PRODUCT MONOGRAPH

PrZYTIGA®

Abiraterone acetate tablets

250 mg

Androgen Biosynthesis Inhibitor

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Tablet 250 mg	Lactose monohydrate *For a complete listing see **DOSAGE FORMS, COMPOSITION AND PACKAGING** section.*

INDICATIONS AND CLINICAL USE

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

- are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy
- have received prior chemotherapy containing docetaxel after failure of androgen deprivation therapy

Geriatrics (≥ 65 years of age):
In the Phase 3 studies of ZYTIGA®, 75% of the asymptomatic or mildly symptomatic patients and 71% of the patients previously treated with docetaxel were 65 years and over. While 34% of the asymptomatic or mildly symptomatic patients and 28% of the patients previously treated with docetaxel were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Pediatrics:
ZYTIGA® has not been studied in children.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the Product Monograph.
- Women who are or may potentially be pregnant.

WARNINGS AND PRECAUTIONS

General

Gonadotropin releasing hormone (GnRH) agonists must be taken during treatment with ZYTIGA® or patients must have been previously treated with orchiectomy.

ZYTIGA® must be taken on an empty stomach. No solid or liquid 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 **DRUG INTERACTIONS Drug-Food Interactions, DOSAGE AND ADMINISTRATION**, and **ACTION AND CLINICAL PHARMACOLOGY).**

Reproductive Toxicology

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped. In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced fetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic. In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone (see **Product Monograph, Part II, TOXICOLOGY, Reproductive Toxicology**).

Carcinogenesis and Mutagenesis

Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone. The clinical relevance of this finding is not known. Abiraterone acetate was not carcinogenic in female rats (see **Product Monograph, Part II, TOXICOLOGY, Carcinogenesis and Genotoxicity**).

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of *in vitro* and *in vivo* genotoxicity tests (see **Product Monograph, Part II, TOXICOLOGY, Carcinogenesis and Genotoxicity**).

Cardiovascular

ZYTIGA® should be used with caution in patients with a history of cardiovascular disease. The safety of patients with myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or left ventricular ejection fraction (LVEF) < 50% or New York Heart Association Class III or IV heart failure (in the study of metastatic castration-resistant prostate cancer [mCRPC] patients with prior treatment with docetaxel) or NYHA Class II to IV heart failure (in the study of asymptomatic or mildly symptomatic mCRPC patients) has not been established because these patients were excluded from the pivotal studies.

Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess

Before treatment with ZYTIGA®, hypertension must be controlled and hypokalemia must be corrected.

ZYTIGA® may cause hypertension, hypokalemia and fluid retention (see **ADVERSE REACTIONS**) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see **ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action**). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by potential increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Corticosteroid Withdrawal and Coverage of Stress Situations

Caution is advised if patients need to be withdrawn from prednisone. Monitoring for adrenocortical insufficiency should occur. If ZYTIGA® is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

In patients on prednisone who are subjected to unusual stress (e.g., surgery, trauma or severe infections), increased dosage of a corticosteroid may be indicated before, during and after the stressful situation.

Hepatic

Hepatic impairment

ZYTIGA® should not be used in patients with pre-existing moderate or severe hepatic impairment (see **WARNINGS AND PRECAUTIONS – Special Populations**, and **– Monitoring and Laboratory Tests**, and **ACTION AND CLINICAL PHARMACOLOGY**).

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see **ADVERSE REACTIONS**). Serum transaminases (ALT and AST) and bilirubin levels should be measured prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin and serum transaminases (ALT and AST), if clinical symptoms or signs suggestive of hepatotoxicity develop. If at any time the serum transaminases (ALT or AST) rise above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with ZYTIGA® should be interrupted immediately and liver function closely monitored.

Re-treatment with ZYTIGA® may only take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see **DOSAGE AND ADMINSTRATION**).

If patients develop severe hepatotoxicity (ALT or AST 20 times the upper limit of normal) anytime while on therapy, ZYTIGA® should be discontinued and patients should not be re-treated with ZYTIGA®.

Use with Chemotherapy

The safety and efficacy of concomitant use of ZYTIGA® with cytotoxic chemotherapy has not been established.

Skeletal Muscle Effects
Cases of myopathy have been reported in patients treated with ZYTIGA®. Some patients had rhabdomyolysis with renal failure. Most cases developed within the first month of treatment and recovered after ZYTIGA® withdrawal. Caution is recommended in patients concomitantly treated with drugs known to be associated with myopathy/rhabdomyolysis.

Special Populations
Pregnant Women: ZYTIGA® is contraindicated in women who are or may potentially be pregnant (see **CONTRAINDICATIONS, Product Monograph Part II, TOXICOLOGY, Reproductive Toxicology**).

There are no human data on the use of ZYTIGA® in pregnancy and ZYTIGA® is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the fetus (see **CONTRAINDICATIONS**). Based on animal studies, there is potential of fetal harm (see **Product Monograph Part II, TOXICOLOGY, Reproductive Toxicology**)

It is not known if abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of child-bearing potential, a condom is required along with another effective contraceptive method. These measures are required during and for one week after treatment with ZYTIGA®.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle ZYTIGA® without protection, e.g., gloves.

Nursing Women: ZYTIGA® is not for use in women. It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.

Pediatrics (< 18 years of age): ZYTIGA® has not been studied in children.

Geriatrics (> 65 years of age): In the Phase 3 studies of ZYTIGA®, 75% of the asymptomatic or mildly symptomatic patients and 71% of the patients previously treated with docetaxel were 65 years and over. While 34% of the asymptomatic or mildly symptomatic patients and 28% of the patients previously treated with docetaxel were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients.

Patients with Hepatic Impairment: Patients with pre-existing moderate or severe hepatic impairment should not receive ZYTIGA®. ZYTIGA® has not been studied in mCRPC patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment at baseline. For patients who develop hepatotoxicity during treatment, suspension of treatment and dosage adjustment may be required (see **WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, – Special Populations and Conditions**).

Patients with Renal Impairment: No dosage adjustment is necessary for patients with renal impairment (see **DOSAGE AND ADMINISTRATION).**

Monitoring and Laboratory Tests

Serum transaminases and bilirubin should be measured prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see **WARNINGS AND PRECAUTIONS**).

Caution is advised if patients need to be withdrawn from prednisone. Monitoring for adrenocortical insufficiency should occur. If ZYTIGA® is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess (see **WARNINGS AND PRECAUTIONS**, **Corticosteroid Withdrawal and Coverage of Stress Situations**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

In combined data from the Phase 3 pivotal trials, the most common adverse reactions seen with ZYTIGA® are peripheral edema, hypokalemia, urinary tract infection, alanine aminotransferase increased, aspartate aminotransferase increased, dyspepsia, hematuria, hypertension, and fractures. The most common ZYTIGA® adverse reactions leading to clinical intervention were AST elevation and ALT elevation. The most common adverse drug reactions that resulted in drug discontinuation were alanine aminotransferase increased and aspartate aminotransferase increased (each in < 1% of patients taking ZYTIGA®). ZYTIGA® may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. Generally, these effects, due to mineralocorticoid excess, were successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse drug reactions (see **WARNINGS AND PRECAUTIONS**).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Placebo-controlled Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302)

In a placebo-controlled, multicentre Phase 3 clinical study of asymptomatic or mildly symptomatic patients with mCRPC who were using a GnRH agonist or were previously treated with orchiectomy, ZYTIGA® was administered at a dose of 1 g daily in combination with low dose prednisone (10 mg daily) in the active treatment arm. Placebo plus low dose prednisone (10 mg daily) was given to control patients. The average duration of treatment with ZYTIGA® was 13.8 months.

The most common all grade adverse reactions observed with ZYTIGA® compared to placebo were joint pain or discomfort (32% vs. 27%), peripheral edema (25% vs. 20%), hot flush (22% vs. 18%), diarrhea (22% vs. 18%), hypertension (22% vs. 13%), cough (17% vs. 14%), hypokalemia (17% vs. 13%), upper respiratory tract infection (13% vs. 8%), dyspepsia (11% vs. 5%), hematuria (10% vs. 6%), nasopharyngitis (11% vs. 8%), vomiting (13% vs. 11%), fatigue (39% vs. 34%), constipation (23% vs. 19%), contusion (13% vs. 9%), insomnia (14% vs. 11%), anemia (11% vs. 9%) and dyspnea (12% vs. 10%).
The most common serious adverse drug reactions observed with ZYTIGA® compared to placebo was urinary tract infection (1.5% vs. 0.6%), hypokalemia (0.4% vs. 0.2%) and hematuria (1.8% vs. 0.7%).

The most common adverse reactions leading to clinical intervention with ZYTIGA® compared to placebo were AST elevation (4.2% vs. 0.6%), and ALT elevation (5.2% vs. 0.7%).
Anticipated mineralocorticoid effects were seen more commonly in patients treated with ZYTIGA® versus patients treated with placebo: hypokalemia (17% vs. 13%), hypertension (22% vs. 13%) and fluid retention (peripheral edema) (25% vs. 20%), respectively. In patients treated with ZYTIGA®, Grades 3 and 4 hypokalemia and Grades 3 and 4 hypertension were observed in 2% and 4% of patients, respectively.

Table 1.1: Adverse Drug Reactions that Occurred in the Phase 3 Study with Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302) at an Incidence Rate ≥2% (all grades) in the ZYTIGA® Group

	ZYTIGA® 1g Daily with Prednisone N=542			Placebo with Prednisone N=540		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cardiac Disorders						
Cardiac failure[a]	10 (1.9%)	4 (0.8%)	1 (0.2%)	1 (0.2%)	0	0
Angina pectoris[b]	14 (2.6%)	2 (0.4%)	0	6 (1.1%)	2 (0.4%)	0
General Disorders and Administrative Site Conditions						
Edema peripheral	134(24.7%)	2(0.4%)	0	108 (20.0%)	5 (0.9%)	0
Fatigue	212 (39.1%)	12 (2.2%)	0	185 (34.3%)	9 (1.7%)	0
Gastrointestinal Disorders						
Diarrhea	117 (21.6%)	5 (0.9%)	0	96 (17.8%)	5 (0.9%)	0
Dyspepsia	60 (11.1%)	0	0	27 (5.0%)	1 (0.2%)	0
Constipation	125 (23.1%)	2 (0.2%)	0	103 (19.1%)	3 (0.6%)	0

	ZYTIGA® 1g Daily with Prednisone N=542			Placebo with Prednisone N=540		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Vomiting	69 (12.7%)	4 (0.7%)	0	58 (10.7%)	0	0
Infections and Infestations						
Upper respiratory tract infection	69 (12.7%)	0	0	43 (8.0%)	0	0
Nasopharyngitis	58 (10.7%)	0	0	44 (8.1%)	0	0
Injury, Poisoning and Procedural Complications						
Contusion	72 (13.3%)	0	0	49 (9.1%)	0	0
Fall	32 (5.9%)	0	0	18 (3.3%)	0	0
Musculoskeletal and Connective Tissue Disorders						
Joint pain or discomfort[c]	172(31.7%)	11 (2.0%)	0	144 (26.7%)	11 (2.0%)	0
Metabolism and Nutrition Disorders						
Hypokalemia	91 (16.8%)	12 (2.2%)	1 (0.2%)	68 (12.6%)	10 (1.9%)	0
Skin and Subcutaneous Tissue Disorders						
Rash	44 (8.1%)	0	0	20 (3.7%)	0	0
Skin lesion	19 (3.5%)	0	0	5 (0.9%)	0	0
Psychiatric Disorders						
Insomnia	73 (13.5%)	1 (0.2%)	0	61 (11.3%)	0	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	94 (17.3%)	0	0	73 (13.5%)	1 9 (0.2%)	0
Dyspnea	64 (11.8%)	11 (2.0%)	2 (0.4%)	52 (9.6%)	4 (0.7%)	1 (0.2%)
Renal and Urinary Disorders						
Hematuria	56 (10.3%)	7 (1.3%)	0	30 (5.6%)	3 (0.6%)	0
Vascular Disorders						
Hot flush	121 (22.3%)	1 (0.2%)	0	98 (18.1%)	0	0
Hypertension	117 (21.6%)	21 (3.9%)	0	71 (13.1%)	16 (3.0%)	0
Hematoma	19 (3.5%)	0	0	6 (1.1%)	0	0

[a] Cardiac failure also included cardiac failure congestive, ejection fraction decreased, and left ventricular dysfunction.

[b] Angina pectoris included due to its clinical relevance.

[c] Joint pain or discomfort included: arthralgia, arthritis, bursitis, joint swelling, joint stiffness, joint range of motion decreased, joint effusion, osteoarthritis, spinal osteoarthritis, tendonitis, rheumatoid arthritis

Placebo-controlled Phase 3 Study in mCRPC Patients with prior treatment with Docetaxel (Study 301)

In a second placebo-controlled, multicentre Phase 3 clinical study of patients with mCRPC who were using a gonadotropin releasing hormone (GnRH) agonist or were previously treated with orchiectomy, and previously treated with docetaxel, ZYTIGA® was administered at a dose of 1 g daily in combination with low dose prednisone (10 mg daily) in the active treatment arm; placebo plus low dose prednisone (10 mg daily) was given to control patients. Patients enrolled were intolerant to or had failed up to two prior chemotherapy regimens, one of which contained

docetaxel. The average duration of treatment with ZYTIGA® was 32 weeks and the duration of treatment for placebo was 16 weeks.

The most common all grade adverse reactions observed with ZYTIGA® compared to placebo were myopathy (36.3% vs. 30.9%), joint pain or discomfort (30.7% vs. 24.1%), peripheral edema (24.9% vs. 17.3%), hot flush (19.0% vs. 16.8%), diarrhea (17.6% vs. 13.5%), hypokalemia (17.1% vs. 8.4%), urinary tract infection (11.5% vs. 7.1%), and cough 10.6% vs. 7.6%).

The most common serious adverse reactions observed with ZYTIGA® compared to placebo were urinary tract infection (1.8% vs. 0.8%), bone fracture (1.6% vs. 0.6%), and hypokalemia (0.8% vs. 0%).

The most common adverse reactions leading to clinical intervention with ZYTIGA® compared to placebo were AST elevation (1.4% vs. 0.5%), ALT elevation (1.1% vs. 0%), hypokalemia (1.1% vs. 0.5%), urinary tract infection (0.9% vs. 0.3%), hypertension (0.9% vs. 0.3%), congestive heart failure (0.5% vs. 0%), and angina pectoris (0.3% vs. 0%).

Anticipated mineralocorticoid effects were seen more commonly in patients treated with ZYTIGA® versus patients treated with placebo: hypokalemia (17% vs. 8%), hypertension (9% vs. 7%) and fluid retention (peripheral edema) (25% vs. 17%), respectively. In patients treated with ZYTIGA®, Grades 3 and 4 hypokalemia and Grades 3 and 4 hypertension were observed in 4% and 1% of patients, respectively.

Table 1.2: Adverse Drug Reactions that Occurred in a Phase 3 Study with mCRPC Patients with Prior Treatment with Docetaxel (Study 301) at an Incidence Rate ≥2% (all grades) in the ZYTIGA® Group

	ZYTIGA® 1g Daily with Prednisone N=791			Placebo with Prednisone N=394		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Cardiac Disorders						
Arrhythmia[a]	56 (7.0%)	7 (0.9%)	2 (0.2%)	15 (4.0%)	2 (0.5%)	1 (0.3%)
Cardiac failure[b]	16 (2.0%)	12 (1.5%)	1 (0.1%)	4 (1.0%)	0	1 (0.3%)
Angina pectoris[c]	10 (1.3%)	2 (0.3%)	0	2 (0.5%)	0	0
General Disorders and Administrative Site Conditions						
Edema peripheral	197 (24.9%)	11 (1.4%)	1 (0.1%)	68 (17.3%)	3 (0.8%)	0
Gastrointestinal Disorders						
Diarrhea	139 (17.6%)	5 (0.6%)	0	53 (13.5%)	5 (1.3%)	0
Dyspepsia	48 (6.1%)	0	0	13 (3.3%)	0	0
Injury, Poisoning and Procedural Complications						
Fractures[d]	47 (5.9%)	8 (1.0%)	3 (0.4%)	9 (2.3%)	0	0
Infections and Infestations						
Urinary tract infection	91 (11.5%)	17 (2.1%)	0	28 (7.1%)	2 (0.5%)	0
Upper respiratory tract infection	43 (5.4%)	0	0	10 (2.5%)	0	0

	ZYTIGA® 1g Daily with Prednisone N=791			Placebo with Prednisone N=394		
System Organ Class / MedDRA Preferred Term (PT)	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Musculoskeletal and Connective Tissue Disorders						
Joint pain or discomfort[e]	243(30.7%)	37 (4.7%)	0	95 (24.1%)	17 (4.3%)	0
Myopathy[f]	287 (36.3%)	43 (5.4%)	2 (0.2%)	122 (30.9%)	14 (4.6%)	1 (0.3%)
Metabolism and Nutrition Disorders						
Hypokalemia	135 (17.1%)	27 (3.4%)	3 (0.4%)	33 (8.4%)	3 (0.8%)	0
Respiratory, Thoracic and Mediastinal Disorders						
Cough	84 (10.6%)	0	0	30 (7.6%)	0	0
Renal and Urinary Disorders						
Urinary frequency	57 (7.2%)	2 (0.3%)	0	20 (5.1%)	1 (0.3%)	0
Nocturia	49 (6.2%)	0	0	16 (4.1%)	0	0
Vascular Disorders						
Hot flush	150 (19.0%)	2 (0.3%)	0	66 (16.8%)	1 (0.3%)	0
Hypertension	67 (8.5%)	10 (1.3%)	0	27 (6.9%)	1 (0.3%)	0

[a] Arrhythmia included: tachycardia, atrial fibrillation, arrhythmia, bradycardia, supraventricular tachycardia, atrial tachycardia, atrioventricular block complete, conduction disorder, ventricular tachycardia, atrial flutter, bradyarrhythmia.

[b] Cardiac failure also included cardiac failure congestive, ejection fraction decreased, and left ventricular dysfunction.

[c] Angina pectoris included due to its clinical relevance.

[d] Fractures included all fractures with the exception of pathological fracture.

[e] Joint pain or discomfort included: arthralgia, arthritis, arthropathy, bursitis, joint swelling, joint stiffness, joint range of motion decreased, joint effusion, joint ankylosis, osteoarthritis, rheumatoid arthritis, spinal osteoarthritis, spondylolisthesis, tendonitis.

[f] Myopathy included: musculoskeletal pain, musculoskeletal stiffness, musculoskeletal chest pain, myalgia, muscular weakness, musculoskeletal discomfort, myopathy, limb discomfort, blood creatine phosphokinase increased, muscle atrophy, muscle fatigue, muscle twitching, myopathy steroid.

Cardiovascular Effects: The Phase 3 studies excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart disease (in mCRPC patients with prior treatment with docetaxel), or NYHA Class II to IV heart disease (in asymptomatic or mildly symptomatic mCRPC patients). All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy (ADT), predominantly the use of GnRH agonists, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death.

Cardiovascular adverse reactions in asymptomatic or mildly symptomatic patients occurred in 16% of patients who received ZYTIGA® and in 14% of patients who received placebo and in patients with prior exposure to docetaxel the incidence was 11% in patients who received ZYTIGA® and in 7% of patients who received placebo.

Hepatotoxicity: Drug-associated hepatotoxicity with elevated serum transaminases (ALT and AST) and total bilirubin has been reported in patients treated with ZYTIGA®. Liver function test elevations (ALT or AST increases of > 5X ULN or bilirubin increases > 1.5X ULN) were reported in approximately 8% of asymptomatic or mildly symptomatic mCRPC patients who

received ZYTIGA® and in approximately 2% of patients with prior treatment with docetaxel who received ZYTIGA®, typically during the first 3 months after starting treatment. In the Phase 3 clinical study in mCRPC patients with prior treatment with docetaxel, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST > 5X ULN, or elevations in bilirubin > 3X ULN were observed, ZYTIGA® was withheld or discontinued. In two instances marked increases in liver function tests occurred (see **WARNINGS AND PRECAUTIONS**). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40X ULN and bilirubin elevations 2 to 6X ULN. Upon interruption of ZYTIGA®, both patients had normalization of their liver function tests. One patient was re-treated with ZYTIGA®. Recurrence of the elevations was not observed in this patient. In the Phase 3 clinical study of asymptomatic or mildly symptomatic mCRPC patients, Grade 3 or 4 ALT or AST elevations were observed in 35 (6.5%) patients treated with ZYTIGA®. Aminotransferase elevations resolved in all but 3 patients (2 with new multiple liver metastases, and 1 with AST elevation approximately 3 weeks after the last dose of ZYTIGA®). Treatment discontinuations due to ALT and AST increases were reported in 1.7% and 1.3% of patients treated with ZYTIGA® and 0.2% and 0% of patients treated with placebo, respectively. No deaths were reported due to hepatotoxicity event.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with active hepatitis or baseline hepatitis or significant abnormalities of liver function tests. In the trial with mCRPC patients who had received prior treatment with docetaxel, patients with baseline ALT and AST ≥ 2.5X ULN in the absence of liver metastases and > 5X ULN in the presence of liver metastases were excluded. In the trial with asymptomatic or mildly symptomatic mCRPC patients, those with liver metastases were not eligible and patients with baseline ALT and AST ≥2.5X ULN were excluded. Abnormal liver function tests developing in patients participating in clinical trials were managed by treatment interruption and by permitting re-treatment only after return of liver function tests to the patient's baseline (see **DOSAGE AND ADMINISTRATION**). Patients with elevations of ALT or AST > 20X ULN were not re-treated. The safety of re-treatment in such patients is unknown.

Less Common Clinical Trial Adverse Drug Reactions (< 2%)
General Disorders and Administrative Site Conditions: Influenza-like illness
Investigations: Blood creatinine increased, weight increased
Infections and Infestations: Lower respiratory tract infection
Metabolism and Nutrition Disorders: Hypertriglyceridaemia
Endocrine Disorders: Adrenal insufficiency

Abnormal Hematologic and Clinical Chemistry Findings:
Tables 1.3 and 1.4 show laboratory values of interest from the Phase 3, placebo-controlled trials.

Table 1.3: Selected Laboratory Abnormalities in mCRPC Asymptomatic or Mildly Symptomatic Patients who Received ZYTIGA®

	ZYTIGA® 1g Daily with Prednisone N=542		Placebo with Prednisone N=540	
Chemistry Parameters	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
ALT increased	41	6	28	1
AST increased	36	3	27	1
Bilirubin increased	11	<1	4	<1
Hypokalemia	14	2	8	1
Hypophosphatemia	26	5	14	2
Hypertriglyceridemia	22	0	17	0
Hypernatremia	30	<1	24	<1
Hypercalcemia	10	0	4	0
Lymphopenia	36	7	30	0

Table 1.4: Selected Laboratory Abnormalities in mCRPC Patients Patients with Prior Treatment with Docetaxel who Received ZYTIGA®

	ZYTIGA® 1g Daily with Prednisone N=791		Placebo with Prednisone N=394	
Chemistry Parameters	All Grades %	Grade 3/4 %	All Grades %	Grade 3/4 %
ALT increased	11	1	10	<1
AST increased	30	2	34	1
Bilirubin increased	6	<1	3	0
Hypokalemia	19	3	10	<1
Cholesterol	55	<1	48	<1
Low phosphorus	23	7	15	5
Triglycerides	62	<1	53	0

Post-Market Adverse Drug Reactions

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

Respiratory, thoracic and mediastinal disorders: allergic alveolitis
Musculoskeletal and connective tissue disorders: rhabdomyolysis, myopathy

DRUG INTERACTIONS

Overview

In vitro studies indicated that CYP3A4 and SULT2A1 are the major isoenzymes involved in the metabolism of abiraterone (see **DETAILED PHARMACOLOGY, Non-clinical Pharmacokinetics**). Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes

CYP2C8 and CYP2D6 (see **Drug-Drug Interactions**).

Drug-Drug Interactions

Potential for other medicinal ingredients to affect ZYTIGA®

CYP3A4 inducers: Based on *in vitro* data, the active metabolite abiraterone is a substrate of CYP3A4. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampicin, 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%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital) during treatment with ZYTIGA® are to be avoided. If patients must be co-administered a strong CYP3A4 inducer, careful evaluation of clinical efficacy must be undertaken as there are no clinical data recommending an appropriate dose adjustment.

CYP3A4 inhibitors: In a clinical pharmacokinetic interaction study, healthy subjects were administered ketoconazole, a strong CYP3A4 inhibitor, 400 mg daily for 6 days. No clinically meaningful effect on the pharmacokinetics of abiraterone was demonstrated following co-administration of a single dose of abiraterone acetate, 1000 mg at day 4.

Potential for ZYTIGA® to affect other drugs

CYP1A2:
In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

CYP2D6: In the same study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased by approximately 200%. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased by approximately 33%.

ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Caution is advised when ZYTIGA® is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

CYP2C8: In a CYP2C8 drug-drug interaction trial in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of the CYP2C8 substrate pioglitazone, each decreased by 10%, when a single dose of pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Although ZYTIGA® is an inhibitor of CYP2C8, these results indicate that no clinically meaningful increases in exposure are expected when ZYTIGA® is combined with drugs that are predominantly eliminated by CYP2C8. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with ZYTIGA®.

CYP2C9, CYP2C19 and CYP3A4/5: *In vitro* studies with human hepatic microsomes demonstrated that abiraterone was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5.

No clinical DDI studies have been performed to confirm these *in vitro* findings **(see DETAILED PHARMACOLOGY, Non-clinical Pharmacokinetics**).

OATP1B1:
In vitro, abiraterone and its major metabolites were shown to inhibit the hepatic uptake transporter OATP1B1 and as a consequence it may increase the concentrations of drugs that are eliminated by OATP1B1. There are no clinical data available to confirm transporter based interaction.

Drug-Food Interactions
Administration of ZYTIGA® with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of ZYTIGA® given with food has not been established. **ZYTIGA® must not be taken with solid or liquid food (see DOSAGE AND ADMINISTRATION** and **ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics**).

Drug-Herb Interactions
Co-administration of ZYTIGA® with St. John's wort (*Hypericum perforatum*) may potentially reduce the plasma concentrations of ZYTIGA®. Concomitant use with St. John's wort or products containing St. John's wort is to be avoided.

Drug-Lifestyle Interactions
No studies on the effects of ZYTIGA® on the ability to drive or use machines have been performed. It is not anticipated that ZYTIGA® will affect the ability to drive and use machines.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment
The recommended dosage of ZYTIGA® is 1 g (four 250 mg tablets) as a single daily dose that **must be taken on an empty stomach**. No solid or liquid 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.

ZYTIGA® is used with low-dose prednisone. The recommended dosage of prednisone is 10 mg daily.

Patients started on ZYTIGA® who were receiving a GnRH agonist should continue to receive a GnRH agonist.

Serum transaminases and bilirubin should be measured prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment and monthly thereafter.

Blood pressure, serum potassium and fluid retention should be monitored monthly (see **WARNINGS AND PRECAUTIONS**, **Cardiovascular**, ***Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess***).

Missed Dose

In the event of a missed daily dose of either ZYTIGA® or prednisone, treatment should be resumed the following day with the usual daily dose.

Dose Adjustment in Patients with Hepatic Impairment

ZYTIGA® should not be used in patients with pre-existing moderate or severe hepatic impairment (see **ACTION AND CLINICAL PHARMACOLOGY**).

No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment.

For patients who develop hepatotoxicity during treatment with ZYTIGA® (serum transaminases, ALT or AST rise above 5 times the upper limit of normal or bilirubin rises above 3 times the upper limit of normal) treatment should be withheld immediately until liver function tests normalize (see **WARNINGS AND PRECAUTIONS, Hepatic**).

Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, discontinue treatment with ZYTIGA®. Reduced doses should not be taken with food (see **DOSAGE AND ADMINISTRATION, Recommended Dose and Dosage Adjustment**).
If patients develop severe hepatotoxicity (ALT 20 times the upper limit of normal) anytime while on therapy, ZYTIGA® should be discontinued and patients should not be re-treated with ZYTIGA®.

Dose Adjustment in Patients with Renal Impairment

No dosage adjustment is necessary for patients with renal impairment.

OVERDOSAGE

Human experience of overdose with ZYTIGA® is limited.

There is no specific antidote. In the event of an overdose, administration of ZYTIGA® should be stopped and general supportive measures undertaken, including monitoring for arrhythmias. Liver function also should be assessed.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Abiraterone acetate (ZYTIGA®) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumor tissues. It catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17-α hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid

production by the adrenals (see **WARNINGS AND PRECAUTIONS, *Hypertension, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess***).
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® decreases serum testosterone and other androgens in patients to levels lower than those achieved by the use of GnRH agonists alone or by orchiectomy. Commercial testosterone assays have inadequate sensitivity to detect the effect of ZYTIGA® on serum testosterone levels, therefore, 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.

Pharmacodynamics

Cardiac Electrophysiology: A multicentre, open-label, uncontrolled, singlearm ECG assessment study was performed in 33 patients with metastatic castration-resistant prostate cancer who were medically (N=28) or surgically castrated (N=5). Patients had serial ECG recordings at baseline and on day 1 of the first and second 28-day cycles of treatment with abiraterone acetate 1g/day plus prednisone 5 mg twice daily. At steady-state on day 1 of cycle 2, the QTc interval was significantly shortened at most time points, with a maximum decrease from baseline of mean -10.7 (90% CI -14.8, -6.5) ms at 24 h post-dosing.

Androgen deprivation is associated with QTc prolongation. In this study the QTc interval averaged 435−440 ms at baseline and 57.6% of subjects had baseline QTc values > 450 ms prior to initiation of abiraterone acetate. Because the subjects in this trial were already androgen-deprived, the results of this study cannot be extrapolated to non-castrated populations.
Mineralocorticoid receptor antagonists: Patients in the pivotal clinical trials (COU-AA-302 and COU-AA-301) were not allowed to use the mineralocorticoid receptor antagonist spironolactone with ZYTIGA® since spironolactone has the ability to bind and activate the wild type androgen receptor, which could stimulate disease progression. The use of spironolactone with ZYTIGA® should be avoided.

Prior use of ketoconazole: Based on experience in an early abiraterone acetate trial, lower rates of response might be expected in patients previously treated with ketoconazole for prostate cancer.

Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

Absorption: The AUC and C_{max} values in patients with castration-resistant prostate cancer were 979 ng•h/mL and 216.5 ng/mL respectively. In addition, there was large inter-patient variability observed for healthy subjects and patients with castration-resistant prostate cancer.

There was an observed reduction in the clearance of patients with castration-resistant prostate cancer (33%) compared to healthy subjects. This reduction could translate to a 40% mean increase of mean population predicted exposure in patients relative to healthy subjects, but this increase may be confounded with effects of concomitant medications and food intake conditions. This difference is not considered to be clinically relevant.

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours in patients with castration-resistant prostate cancer.

Systemic exposure of abiraterone is increased when abiraterone acetate is administered with food. Abiraterone C_{max} and AUC 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 meal (57% fat, 825 calories).

Given the normal variation in the content and composition of meals, taking ZYTIGA® with meals has the potential to result in highly variable exposures. Therefore, ZYTIGA® **must be taken on an empty stomach**. No solid or liquid food should be consumed at least two hours before taking ZYTIGA® and for at least one hour after taking ZYTIGA®. The tablets should be swallowed whole with water (see **DOSAGE AND ADMINISTRATION**).

Distribution: The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues. *In vitro* studies show that at clinically relevant concentrations, abiraterone acetate and abiraterone are not substrates of P-glycoprotein (P-gp). *In vitro* studies show 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 rapidly hydrolyzed to the active metabolite abiraterone. This reaction is not CYP mediated but hypothesized to occur via an unidentified esterase(s). Abiraterone then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. This results in the formation of two main plasma circulating inactive metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each accounting for approximately 43% of total radioactivity. The formation of N-oxide abiraterone sulphate is predominantly catalyzed by CYP3A4 and SULT2A1 while the formation of abiraterone sulphate is catalyzed by SULT2A1.

Excretion: The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects and approximately 12 hours based on data from patients with metastatic castration-resistant prostate cancer. 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).

Special Populations and Conditions

The effect of intrinsic factors such as age and body weight has been evaluated using population pharmacokinetic approaches and no statistically significant effect was evident for any of these covariates.

Pediatrics: Abiraterone acetate has not been investigated in pediatric subjects.

Gender: All clinical study information thus far is derived from male subjects.

Hepatic Insufficiency: The pharmacokinetics of abiraterone was examined in non-mCRPC subjects with pre-existing mild (N=8) or moderate (N=8) hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control subjects (N=8). Systemic exposure (AUC) to abiraterone after a single oral 1 g dose increased by approximately 1.1 fold and 3.6 fold in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone was prolonged from approximately 13 hours in healthy subjects to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dosage adjustment is necessary for mCRPC patients with pre-existing mild hepatic impairment. ZYTIGA® should not be used in patients with pre-existing moderate or severe hepatic impairment. The safety of ZYTIGA® has not been studied in mCRPC patients with moderate or severe (Child-Pugh Class B or C) hepatic impairment at baseline.

For patients who develop hepatotoxicity during treatment with ZYTIGA® suspension of treatment and dosage adjustment may be required (see **DOSAGE AND ADMINISTRATION** and **WARNINGS AND PRECAUTIONS**).

Renal Insufficiency: The pharmacokinetics of abiraterone following the administration of a single oral 1 g dose of abiraterone acetate was compared in patients with end-stage renal disease on a stable hemodialysis schedule (N=8), versus matched control subjects with normal renal function (N=8). Systemic exposure to abiraterone after a single oral 1 g dose did not increase in patients with end-stage renal disease on dialysis.

Administration of ZYTIGA® in patients with renal impairment including severe renal impairment does not require dose adjustment (see **DOSAGE AND ADMINISTRATION**).
Genetic Polymorphism: The effect of genetic differences on the pharmacokinetics of abiraterone has not been evaluated.

STORAGE AND STABILITY

Store at 15–30°C.

SPECIAL HANDLING INSTRUCTIONS

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 section **WARNINGS AND PRECAUTIONS, Special Populations**).

Any unused product or waste material should be disposed of in accordance with local requirements.

DOSAGE FORMS, COMPOSITION AND PACKAGING

ZYTIGA® 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 fitted with a polypropylene cap. Package size is 120 tablets. Inactive ingredients in the tablets are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

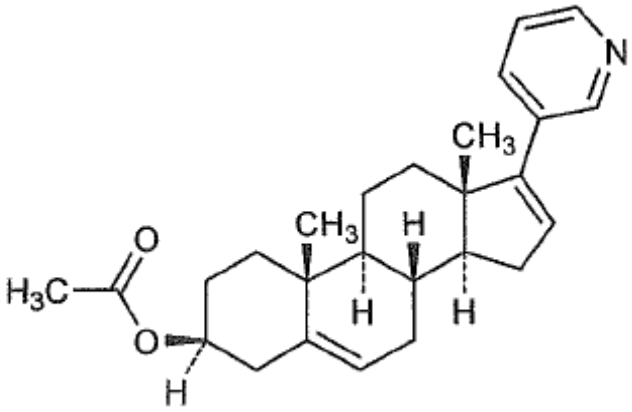
Drug Substance

Common name: abiraterone acetate

Chemical name: (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate

Molecular formula and molecular mass: $C_{26}H_{33}NO_2$ and 391.55

Structural formula:



Physicochemical properties: Abiraterone acetate is a white to off-white crystalline powder. Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH values (pH=2.0 to 12.9). The melting point is between 147ºC and 148ºC. The pKa is 5.19.

CLINICAL TRIALS

The efficacy of ZYTIGA® has been established in two separate randomized, placebo-controlled multicentre Phase 3 clinical studies of patients with metastatic prostate cancer (castration-resistant prostate cancer (mCRPC)).

Placebo-controlled Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients (Study 302)

Study demographics and trial design

In this study, the efficacy of ZYTIGA® was established in patients with mCRPC (documented by positive bone scans and/or metastatic lesions on CT, MRI other than visceral metastasis) who were asymptomatic (as defined by a score of 0-1 on BPI-SF, worst pain over the last 24 hours) or mildly symptomatic (as defined by a score of 2-3 on BPI-SF, worst pain over the last 24 hours)

after failure of ADT, who were using a GnRH agonist during study treatment or were previously treated with orchiectomy (N=1088). Patients were randomized 1:1 to receive either ZYTIGA® or placebo. In the active treatment arm, ZYTIGA® was administered orally at a dose of 1 g daily in combination with low dose prednisone 5 mg twice daily (N=546). Control patients received placebo and low dose prednisone 5 mg twice daily (N=542).

Patients were not included in the study if they had moderate or severe pain, opiate use for severe pain, liver or visceral organ metastases, known brain metastasis, clinically significant heart disease, (as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or LVEF < 50% or New York Heart Association Class II to IV heart failure), prior ketoconazole for the treatment of prostate cancer, a history of adrenal gland or pituitary disorders or prostate tumor showing extensive small cell (neuroendocrine) histology. Spironolactone was a restricted concomitant therapy due to its potential to stimulate disease progression. Patients who had received prior chemotherapy or biologic therapy were excluded from the study.

The co-primary efficacy endpoints for this study were overall survival and radiographic progression free survival (rPFS). In addition to the co-primary endpoint measures, benefit was also assessed using time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy, time to deterioration in ECOG performance score by ≥ 1 point and time to PSA progression based on Prostate Cancer Working Group-2 (PCWG2) criteria. Study treatments were discontinued at the time of unequivocal clinical progression. Unequivocal clinical progression was characterized as cancer pain requiring initiation of chronic administration of opiate analgesia (oral opiate use for ≥3 weeks; parenteral opiate use for ≥7 days), or immediate need to initiate cytotoxic chemotherapy or the immediate need to have either radiation therapy or surgical intervention for complications due to tumor progression, or deterioration in ECOG performance status to Grade 3 or higher. Treatments could also be discontinued at the time of confirmed radiographic progression at the discretion of the investigator.

Radiographic progression free survival was assessed with the use of sequential imaging studies as defined by Prostate Cancer Working Group-2 (PCWG2) criteria (for bone lesions) with confirmatory bone scans and modified Response Evaluation Criteria In Solid Tumors (RECIST) criteria (for soft tissue lesions). Analysis of rPFS utilized centrally-reviewed radiographic assessment of progression.

Because changes in PSA serum concentration do not always predict clinical benefit, patients were maintained on ZYTIGA® until discontinuation criteria were met as specified for the study.

Table 2.1 summarizes key demographics and baseline disease characteristics. Demographics and baseline disease characteristics were balanced between the two groups.

Table 2.1: Key Demographics and Baseline Disease Characteristics (Phase 3 Study in Asymptomatic or Mildly Symptomatic mCRPC Patients: ITT Population)

	ZYTIGA® + Prednisone (N=546)	Placebo + Prednisone (N=542)	Total (N=1088)
Age (years)			
N	546	542	1088
Mean (SD)	70.5 (8.80)	70.1 (8.72)	70.3 (8.76)
Median	71.0	70.0	70.0
Range	(44, 95)	(44, 90)	(44, 95)
Sex			
n	546	542	1088
Male	546 (100.0%)	542 (100.0%)	1088 (100.0%)
Race			
n	545	540	1085
White	520 (95.4%)	510 (94.4%)	1030 (94.9%)
Black	15 (2.8%)	13 (2.4%)	28 (2.6%)
Asian	4 (0.7%)	9 (1.7%)	13 (1.2%)
Other	6 (1.1%)	6 (1.1%)	12 (1.1%)
Time From Initial Diagnosis to First Dose (years)			
n	542	540	1082
Mean (SD)	6.7 (4.85)	6.5 (4.77)	6.6 (4.81)
Median	5.5	5.1	5.3
Range	(0, 28)	(0, 28)	(0, 28)
Extent of Disease			
n	544	542	1086
Bone	452 (83.1%)	432 (79.7%)	884 (81.4%)
Bone Only	274 (50.4%)	267 (49.3%)	541 (49.8%)
Soft Tissue or Node	267 (49.1%)	271 (50.0%)	538 (49.5%)
ECOG Performance Status Score			
n	546	542	1088
0	416 (76.2%)	414 (76.4%)	830 (76.3%)
1	130 (23.8%)	128 (23.6%)	258 (23.7%)
Baseline PSA (ng/mL)			
n	546	539	1085
Mean (SD)	133.38 (323.639)	127.63 (387.878)	130.52 (356.846)
Median	42.01	37.74	39.51
Range	(0.0, 3927.4)	(0.7, 6606.4)	(0.0, 6606.4)
Baseline Hemoglobin (g/dL)			
n	545	538	1083
Mean (SD)	12.97 (1.22)	12.99 (1.22)	12.98 (1.22)
Median	13.0	13.1	13.1
Range	(7.2,16.6)	(7.0, 15.7)	(7.0, 16.6)
Baseline Alkaline Phosphatase (IU/L)			
n	546	539	1085
Mean (SD)	137.4 (166.88)	148.1 (248.11,)	142.8 (211.15)
Median	93.0	90.0	91.0
Range	(32, 1927)	(21, 3056)	(21, 3056)
Baseline Lactate Dehydrogenase (IU/L)			
n	543	536	1079
Mean (SD)	199.9 (78.57)	196.8 (59.20)	198.3 (69.61)
Median	187.0	184.0	185.0
Range	(60, 871)	(87, 781)	(60, 871)

Study results

At the planned rPFS analysis there were 401 radiographic progression events; 150 (28%) of patients treated with ZYTIGA® and 251 (46%) of patients treated with placebo had radiographic evidence of progression or had died. A significant difference in rPFS between treatment groups was observed, see Table 2.2 and Figure 2.1.

Table 2.2: Radiographic Progression-free Survival of Patients Treated with Either ZYTIGA® or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy (ITT Population)

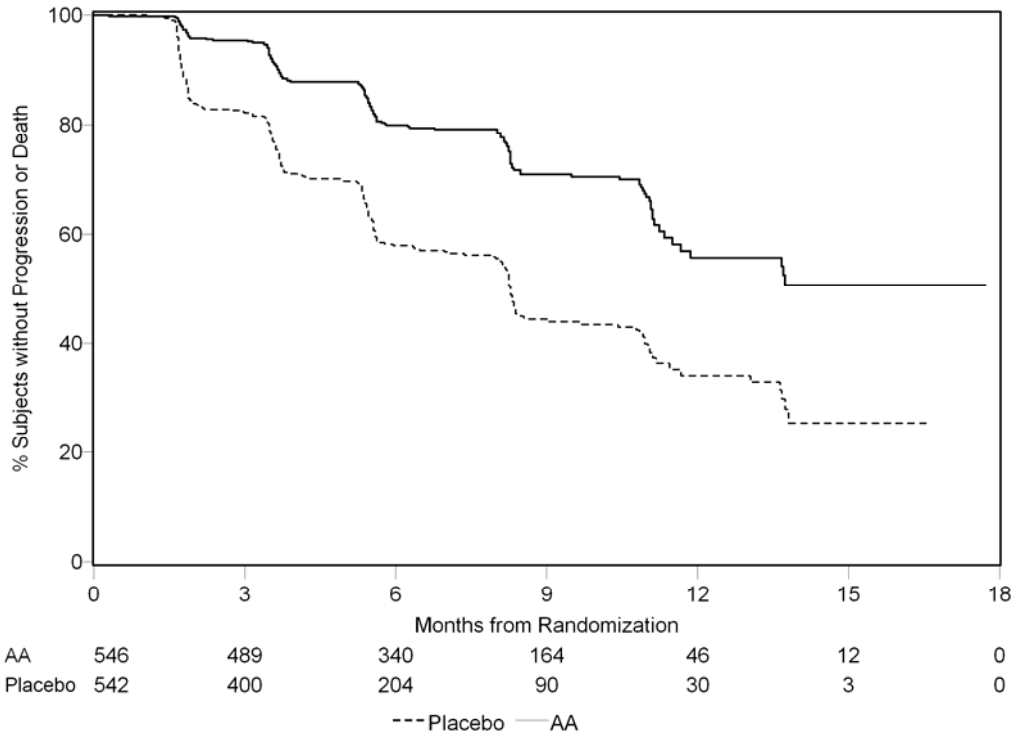
	ZYTIGA® (N=546)	Placebo (N=542)
Radiographic Progression-free Survival (rPFS)		
Progression or death	150 (28%)	251 (46%)
Median rPFS in months (95% CI)	Not reached (11.66, NE)	8.3 (8.12, 8.54)
p-value*	<0.0001	
Hazard ratio** (95% CI)	0.425 (0.347, 0.522)	

NE= Not Estimated

* From a log-rank test of the equality of two survival curves over the time interval, and stratified by baseline ECOG score (0 or 1)

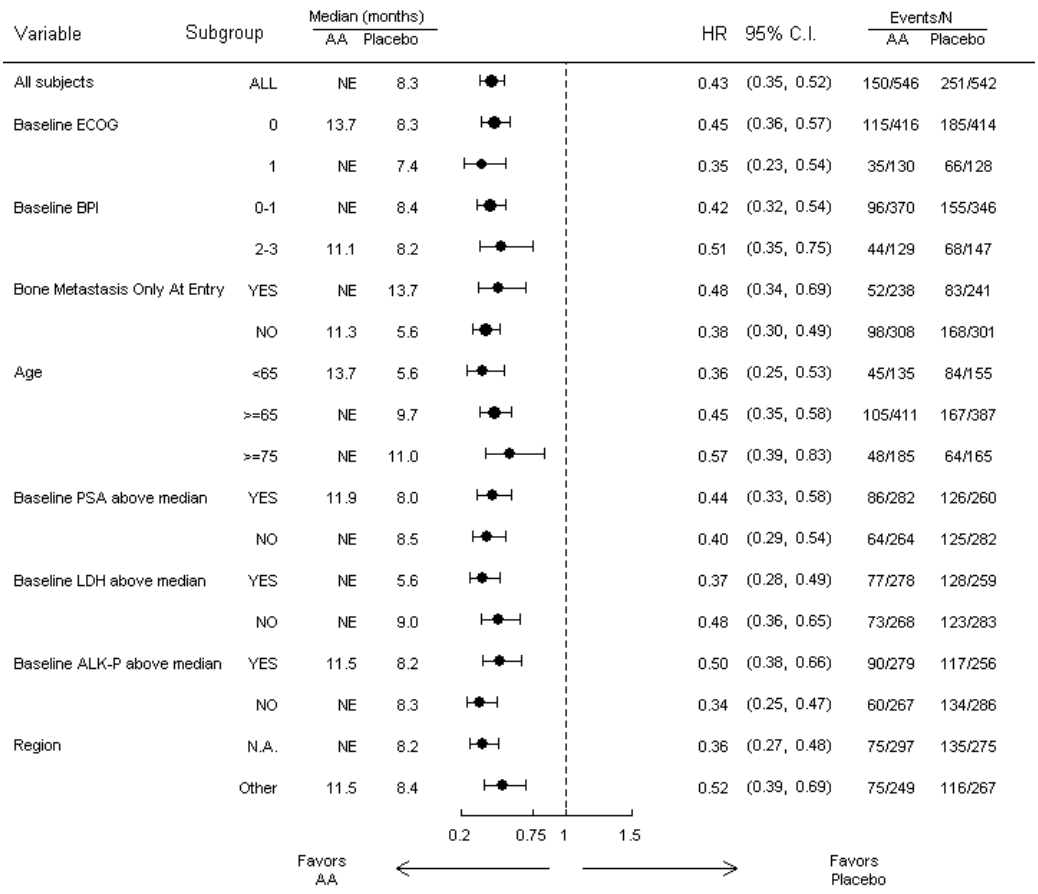
** Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA®

Figure 2.1: Kaplan Meier Curves of Radiographic Progression-free Survival in Patients Treated with Either ZYTIGA® or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy



Radiographic Progression-Free Survival analyses by subgroup are presented in Figure 2.2.

Figure 2.2: Radiographic Progression-Free Survival by Subgroup Hazard Ratio and 95% Confident Interval (ITT Population)



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.
AA=abiraterone acetate; ALP=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

A planned analysis for overall survival was conducted after 333 deaths were observed. The study was unblinded based on the magnitude of clinical benefit observed. Twenty seven percent (147 of 546) of patients treated with ZYTIGA®, compared with 34% (186 of 542) of patients treated with placebo, had died. Overall survival was longer for ZYTIGA® than placebo with a 25% reduction in risk of death (Hazard Ratio = 0.752; 95 % CI: 0.606 - 0.934). The p value was 0.0097 which did not meet the pre-specified value for statistical significance (see Table 2.3 and Figure 2.3).

Table 2.3: Overall Survival of Asymptomatic or mildly symptomatic mCRPC Patients Treated with Either ZYTIGA® or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy (ITT Population)

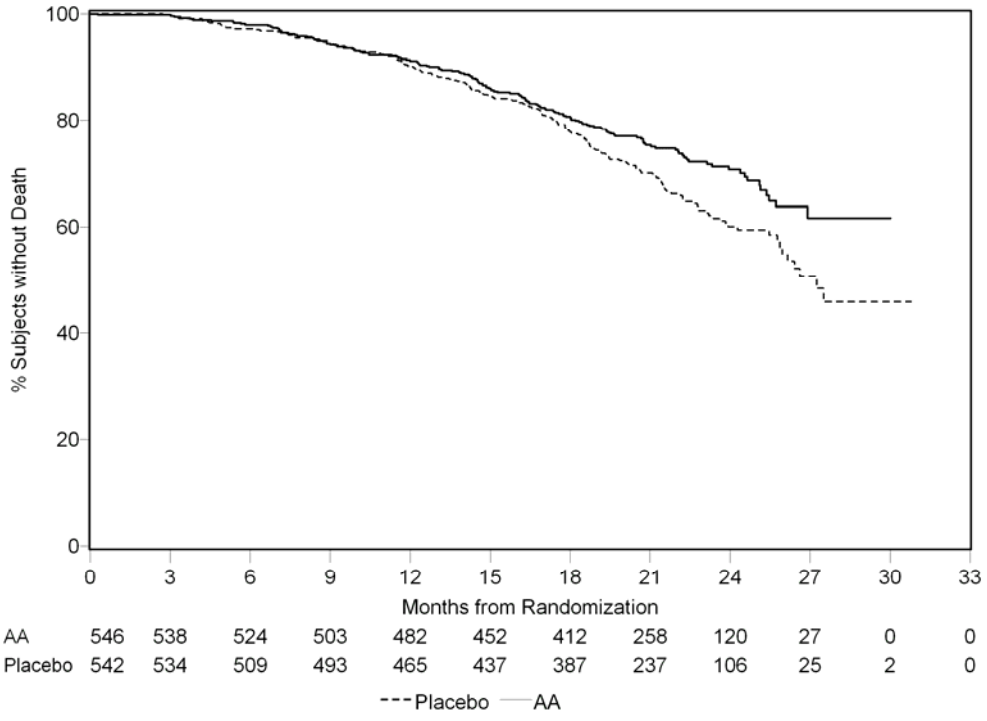
	ZYTIGA® (N=546)	Placebo (N=542)
Overall Survival		
Deaths	147 (27%)	186 (34%)
Median overall survival in months (95% CI)	Not reached (NE, NE)	27.2 (25.95, NE)
p-value*	0.0097	
Hazard ratio** (95% CI)	0.752 (0.606, 0.934)	

NE= Not Estimated

* From a log-rank test of the equality of two survival curves over the time interval, and stratified by baseline ECOG score (0 or 1)

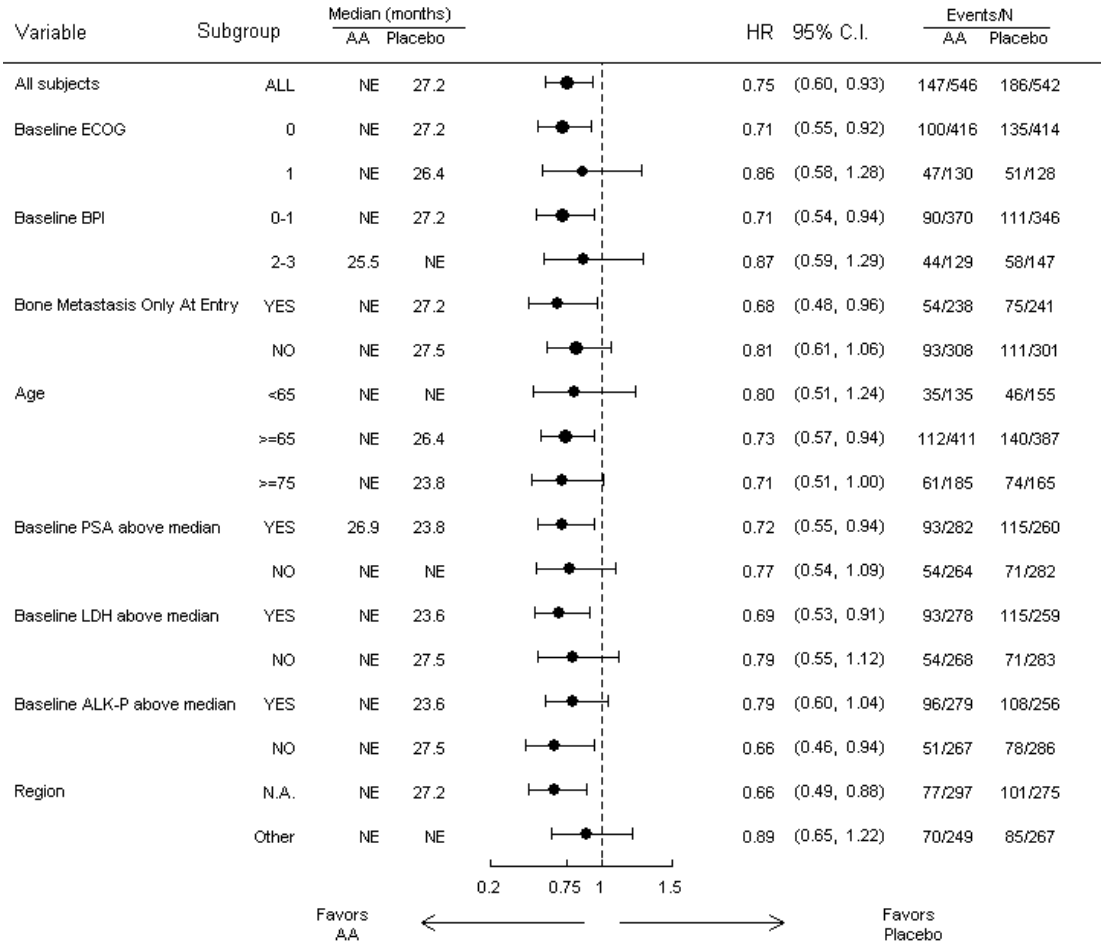
** Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio <1 favors ZYTIGA®

Figure 2.3: Kaplan Meier Survival Curves of Patients Treated with Either ZYTIGA® or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy



Survival analyses by subgroup are presented in Figure 2.4.

Figure 2.4: Overall Survival by Subgroup: Hazard Ratio and 95% Confident Interval (ITT Population)



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.
AA=abiraterone acetate; ALP=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

Subgroup analyses showed a consistent but significant rPFS effect and a consistent trend in overall survival effect favoring treatment with ZYTIGA®.

The observed improvements in the co-primary efficacy endpoints of overall survival and rPFS were supported by clinical benefit favoring ZYTIGA® vs. placebo treatment in the following prospectively assessed secondary endpoint as follows:

Time to opiate use for cancer pain: 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).

Time to initiation of cytotoxic chemotherapy: 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).

In addition, other secondary endpoints had statistically significant results that favored ZYTIGA®. PSA-based endpoints are not validated surrogate endpoints of clinical benefit in this patient population. Nevertheless, patients receiving ZYTIGA® demonstrated a significantly higher total PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo: 62% versus 24%, p<0.0001. The median time to PSA progression (time interval from randomization to PSA progression, according to PSAWG criteria) was 11.1 months for patients treated with ZYTIGA® and 5.6 months for patients treated with placebo (HR=0.488; 95% CI: [0.420, 0.568], p<0.0001). The median time to deterioration in ECOG performance score by ≥ 1 point was 12.3 months for patients receiving ZYTIGA® and 10.9 months for patients receiving placebo (HR=0.821; 95% CI: [0.714, 0.943], p=0.0053).

Placebo-controlled Phase 3 Study in mCRPC Patients with Prior Docetaxel Treatment (Study 301)

Study demographics and trial design

In this study, the efficacy of ZYTIGA® was established in patients with mCRPC who had received prior chemotherapy containing docetaxel. Patients continued to be treated with a GnRH agonist during study treatment or were previously treated with orchiectomy (N=1195). Patients were randomized 2:1 to receive either ZYTIGA® or placebo. In the active treatment arm, ZYTIGA® was administered orally at a dose of 1 g daily in combination with low dose prednisone 5 mg twice daily (N=797). Control patients received placebo and low dose prednisone 5 mg twice daily (N=398).

Patients were not included in the study if they had clinically significant heart disease, (as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or LVEF < 50% or New York Heart Association Class III or IV heart failure), prior ketoconazole for the treatment of prostate cancer, a history of adrenal gland or pituitary disorders or prostate tumor showing extensive small cell (neuroendocrine) histology. Spironolactone was a restricted concomitant therapy due to its potential to stimulate disease progression.

The primary efficacy endpoint was overall survival.

PSA serum concentration independently does not always predict clinical benefit. In this study it was also recommended that patients be maintained on their study drugs until there was PSA progression (confirmed 25% increase over the patient's baseline/nadir) together with protocol-defined radiographic progression and symptomatic or clinical progression.

Table 2.4 summarizes key demographics and baseline disease characteristics. Demographics and baseline disease characteristics were balanced between the two groups.

Table 2.4: Key Demographics and Baseline Disease Characteristics Phase 3 Study in mCRPC patients with prior Docetaxel treatment: ITT Population)

	ZYTIGA®+ Prednisone (N=797)	Placebo + Prednisone (N=398)	Total (N=1195)
Age (years)			
N	797	397	1194
Mean (SD)	69.1 (8.40)	68.9 (8.61)	69.0 (8.46)
Median	69.0	69.0	69.0
Range	(42, 95)	(39, 90)	(39, 95)
Sex			
N	797	398	1195
Male	797 (100.0%)	398 (100.0%)	1195 (100.0%)
Race			
N	796	397	1193
White	743 (93.3%)	368 (92.7%)	1111 (93.1%)
Black	28 (3.5%)	15 (3.8%)	43 (3.6%)
Asian	11 (1.4%)	9 (2.3%)	20 (1.7%)
Other	14 (1.8%)	5 (1.3%)	19 (1.6%)
Time since initial diagnosis to first dose (days)			
N	791	394	1185
Mean (SD)	2610.9 (1630.21)	2510.1 (1712.36)	2577.4 (1657.93)
Median	2303.0	1928.0	2198.0
Range	(175, 9129)	(61, 8996)	(61, 9129)
Evidence of disease progression			
N	797	398	1195
PSA only	238 (29.9%)	125 (31.4%)	363 (30.4%)
Radiographic progression with or without PSA progression	559 (70.1%)	273 (68.6%)	832 (69.6%)
Extent of disease			
Bone	709 (89.2%)	357 (90.4%)	1066 (89.6%)
Soft tissue, not otherwise specified	0	0	0
Node	361 (45.4%)	164 (41.5%)	525 (44.1%)
Viscera, not otherwise specified	1 (0.1%)	0 (0.0%)	1 (0.1%)
Liver	90 (11.3%)	30 (7.6%)	120 (10.1%)
Lungs	103 (13.0%)	45 (11.4%)	148 (12.4%)
Prostate mass	60 (7.5%)	23 (5.8%)	83 (7.0%)
Other viscera	46 (5.8%)	21 (5.3%)	67 (5.6%)
Other tissue	40 (5.0%)	20 (5.1%)	60 (5.0%)
ECOG performance status			
N	797	398	1195
0 or 1	715 (89.7%)	353 (88.7%)	1068 (89.4%)
2	82 (10.3%)	45 (11.3%)	127 (10.6%)
Pain			
N	797	398	1195
Present	357 (44.8%)	179 (45.0%)	536 (44.9%)
Absent	440 (55.2%)	219 (55.0%)	659 (55.1%)
Baseline PSA (ng/mL)			
N	788	393	1181
Mean (SD)	439.18 (888.476)	400.58 (810.549)	426.33 (863.173)
Median	128.80	137.70	131.40
Range	(0.4, 9253.0)	(0.6, 10114.0)	(0.4, 10114.0)

Eleven percent of patients enrolled had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. As required in the protocol, 100% of patients had received docetaxel therapy prior to treatment with ZYTIGA®. All docetaxel containing regimens were considered as one line of therapy. Liver metastasis was present in 11% of patients treated with ZYTIGA®.

Study results

A median of 8 cycles (32 weeks) were administered in the abiraterone acetate group compared with 4 cycles (16 weeks) in the placebo group. The proportion of patients who required dose reductions was low; 4% in the abiraterone acetate group and 1% in the placebo group had dose reductions and 17% and 16%, respectively, required dose interruptions.

In a planned interim analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with ZYTIGA®, compared with 55% (219 of 398) of patients treated with placebo, had died. A statistically significant improvement in median overall survival was seen in patients treated with ZYTIGA® (see Table 2.5 and Figure 2.5).

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 2.5).

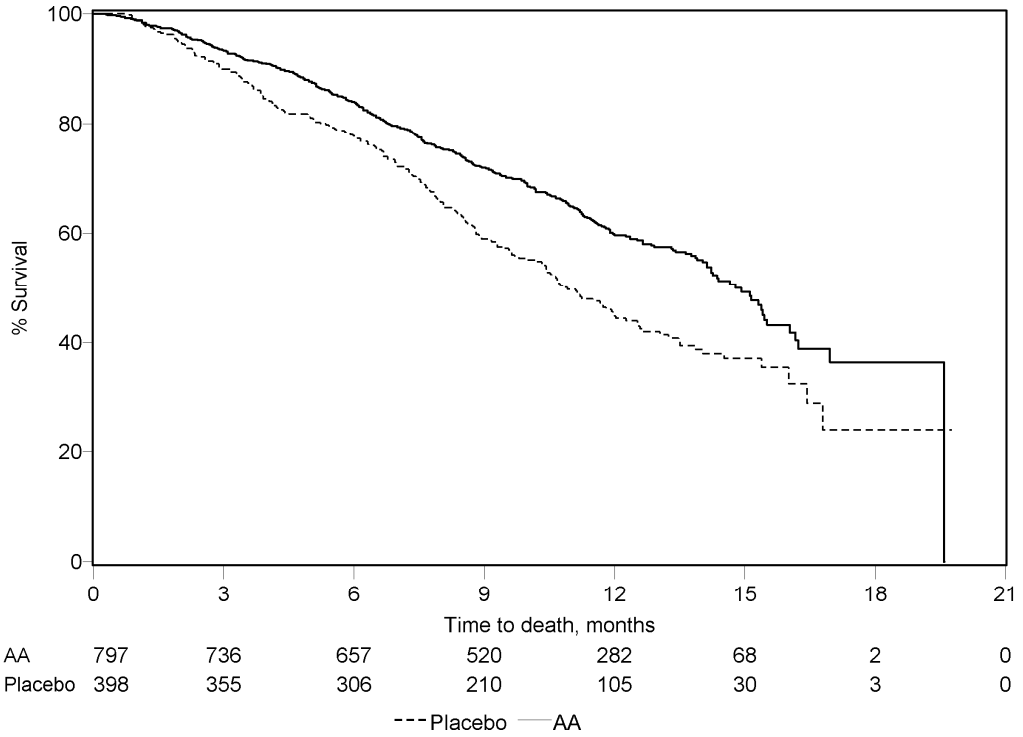
Table 2.5: Overall Survival of Patients Treated with Either ZYTIGA® or Placebo in Combination with Prednisone Plus GnRH Agonists or Prior Orchiectomy

	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®.

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with ZYTIGA® remained alive, compared with the proportion of patients treated with placebo (see Figure 2.5).

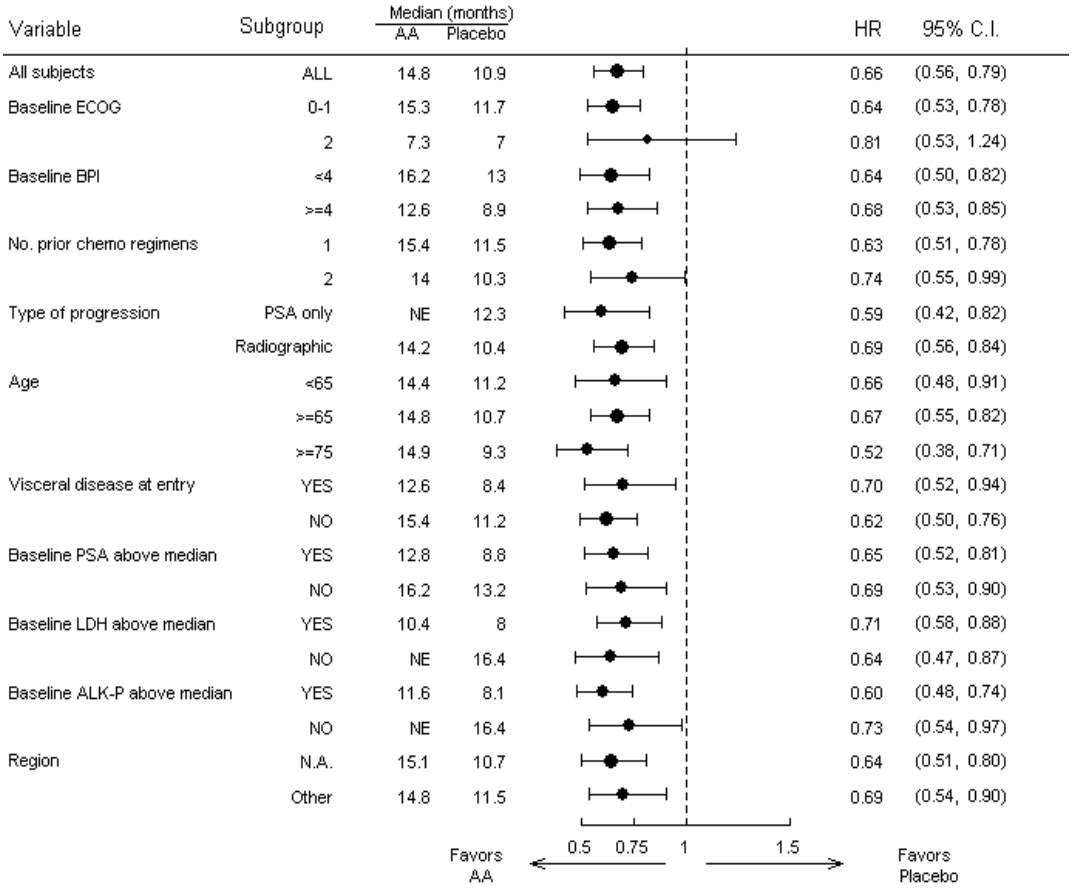
Figure 2.5: Kaplan Meier Survival Curves of Patients Treated with either ZYTIGA® or Placebo in Combination with Prednisone plus GnRH Agonists or Prior Orchiectomy (planned interim analysis)



AA=ZYTIGA®

Survival analyses by subgroup are presented in Figure 2.6.

Figure 2.6: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval



AA=ZYTIGA®; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable

Subgroup analyses showed a consistent favorable survival effect for treatment with ZYTIGA® by presence of pain at baseline, 1 or 2 prior chemotherapy regimens, type of progression, baseline PSA score above median and presence of visceral disease at entry.

In addition to the observed improvement in overall survival, all secondary study endpoints favored ZYTIGA® and were statistically significant after adjusting for multiple testing. PSA-based endpoints are not validated surrogate endpoints of clinical benefit in this patient population. Nevertheless, patients receiving ZYTIGA® demonstrated a significantly higher total PSA response rate (defined as a $\geq$ 50% reduction from baseline), compared with patients receiving placebo: 38% versus 10%, $p<0.0001$. The median time to PSA progression (time interval from randomization to PSA progression, according to PSAWG criteria) was 10.2 months for patients treated with ZYTIGA® and 6.6 months for patients treated with placebo (HR=0.580; 95% CI: [0.462, 0.728], $p<0.0001$).

The radiographic progression-free survival (rPFS) was the time from randomization to the occurrence of either tumor progression in soft tissue according to modified RECIST criteria

(with CT or MRI, until an increase above baseline of at least 20% in the longest diameter of target lesions or the appearance of new lesions), or by bone scan (≥ 2 new lesions). A confirmatory bone scan was not mandatory. The median rPFS was 5.6 months for patients treated with ZYTIGA® and 3.6 months for patients who received placebo (HR=0.673; 95% CI: [0.585, 0.776], p<0.0001).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the ZYTIGA® group than in the placebo group (44% versus 27%, p=0.0002). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the Brief Pain Inventory – Short Form (BPI-SF) worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline pain score of ≥ 4 and at least one post-baseline pain score were analyzed (N=512) for pain palliation.

Pain progression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the previous 24 hours without a decrease in analgesic usage score observed at two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two consecutive visits. The time to pain progression at the 25th percentile was 7.4 months in the ZYTIGA® group, versus 4.7 months in the placebo group.

Skeletal-Related Events

The time to first skeletal-related event at the 25th percentile in the ZYTIGA® group was twice that of the control group at 9.9 months vs. 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

DETAILED PHARMACOLOGY

Non-clinical pharmacokinetics

Several isoenzymes (CYP, UGT and SULT) are responsible for the metabolism of abiraterone into 15 detectable metabolites, accounting for approximately 92% of circulating radioactivity. CYP3A4 and SULT2A1 are the major single isoenzymes involved in metabolite formation with a minor contribution from UGT1A4, SULT1E1 and UGT1A3.

In vitro studies with human hepatic microsomes demonstrated that abiraterone was not an inhibitor for human CYP2A6 and CYP2E1. In these same studies, abiraterone was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. However, the concentrations of abiraterone in patients were lower than the concentration required for clinically meaningful inhibition of these enzymes. Abiraterone was also determined *in vitro* to be a potent inhibitor of CYP1A2, CYP2D6 and CYP2C8 (see **Drug-Drug Interactions**).

The pharmacokinetics of abiraterone in the presence of strong inducers or inhibitors of the above enzymes have not been evaluated *in vitro* or *in vivo* with the exception of CYP3A4 (see **Drug-Drug Interactions**, ***CYP3A4 inducers*** and ***CYP3A4 inhibitors***).

TOXICOLOGY

In 13- and 26- week repeated dose studies in rats and 13- and 39-week repeated dose studies in monkeys, a reduction in circulating testosterone levels occurred with abiraterone at approximately one half the human clinical exposure based on AUC. As a result, morphological and/or histopathological changes were observed in the reproductive organs. These included aspermia/hypospermia, atrophy/weight reductions in the male genital tract organs and testes. In addition, adrenal gland hypertrophy, Leydig cell hyperplasia, pituitary gland hyperplasia and mammary gland hyperplasia were observed. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related changes were partially or fully reversed after a four-week recovery period.

After chronic treatment from 13 weeks onward, hepatocellular hypertrophy was observed in rats only at exposure levels of abiraterone 0.72-fold the human clinical exposure based on AUC. Bile duct/oval cell hyperplasia, associated with increased serum alkaline phosphatase and/or total bilirubin levels, was seen in the liver of rats (at exposure levels of abiraterone 3.2-fold the human clinical exposure based on AUC) and monkeys (at exposure levels of abiraterone 1.2-fold the human clinical exposure based on AUC). After a four-week recovery period, serum parameters reversed, whereas bile duct/oval cell hyperplasia persisted.

A dose dependent increase in cataracts was observed after 26 weeks of treatment in rats at exposure levels of abiraterone 1.1 times the human clinical exposure based on AUC. These changes were irreversible after a four-week recovery period. Cataracts were not observed in monkeys after 13 or 39 weeks of treatment at exposure levels 2 fold greater than the clinical exposure based on AUC.

Reproductive Toxicology

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.

In developmental toxicity study in rats, although abiraterone acetate did not have teratogenic potential, abiraterone acetate caused developmental toxicity when administered at 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 (10, 30, or 100 mg/kg) tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

ZYTIGA® is contraindicated in pregnancy (see **CONTRAINDICATIONS** and **WARNINGS AND PRECAUTIONS, Special Populations**).

Carcinogenesis and Genotoxicity

Abiraterone acetate was not carcinogenic in a 6-month study in the transgenic (Tg.rasH2) mouse. In a 24-month carcinogenicity study in the rat, abiraterone acetate increased the incidence of interstitial cell neoplasms in the testes. This finding is considered related to the pharmacological action of abiraterone. The clinical relevance of this finding is not known. Abiraterone acetate was not carcinogenic in female rats.

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay.

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PART III: CONSUMER INFORMATION

PrZYTIGA®
Abiraterone acetate tablets

This leaflet is Part III of a three-part "Product Monograph" published when ZYTIGA® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about ZYTIGA®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

ZYTIGA®, in combination with prednisone, is used to treat prostate cancer that has spread to other parts of the body in:

- adult patients who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.

or

- adult patients who have had prior cancer treatment with docetaxel after failure of androgen deprivation therapy

Asymptomatic patients are defined as patients who may have no noticeable changes to health. Mildly symptomatic patients may show symptoms or changes in health such as bone pain or fatigue.

What it does:
ZYTIGA® works to stop your body from making androgens; this can slow the growth of prostate cancer to other parts of the body.

When your prostate cancer spreads beyond the prostate to other parts of the body, this is known as metastatic prostate cancer or advanced cancer.

Androgens are a group of hormones, and testosterone belongs to this group. Testosterone is the main type of androgen. Androgens promote cancer cell growth. That is why it's so important to keep these hormones at "castrate levels" (extremely low levels), to stop the growth of cancer.

ZYTIGA® helps to block the production of even small amounts of androgens in the three places that it is produced: in the testes, the adrenal glands and the prostate cancer tumour itself.

When it should not be used:

- If you are allergic (hypersensitive) to abiraterone acetate or any of the other ingredients of ZYTIGA®.
- ZYTIGA® should not be taken by women who are pregnant or might be pregnant.

What the medicinal ingredient is:
Abiraterone acetate

What the nonmedicinal ingredients are:
Colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulfate.

What dosage forms it comes in:
250 mg tablets

WARNINGS AND PRECAUTIONS

ZYTIGA® must be taken on an empty stomach since food can increase the blood level of ZYTIGA® and this may be harmful. Do not eat any solid or liquid food two hours before taking ZYTIGA® and at least one hour after taking ZYTIGA®.

BEFORE you use ZYTIGA® talk to your doctor or pharmacist if:

- you have or have had high blood pressure or low blood potassium
- you have or have had heart failure, heart attack, or other heart problems
- you have liver problems
- you have or have had adrenal problems

ZYTIGA® may harm an unborn baby. Male patients must use a condom and another effective birth control method when having sexual activity with a woman who is pregnant or can become pregnant while taking ZYTIGA® and for one week after the last dose of ZYTIGA®.

Women who are pregnant or may become pregnant should not handle ZYTIGA® tablets without protective gloves.

ZYTIGA® should not be used in patients under 18 years of age.

INTERACTIONS WITH THIS MEDICATION

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines. This includes medicines obtained without a prescription, including herbal medicines.

Tell your physician if you are taking phenytoin, carbamazepine, rifampicin, rifabutin, phenobarbital, or St. John's wort because these medications may decrease the effect of ZYTIGA®. This may lead to ZYTIGA® not working as well as it should.

PROPER USE OF THIS MEDICATION

Always take ZYTIGA® exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure.

Usual dose:
The usual dose is four tablets (1g) by mouth once a day.

ZYTIGA® **must be taken on an empty stomach**

- Do not eat any solid or liquid food two hours before taking ZYTIGA® and at least one hour after taking ZYTIGA®. Taking ZYTIGA® with food causes more of this medicine to be absorbed by the body than is needed and this may be harmful.
- Swallow the tablets whole with a glass of water.
- Do not break the tablets.
- ZYTIGA® is taken with a medicine called prednisone to help manage potential side effects such as fluid in your legs or feet and muscle weakness, muscle twitches or a pounding heart beat (palpitations) which may be signs of low blood potassium (see Side Effects section below). Take the prednisone exactly as your doctor has told you.

Overdose

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed dose:
If you forget to take ZYTIGA® or prednisone, take your normal dose the following day.

If you forget to take ZYTIGA® or prednisone for more than one day, talk to your doctor without delay.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, ZYTIGA® can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very Common (affects more than 1 in 10 people):
- Fluid in your legs or feet, low blood potassium
  If you notice any of the following: muscle weakness, muscle twitches or a pounding heart beat (palpitations). These may be signs that the level of potassium in your blood is low. Stop taking ZYTIGA® and see a doctor immediately
- Joint swelling or pain, muscle pain, hot flushes, and cough
- Urinary tract infection,
- Diarrhea
- Fatigue
- Constipation
- Vomiting
- Common cold-like symptoms like runny or stuffy nose or a sore throat
- Contusion
- Insomnia
- Shortness of breath
- Anemia

Common (affects less than 1 in 10 people):
- High fat levels in your blood
- Liver function test increases
- Chest pain, irregular heart beat, rapid heart rate, and heart failure
- High blood pressure
- Upper and lower respiratory infection
- Stomach upset
- Flu-like symptoms
- Weight increase
- Urinary frequency
- Bone break (fracture)
- Indigestion
- Presence of blood in your urine
- Rash and skin lesions
- Falls
- Bruising

Uncommon (affects less than 1 in 100 people):
- Adrenal gland problems

Reported from post-marketing with unknown frequency
- Lung irritation - Symptoms may include shortness of breath, cough and fatigue.
- Breakdown of muscle tissue and muscle weakness and/or muscle pain.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM				
Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Low blood potassium (as described above)		✓	
	Fluid in your legs or feet		✓	
	Burning on urination or cloudy urine		✓	
Common	Chest pain		✓	
	Heart beat disorder		✓	
	Rapid heart rate		✓	
Unknown	Shortness of breath		✓	
	Breakdown of muscle tissue and muscle weakness and/or muscle pain		✓	

This is not a complete list of side effects. For any unexpected effects while taking ZYTIGA®*, contact your doctor or pharmacist.*

HOW TO STORE IT

ZYTIGA® tablets should be stored at 15−30ºC. Keep out of the reach and sight of children.

Do not use ZYTIGA® after the expiry date which is stated on the label. The expiry date refers to the last day of the month.

Medicines should not be thrown away via wastewater or household waste. Throw away any unused product or waste material in accordance with local requirements. If you are not sure, ask your pharmacist how to throw away medicines no longer required. These measures will help to protect the environment.

REPORTING SUSPECTED SIDE EFFECTS

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- **Report online at www.healthcanada.gc.ca/medeffect**
- **Call toll-free at 1-866-234-2345**
- **Complete a Canada Vigilance Reporting Form and:**
  - **Fax toll-free to 1-866-678-6789, or**
  - **Mail to: Canada Vigilance Program**
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect® Canada Web site at www.healthcanada.gc.ca/medeffect.

NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

This document plus the full Product Monograph, prepared for health professionals, can be found at:
http://www.janssen.ca
or by contacting the sponsor, Janssen Inc., at:
1-800-567-3331 and 1-800-387-8781.

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