013
Contraindications, Pregnancy (4.1)	12/2012
Warnings and Precautions, Mineralocorticoid excess (5.1)	12/2012
Warnings and Precautions, Adrenocortical Insufficiency (5.2)	12/2012
Warnings and Precautions, Hepatotoxicity (5.3)	12/2012

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.

DRUG INTERACTIONS

- CYP3A4 Inducers: Avoid concomitant strong CYP3A4 inducers during Zytiga treatment. If a strong CYP3A4 inducer must be coadministered, 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: [09/2013]

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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)*].

Avoid ZYTIGA in patients with baseline severe hepatic impairment (Child-Pugh Class C), as ZYTIGA has not been studied in this population, and no dose adjustment can be predicted.

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

¹ Adverse events graded according to CTCAE version 3.0

² Includes terms Arthritis, Arthralgia, Joint swelling, and Joint stiffness

³ Includes terms Muscle spasms, Musculoskeletal pain, Myalgia, Musculoskeletal discomfort, and Musculoskeletal 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, Bradycardia, Atrioventricular block complete, Conduction disorder, and Bradyarrhythmia

⁷ 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).

⁸ 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 Adverse reaction	ZYTIGA with Prednisone (N=542)		Placebo with Prednisone (N=540)	
	All Grades ¹ %	Grade 3-4 %	All Grades %	Grade 3-4 %
General disorders				
Fatigue	39.1	2.2	34.3	1.7
Edema ²	25.1	0.4	20.7	1.1
Pyrexia	8.7	0.6	5.9	0.2
Musculoskeletal and connective tissue disorders				
Joint swelling/discomfort ³	30.3	2.0	25.2	2.0
Groin pain	6.6	0.4	4.1	0.7
Gastrointestinal disorders				
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
Vascular disorders				
Hot flush	22.3	0.2	18.1	0.0
Hypertension	21.6	3.9	13.1	3.0
Respiratory, thoracic and mediastinal disorders				
Cough	17.3	0.0	13.5	0.2
Dyspnea	11.8	2.4	9.6	0.9
Psychiatric disorders				
Insomnia	13.5	0.2	11.3	0.0
Injury, poisoning and procedural complications				
Contusion	13.3	0.0	9.1	0.0
Falls	5.9	0.0	3.3	0.0
Infections and infestations				
Upper respiratory tract infection	12.7	0.0	8.0	0.0
Nasopharyngitis	10.7	0.0	8.1	0.0
Renal and urinary disorders				
Hematuria	10.3	1.3	5.6	0.6
Skin and subcutaneous tissue disorders				
Rash	8.1	0.0	3.7	0.0

¹ Adverse events graded according to CTCAE version 3.0

² Includes terms Edema peripheral, Pitting edema, and Generalized edema

³ 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 %	Grade 3-4 %	Grade 1-4 %	Grade 3-4 %
Hematology				
Lymphopenia	38.2	8.7	31.7	7.4
Chemistry				
Hyperglycemia ¹	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

¹Based 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.

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 (2.2) 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 ≥ 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.

8.3 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.

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. 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)*].

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.

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)].

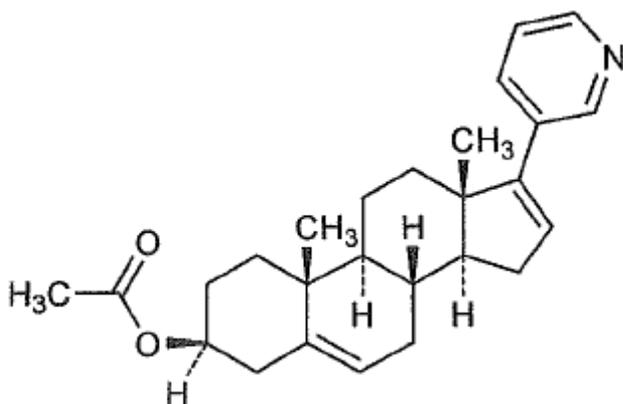
10 OVERDOSAGE

Human experience of overdose with ZYTIGA is limited.¹

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 α -hydroxylase/C17,20-lyase). Each ZYTIGA tablet contains 250 mg of abiraterone acetate. Abiraterone acetate is designated chemically as (3 β)-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 C₂₆H₃₃NO₂ 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 pK_a 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 α -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 α -hydroxy derivatives by 17 α -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 ± 178 ng/mL and of AUC were 1173 ± 690 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}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 ± 5 hours. Following oral administration of ^{14}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. ZYTIGA has not been studied in patients with baseline severe hepatic impairment (Child-Pugh Class C) [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 1000 mg, the mean plasma AUC_{∞} 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

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of abiraterone acetate.

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 ≥ 50 mg/kg/day in rats and ≥ 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 ≥ 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 ≥ 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 1000 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 ≥ 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 ≥ 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).

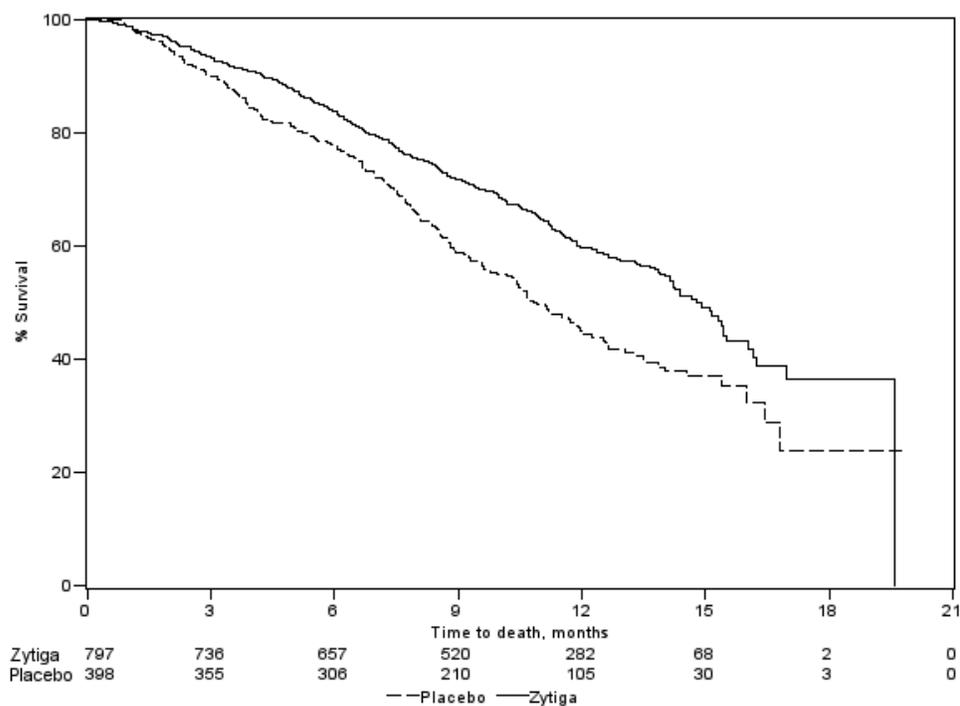
Table 5: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 1 (Intent-to-Treat Analysis)

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

^a 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).

^b 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).

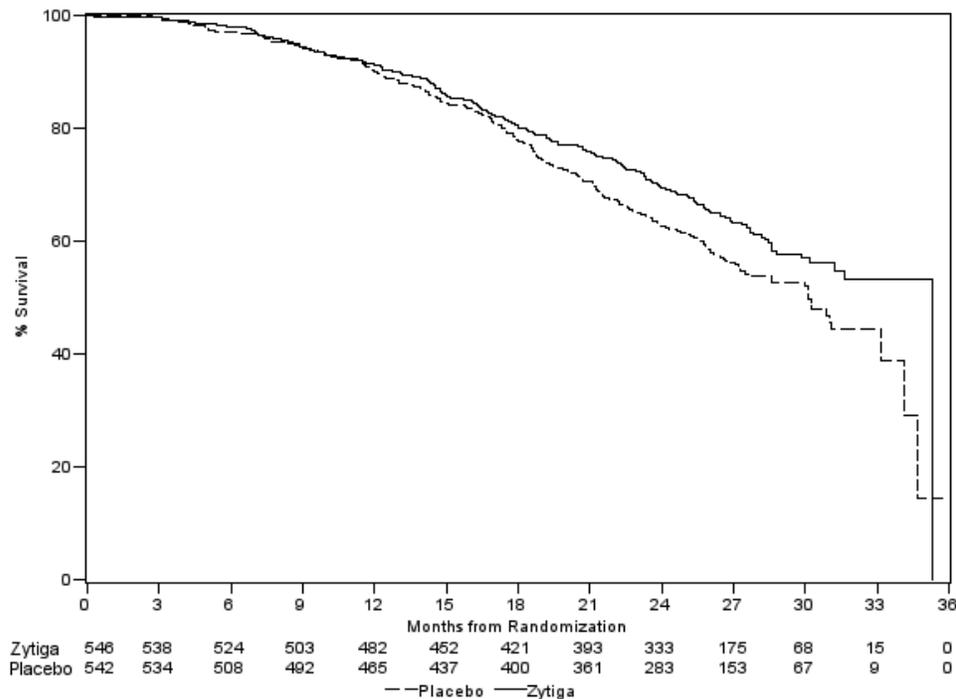
Table 6: Overall Survival of Patients Treated with Either ZYTIGA or Placebo in Combination with Prednisone in Study 2 (Intent-to-Treat Analysis)

Overall Survival	ZYTIGA (N=546)	Placebo (N=542)
Deaths	200 (37%)	234 (43%)
Median survival (months) (95% CI)	35.3 (31.24, 35.29)	30.1 (27.30, 34.10)
p-value ^a	0.0151	
Hazard ratio ^b (95% CI)	0.792 (0.655, 0.956)	

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

^b 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)

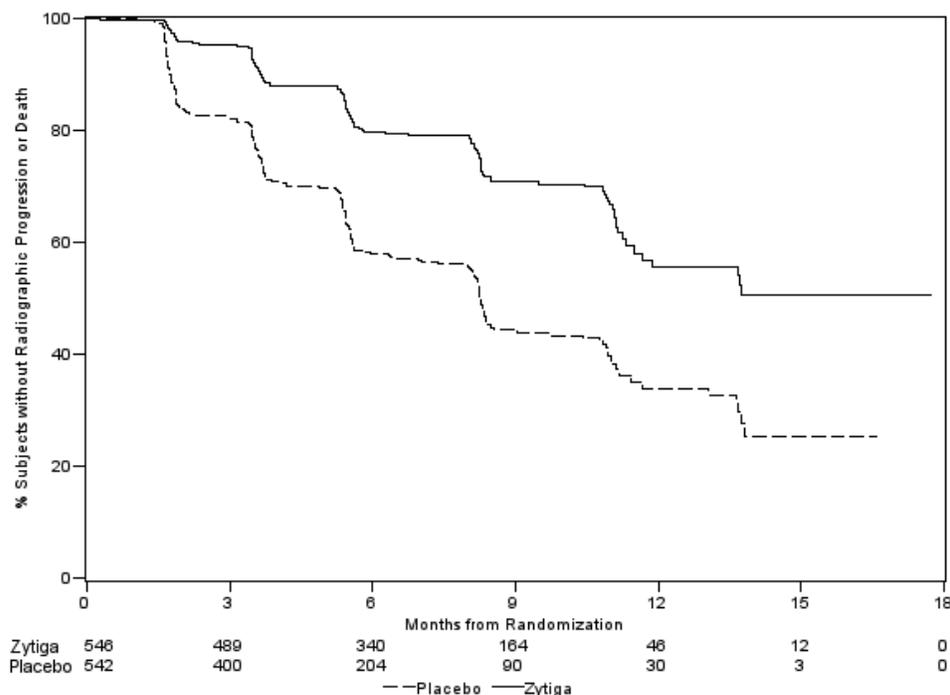
Radiographic Progression-free Survival	ZYTIGA (N=546)	Placebo (N=542)
Progression or death	150 (28%)	251 (46%)
Median rPFS (months) (95% CI)	NR (11.66, NR)	8.28 (8.12, 8.54)
p-value ^a	<0.0001	
Hazard ratio ^b (95% CI)	0.425 (0.347, 0.522)	

NR= Not reached

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

^b 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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Revised: September 2013

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.

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.

Manufactured by:

Patheon Inc.

Mississauga, Canada

Manufactured for:

Janssen Biotech, Inc.

Horsham, PA 19044

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Revised: September 2013

¹ [MODULE 2.5, Clinical Overview, Section 5.0](#)

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/s/

AMNA IBRAHIM
09/12/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s007

MEDICAL REVIEW(S)

Periodic Adverse Drug Experience Report (PADER)

NDA #: 202379, SD-236, SN0088
 Submission date: 2-22-2013
 Time period of Report: 28 Oct 2012 to 27 Jan 2013
 Clinical Reviewer: Paul G. Kluetz
 Product: Abiraterone Acetate
 Sponsor: Janssen

EXECUTIVE SUMMARY:

(1) Is any action necessary based on safety review of this submission: Yes: No:

(a) If yes, please identify the basis for which further action is necessary:

- i. Newly identified serious adverse event: Yes: No:
- ii. Increase in frequency or severity of labeled adverse event: Yes: No:
- iii. Adverse event identified for monitoring at post-approval safety conference:
 Yes: No:

(b) Is follow-up by the Safety RPM indicated: Yes: No:

(c) Is an OSE Consult recommended: Yes: No:

Background:

Abiraterone acetate (Zytiga®) is indicated for the treatment of metastatic CRPC.

Safety Review:

Adverse events:

There were 9 serious labeled initial reports and 55 non-serious initial reports.

Severe Adverse Events (SAEs) - Unlabeled

Unlabeled SAEs were reviewed and there were no significant new safety signals.

Deaths

19 initial and 17 follow-up cases with fatal outcomes were reported. The 16 new initial death cases and 7 follow-up cases were reviewed. There was one case of Addison's crisis when nursing home inadvertently stopped giving concomitant prednisone and one case of death following mis-administration of AA on a full stomach (food-affect error). 2 more cases of pneumonitis were reported.

Major Actions During Reporting Period

- Efficacy supplement -005 was approved 12/14/2012.
- No communications of new safety information were initiated.

Empirica Run of FAERs Database:

Ingredient (S) and Abiraterone Acetate where EB05>2.0 performed 6-5-2013.

	PT	N	EBGM	EB05	RR
Abiraterone	Urinary tract infection	26	2.93	2.107	3.284
Abiraterone	Thrombocytopenia	32	2.847	2.115	3.11
Abiraterone	Pulmonary embolism*	27	3.143	2.274	3.541
Abiraterone	Prostatic specific antigen increased	73	31.446	25.825	32.058
Abiraterone	Prostate cancer metastatic	20	20.843	14.017	22.158
Abiraterone	Prostate cancer	27	4.516	3.265	5.425
Abiraterone	Oedema peripheral	52	2.761	2.189	2.908
Abiraterone	Oedema	17	3.247	2.157	3.984
Abiraterone	Metastases to liver	10	4.115	2.402	6.908
Abiraterone	Metastases to central nervous system	8	4.217	2.295	8.605
Abiraterone	Liver function test abnormal	14	3.369	2.146	4.4
Abiraterone	Hypokalaemia	33	9.776	6.72	11.442
Abiraterone	Hepatotoxicity	11	5.743	3.283	10.713
Abiraterone	Haematuria	21	3.501	2.424	4.183
Abiraterone	Fluid retention	16	4.12	2.699	5.533
Abiraterone	Disease progression	37	3.285	2.493	3.595
Abiraterone	Bone pain	22	5.695	3.945	7.628
Abiraterone	Blood alkaline phosphatase increased	26	8.645	5.749	10.983
	KEY				
	Labeled				
	Likely Disease Related				

* Pulmonary Embolism is known to occur at a higher frequency in patients with metastatic prostate cancer. The frequency of PE will be followed. Comparison of the PE incidence when compared to the FAERs database for cancer therapeutics would be helpful but is currently not an available option.

Prior PADER noted a few cases of rhabdomyolysis, pneumonitis and leukocytoclastic vasculitis. Directed Empirica search was undertaken for rhabdomyolysis, pneumonitis and leukocytoclastic vasculitis and the EB05 were 0.98, 1.3 and 0.9 respectively.

Regulatory Summary:

The data presented in this annual report do not identify any new adverse event signal or other risk that materially alters the risk:benefit of the NDA. There is no regulatory action indicated based on this submission.

This drug will be going through the 915 process for safety review during the summer and fall of 2013. The OSE team and Pulmonary team have been consulted to look further into a possible signal for drug-induced pneumonitis. The OSE team will be alerted to look carefully for possible unlabeled signals of rhabdomyolysis, hemolytic anemia and drug-

induced leukoclastic vasculitis. Thrombocytopenia is likely related to bone marrow infiltration by this malignancy which most commonly metastasizes to bone. Pulmonary embolism will also be reviewed although as stated above, this is seen at a higher frequency in the metastatic CRPC setting and may be disease related rather than drug-related.

We will keep an eye on reports of medication errors (giving without concurrent steroids and giving on a full stomach) and consider stronger labeling language should medication error reports appear with more regularity.

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/s/

PAUL G KLUETZ
06/05/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s007

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

This is a review of data submitted by the sponsor suggesting abiraterone exposure does not increase significantly with an increase in dose from 1000 mg to 2000mg. This additional data was submitted to facilitate the discussion of the recommendations for labeling supplement #7 (SLR-7). SLR-7 (SDN# 246) is a labeling supplement (SLR#7) that was submitted 03/12/13 and contained two study reports in fulfillment of two postmarketing requirements (PMRs):

- PMR 1748-3 required the sponsor to “conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate”.
- PMR 1748-4 required the sponsor to “conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate”.

The following is a summary from the clinical pharmacology review that was signed in DARRTS on 07/24/13:

- *In Trial PCR1003 that was submitted for PMR 1748-3, the geometric mean abiraterone Cmax and AUC were 55% lower when Zytiga was co-administered with rifampicin compared to when given alone. Therefore, it is recommended to avoid concomitant use of strong CYP3A4 inducers. If concomitant use cannot be avoided, we recommend a Zytiga dose of 2000 mg.*
- *In Trial PCR1002 that was submitted for PMR 1748-4, the geometric mean abiraterone Cmax was 9% higher and the AUC was 15% higher when Zytiga was co-administered with ketoconazole. Therefore, we will delete the current labeling language recommending avoiding or using caution with concomitant strong CYP3A4 inhibitors. The language was added in the initial label because abiraterone is a CYP3A4 substrate in vitro and no clinical data were available.*

However regarding the clinical pharmacology recommendations for inducers, the sponsor has submitted PK data (in the current submission) suggesting that the exposure of abiraterone does not increase with an increase in dose from 1000 mg to 2000mg.

Sponsors Submitted Summary of PK data

Dose (mg)		Tmax (hr)	Cmax (nmol/L)	HL_Lambda_z (hr)	AUClast (hr*nmol/L)	AUCINF_obs (hr*nmol/L)	Cl_F_obs (L/hr)	Vz_F_obs (L)
250	Mean	2.050	219	11.6	1253	1369	567.2	10772.0
	SD	0.02	172.77	10.14	519.78	505.39	183.18	11902.44
	% CV	0.83	78.77	87.05	41.48	36.93	32.29	110.49
500	Mean	2.588	284	9.5	1334	1448	1347.2	14032.5
	SD	1.02	132.38	7.02	731.47	749.01	991.12	5660.20
	% CV	39.25	46.62	73.74	54.83	51.74	73.57	40.34
750	Mean	1.709	1032	10.8	4294	4537	494.3	8339.7
	SD	0.41	344.01	5.91	1295.20	1333.42	145.27	6481.80
	% CV	24.13	33.33	54.57	30.17	29.39	29.39	77.72
1000	Mean	3.159	571	10.6	4371	4615	962.7	13372.1
	SD	1.79	443.18	4.69	3427.54	3660.48	595.55	9990.37
	% CV	56.53	77.62	44.02	78.42	79.32	61.86	74.71
2000	Mean	2.672	531	12.0	4754	4983	1280.3	21598.8
	SD	1.14	219.02	2.29	1659.13	1755.24	549.76	7227.17
	% CV	42.50	41.23	19.01	34.90	35.22	42.94	33.46

The sponsor was asked by the Agency to consider a recommendation to increase the dosing frequency from QD to BID when co-administration of strong CYP3A4 inducers with Zytiga cannot be avoided. The sponsor agreed to the recommendation. The conclusion that PMRs # 3 and 4 are fulfilled as stated in the clinical pharmacology review in DARRTS dated 07/24/13 still stands.

Detailed Labeling Recommendations

Only relevant clinical pharmacology sections are included. Please refer to the clinical pharmacology review in DARRTS dated 07/24/13 for details of the sponsor's original labeling language and our original recommendations. The language below reflects the sponsor and FDA agreed on language as of 09/09/13. The agreed on changes from the currently approved label are underlined and proposed deletions have a strikethrough line.



(b) (4)

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Action: The submitted data is acceptable from a clinical pharmacology perspective. The PMRs # 3 and 4 are fulfilled. No action is necessary.

Signatures:

Elimika Pfuma, Pharm.D., Ph.D.
Reviewer
Division of Clinical Pharmacology 5

Qi Liu, Ph.D.
Team Leader
Division of Clinical Pharmacology 5

Cc: DDOP: CSO – **Tilley A**; MTL- **Maher V**; MO – **Ning M**
DCP-5: Reviewer – **E Pfuma**; TL – **Q Liu**; Deputy DD - **B Booth**; DD - **A Rahman**

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/s/

ELIMIKA PFUMA
09/10/2013

QI LIU
09/10/2013

Clinical Pharmacology Review

NDA	202379
Submission Date:	12 th March 2013
Brand Name:	Zytiga®
Generic Name:	Abiraterone Acetate
Formulation:	Immediate release 250 mg tablets
OCP Reviewer:	Elimika Pfuma, Pharm.D. / Ph.D.
OCP Team Leader:	Qi Liu, Ph.D.
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products 1
Sponsor:	Janssen Research
Submission Type; Code:	sNDA: NDA#202379/SDN#246
Dosing regimen:	ZYTIGA 1,000 mg (four 250 mg tablets) administered orally once daily in combination with prednisone 5 mg administered orally twice daily
Indication:	For the treatment of patients with metastatic castration-resistant prostate cancer

Executive Summary

Abiraterone (active metabolite of abiraterone acetate [Zytiga®]) is a steroidal inhibitor of 17 α hydroxylase/C17, 20-lyase (**CYP17**). CYP17 is an enzyme that is required for androgen biosynthesis. Abiraterone acetate is indicated for use in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). It is approved at a dose of 1000 mg once daily in combination with 5 mg twice daily of oral prednisone.

The current submission to NDA#202379 (SDN# 246) is a labeling supplement (SLR#7) containing two study reports. The sponsor is proposing language regarding the results of trials submitted in fulfillment of two postmarketing requirements (PMRs):

- PMR 1748-3 required the sponsor to “conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate”.
- PMR 1748-4 required the sponsor to “conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate”.

The labeling supplement also includes proposed changes to the Overdosage Section.

In Trial PCR1003 that was submitted for PMR 1748-3, the geometric mean abiraterone C_{max} and AUC were 55% lower when Zytiga was co-administered with rifampicin compared to when given alone. Therefore, it is recommended to avoid concomitant use of strong CYP3A4 inducers. If concomitant use cannot be avoided, we recommend a Zytiga dose of 2000 mg.

In Trial PCR1002 that was submitted for PMR 1748-4, the geometric mean abiraterone C_{max} was 9% higher and the AUC was 15% higher when Zytiga was co-administered with ketoconazole. Therefore, we will delete the current labeling language recommending avoiding or

using caution with concomitant strong CYP3A4 inhibitors. The language was added in the initial label because abiraterone is a CYP3A4 substrate *in vitro* and no clinical data were available.

Clinical Pharmacology Summary

Abiraterone acetate is rapidly hydrolyzed to abiraterone after oral administration. The median abiraterone T_{max} is 2 hours and the mean elimination half-life is 12 hours. A high fat meal increased abiraterone C_{max} and AUC_{0-∞} up to 17- and 10-fold, respectively. Approximately 88% of an oral radioactive abiraterone acetate dose was recovered in feces. The label recommends a dose reduction to 250 mg once daily in patients with moderate hepatic impairment. Zytiga has not been assessed in patients with severe hepatic impairment.

Abiraterone is a strong inhibitor of CYP1A2, CYP2D6 and CYP2C8 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5, *in vitro*. *In vivo*, it increased the exposure of dextromethorphan (CYP2D6 substrate) by 200% but did not affect the PK of theophylline (CYP1A2 substrate).

Abiraterone is a substrate of CYP3A4, *in vitro*. The *in vivo* effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone were not evaluated at the time of NDA. Two PMRs were issued for this evaluation and the current submission is a labeling supplement with results from the trials submitted to fulfill the PMRs.

In Trial PCR1003 that was submitted for PMR 1748-3, the geometric mean abiraterone C_{max} and AUC were 55% lower when Zytiga was co-administered with rifampicin compared to when given alone. The sponsor proposes that (b) (4)

(b) (4) However, a dose adjustment may be more appropriate (b) (4) to avoid therapeutic failure in a patient. If concomitant use cannot be avoided, we recommend a Zytiga dose of 2000 mg. A Zytiga dose of 2220 mg would be predicted to achieve exposures similar to the 1000 mg dose when dosed alone based on the mean reduction of 55% observed in Trial PCR1003. Since Zytiga is available as 250 mg tablets, we recommend a dose of 2000 mg.

In Trial PCR1002 that was submitted for PMR 1748-4, the geometric mean abiraterone C_{max} was 9% higher and the AUC was 15% higher when Zytiga was co-administered with ketoconazole. The sponsor proposes to delete the current labeling language recommending avoiding or using caution with concomitant strong CYP3A4 inhibitors. The language was added in the initial label because abiraterone is a CYP3A4 substrate *in vitro* and no clinical data were available. The sponsor's proposal to delete this language is acceptable as no relevant PK changes were observed with concomitant ketoconazole.

1.2 RECOMMENDATIONS

This submission is acceptable from a clinical pharmacology perspective. The applicant's post-marketing requirements # 3 and 4 (NDA 202379) are fulfilled from a clinical pharmacology perspective. Please see Sections 3 for detailed labeling recommendations.

Signatures

Elimika Pfuma, Pharm.D./ Ph.D.	Qi Liu, Ph.D.
Reviewer	Team Leader
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5
CC: DDOP: CSO – J Mwidau; MTL – E Maher; MO - P Kluetz	
DCP- Reviewer - E Pfuma; TL - Q Liu; DDD - B Booth; DD - A	
5: Rahman	

2 QUESTION BASED REVIEW

Zytiga was previously reviewed under NDA 202379 (approved 04/28/2011). This current review will only address questions related to the current supplemental NDA submission.

2.1 What is the effect of concomitant administration of a strong CYP3A4 inducer on the PK of abiraterone?

Abiraterone is a CYP3A4 substrate, *in vitro*. The sponsor performed trial PCR1003 in fulfillment of PMR #1748-3. In this trial, the abiraterone geometric mean C_{max} and AUC were 55% lower when Zytiga was co-administered with rifampicin compared to when given alone.

PCR1003 was a single-center, open-label, 2-period trial in 20 healthy male volunteers (19 received drug). In Period 1, the volunteers received a 1000 mg dose of Zytiga on Day 1. In Period 2, the volunteers received a 600 mg daily dose of rifampicin on Days 8 - 13 and a 1000 mg dose of Zytiga on Day 14.

Zytiga was administered after an overnight fast of at least 10 hours and a fast of 4 hours was continued after the dose. Rifampicin was dosed after an overnight fast, but the fasting time pre- and post- dose were not specified in the protocol. PK samples for analysis of abiraterone and its metabolites (abiraterone sulphate and N-oxide abiraterone sulphate) were collected for 72 hours after the Day 1 and 14 doses. *The original Clinical Pharmacology NDA review states that the inactive metabolites, abiraterone sulphate (SULT1A2 metabolite) and N-oxide abiraterone sulphate (SULT1A2 and CYP3A4 metabolite), account for about 43% of exposure each.* One PK sample to assess rifampicin was taken at two hours after the Zytiga dose on Day 14.

In this trial, the geometric mean abiraterone C_{max} and AUC were 55% lower when Zytiga was co-administered with rifampicin compared to when given alone. The geometric mean abiraterone sulfate C_{max} was 59% lower and the AUC_∞ was 70% lower with the use of rifampicin. The mean metabolite to parent (abiraterone) ratio (corrected for MW) decreased approximately 33% based on AUC_∞ and remained unchanged based on C_{max}. The geometric mean N-oxide abiraterone sulfate C_{max} increased 83% and the AUC_∞ was increased 3% with the use of rifampicin. The mean metabolite to parent

(abiraterone) ratio (corrected for MW) increased approximately 330% based on C_{max} and 126% based on AUC_∞. (**Table 1**)

Table 1: Abiraterone PK and Metabolite /Parent Ratio after Abiraterone Acetate (AA) alone or in Combination with Rifampicin

		Abiraterone (A)			A Sulfate	N-oxide A Sulfate
		AA (N=19)	AA+Rif (N=18)	Geo Ratio (90%CI)	Mean M/P Ratio (N=19)	Mean M/P Ratio Δ (N=19)
C _{max} (ng/mL)	Geo Mean	115.53	51.56	44.63 (35.01 - 56.89)	No change	330% increase
AUC _{last} (hr.ng/mL)		605.22	255.30	42.18 (35.19 - 50.56)	43% decrease	154% increase
AUC _{0-∞} (hr.ng/mL)		656.57	297.17	45.26 (38.04 - 53.85)	33% decrease	126% increase
T _{max} (hr)	Median (Range)	1.5 (1 - 4)	1.5 (0.5-3)	N/A	N/A	N/A
T _{1/2} (hr)	Mean (SD)	16.3 (6.5)	14.9(3.9) ^a	N/A	N/A	N/A

The sponsor proposes that (b) (4). However, a dose adjustment may be more appropriate than (b) (4) to avoid therapeutic failure in a patient. If concomitant use cannot be avoided, we recommend a Zytiga dose of 2000 mg. A Zytiga dose of 2220 mg would be predicted to achieve exposures similar to the 1000 mg dose when dosed alone based on the mean reduction of 55% observed in Trial PCR1003. Since Zytiga is available as 250 mg tablets, we recommend a dose of 2000 mg.

2.2 What is the effect of concomitant administration of a strong CYP3A4 inhibitor on the PK of abiraterone?

Abiraterone is a CYP3A4 substrate, *in vitro*. The sponsor performed trial PCR1002 in fulfillment of PMR #1748-4. In this trial, no significant abiraterone PK change was observed when Zytiga was co-administered with ketoconazole.

PCR1002 was a single-center, open-label, 2-period trial in 20 healthy male volunteers. In Period 1, the volunteers received a 1000 mg dose of Zytiga on Day 1. In Period 2, the volunteers received a 400 mg daily dose of ketoconazole on Days 11 - 16 and a 1000 mg dose of Zytiga on Day 14.

Zytiga was administered after an overnight fast of at least 10 hours and a fast of 4 hours was continued after the dose. Ketoconazole was dosed with food except on Day 14 when it was given at the same time as Zytiga. PK samples for analysis of abiraterone and its metabolites were collected for 72 hours after the Day 1 and 14 doses. One PK sample to assess ketoconazole was taken at two hours post dose on Day 14.

In this trial, the geometric mean abiraterone C_{max} was 9% higher and the AUC was 15% higher when Zytiga was co-administered with ketoconazole. The geometric mean abiraterone sulfate C_{max} was 4% lower and the AUC was unchanged with concomitant ketoconazole. The mean metabolite to parent ratio decreased approximately 15% for both C_{max} and AUC_{last}. The geometric mean N-oxide abiraterone sulfate C_{max} was 25% lower and the AUC_{last} was 7% lower with concomitant ketoconazole. The mean

metabolite to parent ratio decreased approximately 35% based on Cmax and 20% based on AUC. (Table 2)

Table 2: Abiraterone PK and Metabolite /Parent Ratio after Abiraterone Acetate (AA) alone or in Combination with Ketoconazole

		Abiraterone (A) N=20			A Sulfate	N-oxide A Sulfate
		AA	AA+Ket	Geo Ratio (90%CI)	Mean M/P Ratio Δ (N=19)	Mean M/P Ratio Δ (N=19)
Cmax (ng/mL)	Geo Mean	119.05	129.34	108.6 (90.0-131.1)	14 % decrease	35 % decrease
AUC _{last} (hr.ng/mL)		598.11	685.95	114.7 (97.9-134.3)	15 % decrease	21 % decrease
AUC _{0-∞} (hr.ng/mL)		608.66	699.63	115.0 (98.3-134.4)	5 % decrease	19 % decrease
Tmax (hr)	Median (Range)	1.8 (0.5 -3)	2.0 (1 -3)	N/A	N/A	N/A
T _{1/2} (hr)	Mean (SD)	14.8 (2.2)	15.4 (2.6)	N/A	N/A	N/A

The sponsor proposes to delete the current labeling language recommending avoiding or using caution with concomitant strong CYP3A4 inhibitors. The language was added in the initial label because abiraterone is a CYP3A4 substrate *in vitro* and no clinical data were available. The sponsor’s proposal to delete this language is acceptable as no relevant PK changes were observed with concomitant ketoconazole.

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The sponsor’s proposed changes are underlined and proposed deletions have a strikethrough line. The reviewer’s proposed changes are double underlined and proposed deletions have a double strikethrough line.



(b) (4)

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ELIMIKA PFUMA
07/22/2013

QI LIU
07/24/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s007

OTHER REVIEW(S)

Division of Oncology Products 1
REGULATORY PROJECT MANAGER LABELING REVIEW

Application: NDA 0202379/S-007

Name of Drug: Zytiga[®] (abiraterone acetate) Tablets, 250 mg

Applicant: Janssen Research & Development, LLC

Labeling Reviewed

Submission Date: March 12, 2013

Receipt Date: March 12, 2013

BACKGROUND AND SUMMARY DESCRIPTION:

This supplemental application, submitted as a “Changes Being Effected” supplement, proposes the following changes based on the data provided from the final study reports (also included in this supplemental application) required as part of the postmarketing requirements under 505(o):

- Updating the United States Prescribing Information (USPI) to reflect data in the final study reports for the CYP3A4 inhibitor and inducer to strengthen the labeling to avoid use of strong inducers of CYP3A4 during treatment with Zytiga[®] (abiraterone acetate)
- The overdosage of the USPI was updated to reflect overdose cases as follows: ~~There have been no reports of overdose during clinical studies.~~ Human experience of overdose with ZYTIGA is limited.

Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product labeling with this change.

This supplement was also reviewed by Elimika Pfuma, PharmD, PhD, Clinical Pharmacology Reviewer (See Clinical Pharmacology Review in DARRTS dated September 10, 2013). This SLR was reviewed under two internal labeling meetings (July 11, 2013 and September 5, 2013).

RECOMMENDATIONS

This SLR can be approved based on the division’s review during the July 11, 2013 and September 5, 2013 internal labeling meeting where both clinical and division management attended.

Rajesh Venugopal, MPH, MBA

Regulatory Project Manager

Christy Cottrell

Chief, Project Management Staff

REVIEW

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/s/

RAJESH VENUGOPAL
09/12/2013

CHRISTY L COTTRELL
09/12/2013

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202379Orig1s007

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

From: [Venugopal, Rajesh](#)
To: ["Johnson Reid, Kelly \[JRDUS\]"](#)
Subject: RE: Labeling supplement: NDA 202379/S-007
Date: Tuesday, September 10, 2013 10:13:51 AM

Hello Kelly,

Please see below in red FDA's response to your questions.
rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

From: Johnson Reid, Kelly [JRDUS] [mailto:KJohnso6@ITS.JNJ.COM]
Sent: Friday, September 06, 2013 4:34 PM
To: Venugopal, Rajesh
Subject: RE: Labeling supplement: NDA 202379/S-007

Hi Rajesh,

We do have some additional things. Our issues/concerns are outlined as questions below:

Questions for the Division:

1) The Company requests clarification on the statement added in section 7.1. regarding moderate and weak CYP3A4 inducers not being studied, as prednisone (a weak inducer of CYP3A4) is indicated with Zytiga (Section 1) as part of the standard dosing regimen. As currently proposed, the text appears inaccurate.

Does the Agency agree with the Company's proposal to remove this statement, which we have deleted as a matter of accuracy, but we wanted to understand the Division's thinking on this statement.

You may delete the statement.

2) A reference to a new Warnings and Precautions subsection (5.5) is being added in Section 2.3. There is no new subsection. Can you please confirm that this was a typo?

This was a typo.

3) The proposed USPI language outlines a specific 12 hour dosing regimen for the BID

schedule. The current label is specific about NOT taking ZYTIGA with food. The every 12 hour dosing instruction may make dosing without food difficult for patients. As a result, the Company would like to propose to keep the BID schedule, but not specify 12 hours. Can the Division provide their thinking on the preference to have an every 12 hour dosing schedule as well as the BID dosing schedule?

BID is acceptable.

(b) (4)

The Company appreciates your help and clarification on these topics.

Best regards
Kelly

From: Venugopal, Rajesh [<mailto:Rajesh.Venugopal@fda.hhs.gov>]
Sent: Friday, September 06, 2013 12:04 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: RE: Labeling supplement: NDA 202379/S-007

Hello Kelly,

Go ahead and send the PI back adding back the caveat about having no clinical data to support the recommendations being made for dose adjustment. We won't set up a T-con for this. Do you accept the rest of the edits made by FDA?

rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

From: Johnson Reid, Kelly [JRDUS] [<mailto:KJohnso6@ITS.JNJ.COM>]
Sent: Thursday, September 05, 2013 10:29 PM
To: Venugopal, Rajesh
Subject: RE: Labeling supplement: NDA 202379/S-007

Hi Rajesh,

The discussion on the language for CYP3A4 interactions has been back and forth a couple of times now. We are concerned regarding the removal of the important caveat that there are no clinical data to support the recommendations being made for dose adjustment. At this point in the review, we would like to request a brief discussion with the reviewer to discuss this item to understand the rationale for the removal of this statement, as we believe this is a true important fact to disclose to prescribers. I'm thinking a short meeting would be more productive than another round of only correspondence.

Please let me know if it's possible to discuss this further to schedule a meeting. I'd be happy to provide dial-in information.

Thanks
Kelly

From: Venugopal, Rajesh [<mailto:Rajesh.Venugopal@fda.hhs.gov>]
Sent: Thursday, September 05, 2013 2:14 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: Labeling supplement: NDA 202379/S-007

Hello Kelly,

FDA has reviewed your latest proposed text mentioned below for the above mentioned NDA and supplement. Attached please find a copy of the FDA revised Product Insert (PI) for 202379/S-007. We respectfully request your response to this email and agreement to the label by 12 PM Monday, Sept. 9, 2013.

Regards,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

From: Johnson Reid, Kelly [JRDUS] [<mailto:KJohnso6@ITS.JNJ.COM>]
Sent: Thursday, August 29, 2013 3:15 PM
To: Venugopal, Rajesh
Subject: RE: Clinical Pharmacology Information Request NDA 202379/S-007

Hi Rajesh,

As per my voice message, the Company has evaluated the Division's request for clarification, data, and/or simulations for the possibility of changing the dosing frequency to 1000mg BID for those who cannot avoid CYP3A4 inducers. The Company looked at the data to assess a 1000mg BID dose to patients who also take strong inducers compared to an exposure of 1000mg QD in normal patients that have not used inducers. (b) (4)

However, the Company acknowledges that a recommendation to patients who are taking CYP3A4 inducers concomitantly for an extended period of time may be necessary. In the absence of clinical data and simulation, the Company would like to submit proposed text for USPI by EOB tomorrow Aug 30, 2013.

I will not be in the office tomorrow. My colleague, Naomi Nomura NNomura2@its.jnj.com (b) (6), will be handling this submission and she can be contacted should you have questions or concerns.

Best Regards
Kelly

From: Venugopal, Rajesh [<mailto:Rajesh.Venugopal@fda.hhs.gov>]
Sent: Tuesday, August 27, 2013 2:19 PM
To: Johnson Reid, Kelly [JRDUS]
Subject: Clinical Pharmacology Information Request NDA 202379/S-007

Hello Ms. Reid Johnson,

FDA has the following information request that requires your response for your NDA supplement:

For Zytiga that may be used for an extended period of time, it may not be sufficient to only recommend avoiding strong CYP3A4 inducers for patients that may need other chronic therapies that are strong CYP3A4 inducers such as anticonvulsants. Please clarify or provide data or simulations for the possibility of changing the dosing frequency such as 1000 mg BID for patients who cannot avoid these inducers.

Please respond by 4PM EST Thursday August 29, 2013.

Thank you,
Rajesh

Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
Bldg. 22, Rm. 6111
E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845

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/s/

RAJESH VENUGOPAL
09/10/2013

From: [Venugopal, Rajesh](#)
To: ["Johnson Reid, Kelly \[JRDUS\]"](#)
Subject: Labeling supplement: NDA 202379/S-007
Date: Thursday, September 05, 2013 2:14:22 PM
Attachments: [SLR-007-sponsor-original-proposed-annotated-draft-labeling-text_090513.doc](#)

Hello Kelly,

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Regards,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
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E-mail: Rajesh.Venugopal@fda.hhs.gov
Phone: (301) 796-4730
Fax: (301) 796-9845*

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I will not be in the office tomorrow. My colleague, Naomi Nomura NNomura2@its.jnj.com (908)731-1648, will be handling this submission and she can be contacted should you have questions or concerns.

Best Regards
Kelly

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Subject: Clinical Pharmacology Information Request NDA 202379/S-007

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Please respond by 4PM EST Thursday August 29, 2013.

Thank you,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
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/s/

RAJESH VENUGOPAL
09/05/2013

From: [Venugopal, Rajesh](#)
To: kjohnso6@its.jnj.com
Subject: Clinical Pharmacology Information Request NDA 202379/S-007
Date: Tuesday, August 27, 2013 2:18:38 PM

Hello Ms. Reid Johnson,

FDA has the following information request that requires your response for your NDA supplement:

For Zytiga that may be used for an extended period of time, it may not be sufficient to only recommend avoiding strong CYP3A4 inducers for patients that may need other chronic therapies that are strong CYP3A4 inducers such as anticonvulsants. Please clarify or provide data or simulations for the possibility of changing the dosing frequency such as 1000 mg BID for patients who cannot avoid these inducers.

Please respond by 4PM EST Thursday August 29, 2013.

Thank you,
Rajesh

*Rajesh Venugopal, MPH, MBA
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
OND/CDER/FDA
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/s/

RAJESH VENUGOPAL
08/27/2013

Mwidau, Jamila

From: Mwidau, Jamila
Sent: Friday, July 12, 2013 12:46 PM
To: Johnson Reid, Kelly [JRDUS] (KJohnso6@ITS.JNJ.COM)
Subject: NDA 202379/S-007_Zytiga

Kelly,

Attached is the label for Zytiga with edits from the FDA. Please review and submit officially a tracked and clean version of your label.



2013.07.12 - 12:46 PM...
[Redacted]

Kindly acknowledge receipt.

Sincerely, Jamila

Jamila A. Mwidau, RN,BSN,MPH
LCDR, USPHS
Regulatory Health Project Manager
FDA/CDER/OND/OHOP/DOP1
10903 New Hampshire Ave.
WO22 Rm 2133
Silver Spring, MD 20993
Tel: 301-796-4989
Fax: 301-796-9845

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/s/

JAMILA A MWIDAU
07/12/2013



NDA 202379/S-007

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Janssen Research & Development, LLC
Attention: Kelly Reid Johnson, MS, RAC
Associate Director, Regulatory Affairs
920 Route 202,
Raritan, NJ 08869

Dear Ms. Reid Johnson:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 202379
SUPPLEMENT NUMBER: 007
PRODUCT NAME: Zytiga® (abiraterone acetate) Tablets, 250 mg
DATE OF SUBMISSION: March 12, 2013
DATE OF RECEIPT: March 12, 2013

This supplemental application, submitted as a “Changes Being Effected” supplement, proposes the following changes:

- Updating the United States Prescribing Information (USPI) to reflect data in the final study reports for the CYP3A4 inhibitor and inducer to strengthen the labeling to avoid use of strong inducers of CCYP3A4 during treatment with Zytiga® (Abiraterone Acetate)
- The overdosage of the USPI was updated to reflect overdose cases as follows: ~~There have been no reports of overdose during clinical studies.~~ Human experience of overdose with ZYTIGA is limited.

Changes of this kind cannot be put into effect prior to approval of a supplement; we consider this to be a **Prior Approval Supplement**. An approved supplement is required for this proposed change prior to distributing drug product made with this change.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 11, 2013, in accordance with 21 CFR 314.101(a).

If the application is filed, the goal date will be September 12, 2013.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3).

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Products 1
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me, at (301) 796-4989.

Sincerely,

{See appended electronic signature page}

Jamila Mwidau, RN, BSN, MPH
Regulatory Health Project Manager
Division of Oncology Products 1
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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JAMILA A MWIDAU
04/01/2013