European Union Risk Management Plan
ZYTIGA® (abiraterone acetate)

Data lock point for current RMP	28 Apr 2022	Version number	15.1

Final for Procedure EMEA/H/C/002321/II/0072 – Health Authority Approval Date 06 July 2023

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RMP Version Number: 15.1
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QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	15.1
Rationale for submitting an updated RMP (if applicable)	Updated to comply with Revision 2 of the EMA GVP Module V – Risk management systems and Guidance on the format of the RMP in the European Union.
Summary of significant changes in this RMP:	<u>Safety Concerns:</u> The MAH re-evaluated the safety concerns in accordance with the definitions provided in GVP Module V Rev 2. All of the following safety concerns were removed from the RMP: • Important identified risks – Cardiac disorders, Hepatotoxicity, Increased exposure with food, Rhabdomyolysis/myopathy, Osteoporosis including osteoporosis-related fractures, and Allergic alveolitis • Important potential risks – Anemia, Cataract, and Drug-drug interaction (CYP2D6) • Missing information – Use in patients with active or symptomatic viral hepatitis, Use in patients with moderate/severe hepatic impairment and chronic liver disease, Use in patients with severe renal impairment, and Use in patients with heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of <50% <u>Pharmacovigilance Plan:</u> Removal of targeted follow-up questionnaires for fractures, cardiac arrhythmias, heart failure, and LFTs. Annex 4 has been updated for consistency with these changes. <u>Other:</u> Epidemiology section updated with recent literature information. Postauthorization exposure data updated.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable	Not applicable	Not applicable

Details of the Currently Approved RMP:

Version number of last agreed RMP:	14.2
Approved within procedure	EMEA/H/C/002321/II/0047
Date of approval (Competent authority opinion date)	15 November 2017 (European Commission decision date)

TABLE OF CONTENTS

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Abiraterone acetate
Pharmacotherapeutic group(s) (ATC Code)	Endocrine therapy, Other hormone antagonists and related agents (L02BX03)
Marketing Authorization Holder	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	This RMP refers to 1 product: ZYTIGA®
Invented name(s) in the European Economic Area (EEA)	ZYTIGA
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: ZYTIGA (abiraterone acetate) is converted in vivo to abiraterone, an androgen biosynthesis inhibitor.
	Summary of mode of action: Abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (cytochrome P450c17 [CYP17]). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissues and catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Treatment with ZYTIGA decreases serum testosterone to undetectable levels (using commercial assays) when given with luteinizing hormone-releasing hormone analogues (or orchiectomy).
	Important information about its composition: Abiraterone acetate has the chemical name 3β-acetoxy-17-(3 pyridyl) androsta-5,16-diene.
Reference to the Product Information	Module 1.3.1, SmPC, Labelling and Package Leaflet
Indication(s) in the EEA	Current: ZYTIGA is indicated with prednisone or prednisolone for: • the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT. • the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated. • the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

	Proposed: None	
Dosage in the EEA	Current: The recommended dose is 1,000 mg (two 500-mg film-coated tablets or four 250-mg tablets) as a single daily dose that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone. For the mHSPC indication, ZYTIGA is used in combination with 5 mg prednisone or prednisolone daily. For the mCRPC indications, ZYTIGA is used in combination with 10 mg prednisone or prednisolone daily.	
	Proposed: None	
Pharmaceutical form(s) and strengths	Current: Film-coated tablet, 500 mg Tablet, 250 mg	
	Proposed: None	
Is/will the product be subject to additional monitoring in the EU?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication(s)

The approved indications for ZYTIGA, in combination with prednisone or prednisolone, are:

- the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT;
- the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated;
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

Incidence:

Prostate cancer is the fourth most common cancer among both sexes combined and the second most common cancer in men. In the United States and Western Europe, prostate cancer is the most common nonskin cancer in older men (Botrel et al, 2016). In Europe, approximately 473,344 new cases of prostate cancer were diagnosed in 2020 (approximately 20% of all incident cancer cases in men). In the WHO Europe region, the age-standardized incidence rate for prostate cancer is 59.6 per 100,000 men. The age-standardized incidence rates per 100,000 men for selected European countries have been estimated as follows: France, 99.0; Germany, 66.0; United Kingdom, 77.9; Italy, 59.9; Spain, 70.6; the Russian Federation, 43.7; Greece, 48.2 (Ferlay et al, 2020).

Prevalence:

An estimated 1.4 million men worldwide were diagnosed with prostate cancer in 2020, accounting for 14.1% of the cancers diagnosed in men, with over 60% of the cases (897,132) occurring in highly developed regions including Western and Northern Europe (Ferlay et al, 2020; Ferlay et al, 2021).

The 5-year prevalence of prostate cancer in Europe has been estimated to be 518.1 per 100,000 adult men. This rate translates into 1,873,814 cases over the 5-year span. The estimated 5-year prevalence and number of prevalent cases in select European countries per 100,000 adult men in 2020 was as follows: France 819.0 (258,722); Germany 701.2 (290,426); Italy 500.9 (147,452); United Kingdom 704.9 (236,454); Spain 596.2 (136,986); Greece 489.1 (25,019); and the Russian Federation 250.2 (169,221) (Ferlay et al, 2020).

The natural course of prostate cancer is highly variable, with some indolent, slow-growing tumors and some that are highly aggressive (Coleman et al, 2008). Estimates of prostate cancer incidence and prevalence by stage are not uniformly available for the entire European Union; however, the burden of advanced metastatic prostate cancer can be informed by analyses of country-specific population-based cancer registries. Reports of the proportion of prostate cancer patients with advanced metastatic disease are available from a limited number of countries, including the United Kingdom, France, Italy, and Nordic countries. Published estimates from these countries indicate that at any given time the proportion of patients with advanced metastatic disease is approximately

15% to 30% (Thurin et al, 2020; Jack et al, 2010; Jonsson et al, 2006; Flamand et al, 2008; Howard et al, 2001; Nørgaard et al, 2010; Quaglia et al, 2003).

Using data from the population-based National Prostate Cancer Register of Sweden, investigators reported a substantial prostate cancer stage migration over time. Across the interval from 1998 to 2011, the proportion of prostate cancer patients in regional metastatic and distant metastatic categories was 8% and 15%, respectively. However, these estimates are misleading since the disease risk distribution has changed substantially over time due to the introduction of PSA testing. At the beginning of the study period in 1998, 14% and 17% of men were diagnosed with low- and intermediate-risk disease, whereas 25% had distant metastasis at diagnosis. By 2011, 28% and 32% of all cases were low and intermediate risk disease, while 11% had distant metastasis at diagnosis. The number of men with metastatic disease at date of diagnosis decreased from 1,545 in 1998 to 995 in 2011, a 36% decline during the 13 year observation time (Ohmann et al, 2014).

From 2013 to 2017, a total of 39,141 adults were diagnosed with metastatic (stage IV) mCRPC in England (CRUK, 2019).

Demographics of the Population in the Authorized Indication - Age, Racial and/or Ethnic Origin and Risk Factors for the Disease

Age

Incidence of prostate cancer increases greatly with older age. In the United Kingdom, from 2016 to 2018, incidence rates for prostate cancer were highest in males aged 75 to 79 (CRUK, 2021). In the United States, the probability of developing prostate cancer over selected age intervals has been estimated as follows: birth to 39 years, 0.01% (1 in 10,002); 40 to 59 years, 2.43% (1 in 41); 60 to 69 years, 6.42% (1 in 16); 70 years and older, 12.49% (1 in 8) (American Cancer Society, 2009). In the United States from 2007 to 2011, prostate cancer incidence rates were stable in men younger than 65 years and decreased by 2.8% per year in those 65 years and older. About 60% of all prostate cancer cases were diagnosed in men 65 years of age and older (American Cancer Society, 2022) and 97% occurred in men 50 years and older (American Cancer Society, 2015).

Race and/or Ethnic Origin

The incidence of prostate cancer varies by race and ethnicity, with black men disproportionately affected. Black men and Caribbean men of African descent had the highest documented prostate cancer incidence rates in the world (American Cancer Society, 2015). Between 1988 and 2015 in the United States, the adjusted rates of metastatic prostate cancer incidence for non-Hispanic white men significantly increased by 4.3% starting from 2010, while declining for Hispanic, non-Hispanic black, non-Hispanic Asian/Pacific Islander and other racial groups (Dall'Era et al, 2019).

For all ethnicities combined, the lifetime risk of being diagnosed with prostate cancer in England in 2008 to 2010 was 13.4%. Both the lifetime risk of being diagnosed with, and dying from, prostate cancer in white men was similar to all ethnicities combined. Asian men were at a significantly lower risk of being diagnosed with (ranging from 6.3% to 10.5% during the

period 2008 to 2010), and dying from, prostate cancer in their lifetime compared with white men. The lifetime risk of being diagnosed with prostate cancer for black men during the period 2008–2010 ranged from 23.5% to 37.2%, in line with the highest prostate cancer incidence rate in black men compared with other ethnic groups (179.4 per 100,000) (Lloyd et al, 2015; Ng et al, 2021).

Risk Factors for the Disease

Well-established risk factors for prostate cancer include older age, family history of the disease, and race/ethnicity. Prostate cancer is thought to have a strong ethnic propensity, and there is a higher prevalence among Europeans and African Americans (Jefferson et al, 2020). Investigation by Bashir et al showed that family history of prostate cancer was strongly associated with increased risk of prostate cancer (OR 7.32, 95% CI 1.79-29.84) (Bashir et al, 2014).

Environmental factors and exogenous factors have also been found to increase risk of prostate cancer. A diet high in red meat or high-fat dairy products or low in fruits and vegetables may be associated with increased risk of prostate cancer (Brawley, 2012). Multiple studies have demonstrated that consumption of red meat and dairy products may be responsible for higher prostate cancer risk and progression. In contrast, more consumption of fruit, fluid intake and better lifestyle (more physical activity) significantly reduced the risk of developing prostate cancer with OR and corresponding 95% CI of: 0.27 (0.11-0.61); 0.05 (0.02-0.12); and 0.28 (0.13- 0.58), respectively (Bashir et al, 2014). Investigators at the Harvard School of Public Health also found a protective effect of higher intake of tomato sauce with incidence of organ confined prostate cancer (OR 0.75, 95% CI 0.61-0.92) for (Giovannucci et al, 2007).

Main Existing Treatment Options:

ADT, by means of surgical castration or administration of GnRH analogues, is the mainstay of first-line treatment for advanced prostate cancer (Aapro, 2012; Botrel et al, 2016). For prostate cancer resistant to ADT, multiple options for treatment have been developed over recent years: abiraterone acetate (plus prednisone/prednisolone), enzalutamide, apalutamide, and radium-223 (Teo et al, 2019). Docetaxel-based chemotherapy remains the first choice for patients progressing further and requiring cytotoxic therapy (Aapro, 2012). For diseases that progress during or after docetaxel therapy, treatments such as abiraterone acetate (plus prednisone/prednisolone), enzalutamide, radium-223, zoledronic acid, denosumab or cabazitaxel have been approved and can be considered (JEVTANA SmPC, 2014; XTANDI SmPC, 2015; XOFIGO SmPC, 2015; Fragkoulis et al, 2016; Marhold et al 2022).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Prostate cancer is the second most common cause of cancer mortality in older men in the United States and Western Europe (Botrel et al, 2016). Prostate cancer comprises 5.5% of all cancer deaths among males in Europe. The age-standardized mortality rate for prostate cancer in Europe (WHO Region) is 11.0 per 100,000 person-years for all ages, ranging between 5.9 per 100,000 person-years (Italy) and 12.4 per 100,000 person-years (United Kingdom) for most countries (Ferlay et al, 2020). The highest mortality rates worldwide for a specific country were observed in Zimbabwe, at 41.7 per 100,000 person-years.

The age-standardized, 5-year relative survival of patients in Europe is estimated to be approximately 83.4%, whereas for those under 80 years of age in the United States, the rate was more than 97% (Salinas et al, 2014; Siegel et al, 2020).

It is recognized that black men with prostate cancer have worse outcomes compared with men of other races. In the United States, the age-adjusted number of deaths due to prostate cancer per 100,000 population was 49.8 in black men compared with 20.7 in non-Hispanic white men from 2007 to 2011 (Siegel et al, 2015). In a separate US study, the overall 5-year survival for distant stage prostate cancer improved from 28.7% during 2001 to 2005 to 32.3% during 2011 to 2016; during the period 2001 to 2016, 5-year survival was the highest among Asian/Pacific Islanders (42.0%), followed by Hispanics (37.2%), American Indian/Alaska Natives (32.2%), black men (31.6%), and white men (29.1%) (Siegel et al 2020).

It is estimated that 10-20% of prostate cancer patients initially present with metastatic disease (Fragkoulis et al, 2016). Primary ADT achieved either by surgical castration or by pharmaceutical agents is the standard of care in patients initially diagnosed with metastatic disease leading in over 80% of the cases to clinical improvement and reduction of serum PSA levels (Pagliarulo et al, 2012). However, almost all advanced metastatic cancers treated with ADT will eventually develop into CRPC with more than 90% of the patients with mCRPC developing bone metastasis which results in a significant increase in morbidity and mortality (Costa et al, 2008). The average survival for patients with CRPC is 1 to 2 years. (Aly et al, 2020).

Important Co-morbidities:

- Cardiac disease (Crawford & Moul, 2015; Fleming et al, 2006; Jespersen et al, 2014; Keating et al, 2006)
- Hypertension (Jefferson et al, 2020)
- Bone fractures (Ahlborg et al, 2008; Shao et al, 2013)
- Renal insufficiency (Fleming et al, 2006; Launay-Vacher et al, 2009; Oh et al, 2007)
- Diabetes mellitus (Fleming et al, 2006; Keating et al, 2006; Kintzel et al, 2008)
- Genitourinary disorders (Fleming et al, 2006; Woolf, 1995)
- Anemia (Grossmann & Zajac, 2012)
- Sepsis (Loeb et al, 2012; Moriceau et al, 2016)
- Pneumonia (Hicks et al, 2017)

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity:	
Single & Repeat-dose Toxicity	
Repeat-dose toxicity studies of 13 and 26 weeks in the rat and 13 and 39 weeks in the monkey were conducted to characterize the chronic toxicity of abiraterone acetate when administered orally. No signs of gastric irritation were observed. The majority of toxicities were related to interference of abiraterone (acetate) with steroid metabolism and affected the reproductive organs (testis: atrophy, interstitial cell hyperplasia, and reduced spermatogenesis; epididymis: atrophy, hypospermia, and aspermia; seminal vesicles and prostate: atrophy and/or reduced secretion; ovaries: increase follicles/cysts and interstitial tissue proliferation; uterus: atrophy and in monkey, also endometrial hyperplasia/pseudodecidual reaction; cervix and vagina: atrophy), male mammary glands (*rat*: atrophy*; monkey*: hyperplasia and fibrosis/edema), pituitary gland (hypertrophy/hyperplasia, *rat only*) and adrenal glands (cortical hypertrophy). Bile duct/oval cell hyperplasia was seen in both species from 13 weeks onwards and hepatocellular hypertrophy in the rat only. The maximum tolerated dose of abiraterone acetate after long-term repeated dosing was 250 mg/kg/day in the rat. In the monkey, the maximum tolerated dose exceeded the highest dose tested (ie, >2,000 mg/kg/day). After a 4-week recovery period, full or partial reversibility was noted for each of the toxicities as listed above, with the exception of some findings in the rat, ie, testicular atrophy, bile duct/oval cell hyperplasia, and cataract.	In general, the toxicity of abiraterone acetate was similar across species and was related to the pharmacological activity of abiraterone. Target organ toxicity in animals has been predictive of human toxicity except for changes in the liver and eye lens.
Reproductive and Developmental Toxicity	
Fertility studies were performed in male and female rats. A developmental toxicology study was performed in the rat. In male rats, a reduction in organ weights of the reproductive system; decrease in sperm counts, motility, and altered sperm morphology; and a	Findings in fertility studies in male and female rats and in the developmental toxicology study in the rat were consistent with the pharmacological activity of abiraterone (ie, decrease in androgens and estrogens resulting from CYP17 inhibition). In humans, abiraterone is likely to affect male and

Key Safety Findings	Relevance to Human Usage
decrease in fertility were observed. Sperm motility and morphology as well as fertility fully recovered. In female rats, abiraterone acetate reduced fertility which fully reversed after a recovery period of 4 weeks. In an oral developmental toxicity study in the rat, abiraterone acetate was not teratogenic. The observed effects on pregnancy, fetal survival, fetal weight, and external genitalia were related to the pharmacological effect of abiraterone.	female fertility. Fetal abnormalities or miscarriage may occur if the drug is administered during pregnancy. The current indications are for the treatment of mCRPC and mHSPC. Therefore, ZYTIGA should not be prescribed to women. ZYTIGA is contraindicated in women who are or may potentially be pregnant and they should not handle the 250-mg uncoated tablets without protection, eg, gloves. It is not known whether abiraterone or its metabolites are present in semen.
Genotoxicity	
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.	Based on the nonclinical data, the risk for genotoxicity is considered limited.
Carcinogenicity	
A 6-month carcinogenicity study was performed in the Tg.ras.H2 mouse at abiraterone acetate dose levels of 125, 375, and 750 mg/kg/day. Abiraterone acetate was not carcinogenic in this assay. Toxicological findings were related to the pharmacological activity of abiraterone.	Toxicity of abiraterone acetate in mice was comparable with that in rats and monkeys and was related to the pharmacological activity of abiraterone acetate. Abiraterone acetate was not carcinogenic.
A 2-year carcinogenicity study was performed in Crl:CD (SD) rats by oral administration of abiraterone acetate at 5, 15, and 50 mg/kg/day in male rats and at 15, 50, and 150 mg/kg/day in female rats. Toxicological findings were related to the pharmacological activity of abiraterone. In male rats, there was an increased incidence of interstitial cell neoplasms in the testes which is considered a sequential response to the pharmacological action of the test substance. Ophthalmic findings from both studies are presented in the section for Cataract below.	The toxicity of abiraterone acetate was similar to that in previous studies in rats. The increased incidence of interstitial cell neoplasms in the testes was considered rat specific, as the interstitial cells of the rodent possess a significantly increased number of luteinizing hormone receptors than in humans (Alison et al 1994). Therefore, rats can be considered as genetically predisposed, in contrast to man, where this tumor type occurs at a very low incidence, estimated to be 0.4 per million (Clegg et al 1997) and thus is not of concern to humans.
Cataract	
In repeat-dose toxicity studies, dose-dependent posterior cortical cataracts were observed in rats following dosing of abiraterone acetate for 26 weeks at plasma exposure levels of abiraterone similar to or higher than the therapeutic exposure in patients. These changes were still present after a 4-week recovery	Although the mechanism is unclear, a species-specific effect cannot be excluded. The exposure in monkeys was similar to that in rats at steady state and the exposure in mice was much higher, but no cataracts were observed in monkeys and mice even after a longer period of treatment. There is also a fundamental difference in steroidogenesis in rats and humans.

Key Safety Findings	Relevance to Human Usage
period. In monkeys, no cataracts were observed when abiraterone acetate was dosed for 39 weeks at plasma exposure levels of abiraterone comparable to the therapeutic exposure. In mice, no cataracts were observed when abiraterone acetate was dosed for 26 weeks at exposure levels up to 7 times the clinical exposure. There were no ophthalmic findings considered related to dosing with abiraterone acetate at the end of the 2-year carcinogenicity study in the rat. In contrast, at earlier time points, unilateral or bilateral posterior subcapsular opacities in the lens were observed in males given 50 mg/kg/day (at Weeks 50 and 79) and in females given 150 mg/kg/day (at Week 79). An effect of abiraterone acetate on the opacities seen at these earlier time points in the 2-year study cannot be excluded.	In humans, exogenous glucocorticoid therapy has been described to induce cataracts. In vitro studies have shown that abiraterone does not bind to the glucocorticoid receptor unlike the glucocorticoid dexamethasone. Therefore, based on absence of ocular findings in monkeys and mice following similar or longer durations of treatment at comparable exposures or higher exposure and the species differences in pharmacodynamics, and the absence of a direct interaction of abiraterone with the human and rat or mouse glucocorticoid receptor, the cataract findings in rats might be rat specific and are considered to represent a low risk to humans.
Safety Pharmacology:	
Cardiovascular System (including potential for QT interval prolongation) In vitro and in vivo studies evaluated the effects of abiraterone and abiraterone acetate on the cardiovascular system. In vitro, abiraterone did not have a significant effect on the human ether-á-go-go-related gene potassium current. Abiraterone acetate inhibited human ether-á-go-go-related gene potassium current up to 84% at a concentration greatly exceeding clinically relevant levels. In telemetered male monkeys administered up to 2,000 mg/kg abiraterone acetate, no effects on hemodynamic and electrocardiographic parameters were recorded following a 24-hour monitoring period. In the 39-week repeat-dose toxicity study, infrequent ventricular premature complexes were seen in 3 males at 1,000 mg/kg, both at pre- and post-dosing. The toxicological relevance of these arrhythmias was considered limited based on the fact that there were no abnormalities in the ECG recording at the end of the treatment period, and in most cases it could not be related to an abiraterone peak plasma effect. Moreover, no ECG abnormalities were seen in the 13-week monkey study at more or less similar abiraterone plasma exposure, and no effects were noted in the cardiovascular safety study in	Although no cardiac findings were reported in the nonclinical studies, cardiac disorders, in theory, could develop considering the primary pharmacological effect of abiraterone (selective inhibition of CYP17 that results in an inhibition of androgen synthesis).

Key Safety Findings	Relevance to Human Usage
the telemetered monkey after a single oral dose up to 2,000 mg/kg. There was no histological evidence of cardiomyopathy in any of the monkey studies.	
Nervous System	
In the nonclinical toxicity studies, there was no indication of any significant abiraterone acetate treatment-related effects on the central nervous system.	Based on the nonclinical data, the risk for effects on the central nervous system are considered limited.
Other	
Nephrotoxicity	
In the nonclinical toxicity studies, there was no indication of any significant abiraterone acetate treatment-related effects on the renal system.	Based on the nonclinical data, the risk for nephrotoxicity is considered limited.
Hepatotoxicity	
In pivotal toxicity studies in rats and monkeys, increased liver and gallbladder weights correlated with microscopic findings of hepatocyte hypertrophy (rat only), bile duct/oval cell hyperplasia and (reversible) increases in serum ALP and total bilirubin. Bile duct/oval cell hyperplasia, observed from 13 weeks of treatment, partially reversed after 4 weeks in the monkey but not in rat. Hepatocellular hypertrophy (rat only) was fully reversible.	Based on nonclinical studies, abiraterone has the potential to affect liver function in humans.
Endocrine-related Toxicity	
In a hormone profiling study in male and female rats dosed for 2 weeks with abiraterone acetate at 50 or 400 mg/kg, no significant changes were noted in corticosterone concentrations during the dosing period. Serum progesterone was increased in male rats only. At the end of the dosing period in males, serum testosterone was decreased and serum luteinizing hormone increased. These changes resulted from the pharmacological activity of the compound. In an in vitro study of glucocorticoid agonist activity, abiraterone, and the 2 major human metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, were not active in the glucocorticoid rat or mouse receptor assay.	Findings in hormone profiling studies in male and female rats were consistent with the pharmacological activity of abiraterone (ie, decrease in androgens resulting from CYP17 inhibition).

Key Safety Findings	Relevance to Human Usage
Other Toxicity-related Information or Data	
Mechanisms for Drug Interactions	
The drug-drug interaction potential of abiraterone was evaluated in vitro in liver microsomes**.** Abiraterone was not an inhibitor of CYP2A6 or CYP2E1, but was a weak inhibitor of CYP2B6 (IC_{50} of >30 µM; ie, 10,000 ng/mL), a moderate inhibitor of CYP2C9, CYP2C19, and CYP3A4/5 (Ki >8.9 µM; ie, >3100 ng/mL), and a strong inhibitor of CYP1A2, CYP2D6 (Ki 0.44 and 0.39 µM, respectively; ie, 136 to 154 ng/mL), and CYP2C8 (IC_{50} of 1.6 µM; ie, 559 ng/mL).	A clinical drug-drug interaction trial for possible CYP1A2 and CYP2D6 interaction (Trial COU-AA-015) was conducted based on these nonclinical findings. Abiraterone may interfere with drugs metabolized by CYP2D6. Abiraterone has been shown to be a moderate inhibitor of CYP3A4. In addition, it is a substrate of CYP3A4. Clinical trial data have demonstrated that the inhibition of CYP2C8 is unlikely to result in clinical meaningful drug-drug interactions excluding CYP2C8 substrates with a narrow therapeutic index.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The approved indications for ZYTIGA, in combination with prednisone or prednisolone, are:

- the treatment of newly diagnosed high-risk mHSPC in adult men in combination with ADT;
- the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated;
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

The original pivotal trial, Trial COU-AA-301, was the basis for the Marketing Authorization in the post-chemotherapy setting (EU approval received on 05 September 2011). This indication was extended based on the pivotal trial, Trial COU-AA-302, to include chemotherapy-naïve patients (Type II variation EMEA/H/C/02321/II/004 approved on 18 December 2012). The MAH further expanded the indication based on Trial 212082PCR3011 to include hormone-sensitive patients in combination with ADT (Type II variation EMEA/H/C/002321/II/0047, approved on 15 November 2017).

In the Trial 212082PCR3011 protocol, the term "metastatic hormone-naïve prostate cancer" ("mHNPC") was used to describe the patient population. Subjects in Trial 212082PCR3011 were to have newly diagnosed metastatic prostate cancer; however, subjects were allowed up to 3 months of ADT use prior to the start of study treatment. Therefore, the 212082PCR3011 population included subjects who had never received hormonal therapy (hormone-naïve) as well as subjects who received up to 3 months of hormonal therapy but were still responsive to treatment (hormone-sensitive). To maintain consistency with the study protocol, this EU-RMP continues to use the term "mHNPC" to refer to either metastatic hormone-naïve or hormone-sensitive prostate cancer.

SIII.2. Clinical Trial Exposure

All subjects received the 1,000 mg daily dose of abiraterone acetate (with prednisone/prednisolone) (Table SIII.3, Table SIII.4, Table SIII.13, and Table SIII.14).

Exposure in Randomized Clinical Trials

The randomized clinical trials population included patients with mCRPC post-chemotherapy (Trials COU-AA-301 and ABI-PRO-3001), patients with mCRPC pre-chemotherapy (Trials COU-AA-302 and ABI-PRO-3002), and patients with metastatic hormone-naïve prostate cancer (mHNPC) (Trial 212082PCR3011).

Exposure to abiraterone acetate in the randomized clinical trials population is summarized by duration, by dose, by age group, by ethnic or racial origin, and by baseline renal status and baseline hepatic status in Tables SIII.1, SIII.3, SIII.5, SIII.7, and SIII.9 by indication, and in Tables SIII.2, SIII.4, SIII.6, SIII.8, and SIII.10 overall.

The mHNPC component of the randomized clinical trial population (Trial 212082PCR3011) included 597 subjects (all men) randomized to abiraterone acetate:

- Exposure to abiraterone acetate: 57,922.9 person-weeks. In this trial, 467 subjects received >48 weeks of treatment (Table SIII.1);
- 253 (42.4%) subjects were 65 to 74 years of age; 114 (19.1%) subjects were 75 to 84 years of age; and 9 (1.5%) subjects were 85 years of age or older (Table SIII.5);
- Most subjects (409 [68.5%]) were white while 125 (20.9%) subjects were Asian and 15 (2.5%) subjects were black or African American (Table SIII.7);
- Renal impairment (measured by CrCl) at baseline: 270 (45.2%) subjects with mild (CrCl >50 to <80 mL/min), 36 (6.0%) subjects with moderate (CrCl >30 to ≤50 mL/min), and 1 (0.2%) subject with severe (CrCl ≤30 mL/min) (Table SIII.9);
- Liver function abnormality at baseline: no subjects with ALT >2.5 times the ULN and no subjects with AST >2.5 times the ULN (Table SIII.9).

The Trial mCRPC post-chemotherapy component of the randomized clinical trial population (Trials COU-AA-301 and ABI-PRO-3001) included 934 abiraterone acetate-treated subjects (all men):

- Exposure to abiraterone acetate: 36,581.6 person-weeks. In these pooled trials, 297 subjects received >48 weeks of treatment (Table SIII.1);
- 406 (43.5%) subjects were 65 to 74 years of age; 235 (25.2%) subjects were 75 to 84 years of age; and 19 (2.0%) subjects were 85 years of age or older (Table SIII.5);
- Most subjects (737 [78.9%]) were white while 154 (16.5%) subjects were Asian and 28 (3.0%) subjects were black or African American (Table SIII.7);
- Renal impairment (measured by CrCl) at baseline: 225 (28.4%) subjects with mild (CrCl >50 to <80 mL/min), 54 (6.8%) subjects with moderate (CrCl >30 to ≤50 mL/min), and 4 (0.5%) with severe (CrCl ≤30 mL/min) (Table SIII.9);
- Liver function abnormality at baseline: 5 (0.5%) subjects with ALT >2.5 and ≤5.0 times the ULN and 1 (0.5%) subject with ALT >5.0 to ≤20.0 times the ULN; 14 (1.5%) subjects with AST >2.5 and ≤5.0 times the ULN and 2 (0.2%) subjects with AST >5.0 times to ≤20.0 times the ULN (Table SIII.9).

The mCRPC pre-chemotherapy component of the randomized clinical trial population (Trials COU-AA-302 and ABI-PRO-3002) included 699 subjects (all men) randomized to abiraterone acetate:

- Exposure to abiraterone acetate: 39,891.1 person-weeks. In these trials, 334 subjects received >48 weeks of treatment (Table SIII.1);
- 287 (41.1%) subjects were 65 to 74 years of age; 202 (28.9%) subjects were 75 to 84 years of age; and 33 (4.7%) subjects were 85 years of age or older (Table SIII.5);
- Most subjects (551 [78.8%]) were white while 126 (18.0%) subjects were Asian and 15 (2.1%) subjects were black or African American (Table SIII.7);

- Renal impairment (measured by CrCl) at baseline: 233 (33.3%) subjects with mild (CrCl >50 to <80 mL/min), 56 (8.0%) subjects with moderate (CrCl >30 to ≤50 mL/min), and 2 (0.3%) subjects with severe (CrCl ≤30 mL/min) (Table SIII.9);
- Liver function abnormality at baseline: no subjects with ALT >2.5 times the ULN and 1 (0.1%) subject with AST >2.5 to ≤5.0 times the ULN (Table SIII.9).

For the randomized clinical trials population (total) of 2,230 abiraterone acetate-treated subjects (all men):

- Exposure to abiraterone acetate: 134,395.6 person-weeks. In these trials, 1,098 subjects received >48 weeks of treatment (Table SIII.2);
- 946 (42.4%) subjects were 65 to 74 years of age; 551 (24.7%) subjects were 75 to 84 years of age; and 61 (2.7%) subjects were 85 years of age or older (Table SIII.6);
- Most subjects (1,697 [76.1%]) were white while 405 (18.2%) subject were Asian and 58 (2.6%) subjects were black or African American (Table SIII.8);
- Renal impairment (measured by CrCl) at baseline: 728 (34.9%) subjects with mild (CrCl >50 to <80 mL/min), 146 (7.0%) subjects with moderate (CrCl >30 to ≤50 mL/min), and 7 (0.3%) subjects with severe (CrCl ≤30 mL/min) (Table SIII.10);
- Liver function abnormality at baseline: 5 (0.2%) subjects with ALT >2.5 to ≤5.0 times the ULN and 1 (<0.1%) subject with ALT >5.0 to ≤20.0 times the ULN; 15 (0.7%) subjects with AST >2.5 to ≤5.0 times the ULN and 2 (0.1%) subjects with AST >5.0 to ≤20.0 times the ULN (Table SIII.10).

Table SIII.1: Exposure BY DURATION, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
Cumulative up to 12 weeks	25 (4.2%)	
Cumulative up to 24 weeks	59 (9.9%)	
Cumulative up to 36 weeks	99 (16.6%)	
Cumulative up to 48 weeks	130 (21.8%)	
Cumulative up to 60 weeks	172 (28.8%)	
Cumulative up to 72 weeks	203 (34.0%)	
Cumulative up to 84 weeks	235 (39.4%)	
Cumulative up to 96 weeks	258 (43.2%)	
Cumulative up to 108 weeks	316 (52.9%)	
Cumulative up to 120 weeks	355 (59.5%)	
Cumulative up to 132 weeks	424 (71.0%)	
Cumulative up to 144 weeks	481 (80.6%)	
Cumulative up to 156 weeks	525 (87.9%)	
Cumulative up to 168 weeks	556 (93.1%)	
Cumulative up to 180 weeks	585 (98.0%)	55725.1
Total person time	597	57922.9

Table SIII.1: Exposure BY DURATION, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mCRPC Pre-chemotherapy		
Cumulative up to 12 weeks	81 (11.6%)	
Cumulative up to 24 weeks	196 (28.0%)	
Cumulative up to 36 weeks	285 (40.8%)	
Cumulative up to 48 weeks	365 (52.2%)	
Cumulative up to 60 weeks	429 (61.4%)	
Cumulative up to 72 weeks	472 (67.5%)	
Cumulative up to 84 weeks	509 (72.8%)	
Cumulative up to 96 weeks	536 (76.7%)	
Cumulative up to 108 weeks	556 (79.5%)	
Cumulative up to 120 weeks	615 (88.0%)	
Cumulative up to 132 weeks	669 (95.7%)	
Cumulative up to 144 weeks	691 (98.9%)	
Cumulative up to 156 weeks	699 (100.0%)	
Cumulative up to 168 weeks	699 (100.0%)	
Cumulative up to 180 weeks	699 (100.0%)	39891.1
Total person time	699	39891.1
INDICATION: mCRPC Post-chemotherapy		
Cumulative up to 12 weeks	171 (18.3%)	
Cumulative up to 24 weeks	366 (39.2%)	
Cumulative up to 36 weeks	519 (55.6%)	
Cumulative up to 48 weeks	637 (68.2%)	
Cumulative up to 60 weeks	705 (75.5%)	
Cumulative up to 72 weeks	756 (80.9%)	
Cumulative up to 84 weeks	835 (89.4%)	
Cumulative up to 96 weeks	893 (95.6%)	
Cumulative up to 108 weeks	929 (99.5%)	
Cumulative up to 120 weeks	934 (100.0%)	
Cumulative up to 132 weeks	934 (100.0%)	
Cumulative up to 144 weeks	934 (100.0%)	
Cumulative up to 156 weeks	934 (100.0%)	
Cumulative up to 168 weeks	934 (100.0%)	
Cumulative up to 180 weeks	934 (100.0%)	36581.6
Total person time	934	36581.6

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302 and ABI-PRO-3002; mCRPC Post-chemotherapy includes Trials COU-AA-301 and ABI-PRO-3001

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Table SIII.2: Exposure BY DURATION, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
Cumulative up to 12 weeks	277 (12.4%)	
Cumulative up to 24 weeks	621 (27.8%)	
Cumulative up to 36 weeks	903 (40.5%)	
Cumulative up to 48 weeks	1132 (50.8%)	
Cumulative up to 60 weeks	1306 (58.6%)	
Cumulative up to 72 weeks	1431 (64.2%)	
Cumulative up to 84 weeks	1579 (70.8%)	
Cumulative up to 96 weeks	1687 (75.7%)	
Cumulative up to 108 weeks	1801 (80.8%)	
Cumulative up to 120 weeks	1904 (85.4%)	
Cumulative up to 132 weeks	2027 (90.9%)	
Cumulative up to 144 weeks	2106 (94.4%)	
Cumulative up to 156 weeks	2158 (96.8%)	
Cumulative up to 168 weeks	2189 (98.2%)	
Cumulative up to 180 weeks	2218 (99.5%)	132197.9
Total person time	2230	134395.6

Note: Randomized Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, and ABI-PRO-3001.

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Table SIII.3: Exposure BY DOSE, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
1,000 mg/day	597 (100.0%)	57922.9
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
1,000 mg/day	699 (100.0%)	39891.1
Total	699	39891.1
INDICATION: mCRPC Post-chemotherapy		
1,000 mg/day	934 (100.0%)	36581.6
Total	934	36581.6

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302 and ABI-PRO-3002; mCRPC Post-chemotherapy includes Trials COU-AA-301 and ABI-PRO-3001.

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Table SIII.4: Exposure BY DOSE, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
1,000 mg/day	2230 (100.0%)	134395.6
Total	2230	134395.6

Note: Randomized Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, and ABI-PRO-3001.

[RMP02B.RTF] [JNJ-212082\Z_RMP\DBR_M1RMP_2016\RE_M1RMP_2016\PROD\RMP02B.SAS] 31JAN2017, 07:16.

Table SIII.5: Exposure BY AGE GROUP, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
<50 years	11 (1.8%)	1115.7
50 - 64 years	210 (35.2%)	20441.0
65 - 74 years	253 (42.4%)	24862.7
75 - 84 years	114 (19.1%)	10881.0
≥85 years	9 (1.5%)	622.4
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
<50 years	8 (1.1%)	404.4
50 - 64 years	169 (24.2%)	9539.0
65 - 74 years	287 (41.1%)	17729.7
75 - 84 years	202 (28.9%)	10764.3
≥85 years	33 (4.7%)	1453.7
Total	699	39891.1
INDICATION: mCRPC Post-chemotherapy		
<50 years	14 (1.5%)	493.6
50 - 64 years	260 (27.8%)	9457.6
65 - 74 years	406 (43.5%)	16132.0
75 - 84 years	235 (25.2%)	9806.3
≥85 years	19 (2.0%)	692.1
Total	934	36581.6

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302 and ABI-PRO-3002; mCRPC Post-chemotherapy includes Trials COU-AA-301 and ABI-PRO-3001.

Note: There were no patients <18 years of age.

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Table SIII.6: Exposure BY AGE GROUP, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
<50 years	33 (1.5%)	2013.7
50 - 64 years	639 (28.7%)	39437.6
65 - 74 years	946 (42.4%)	58724.4
75 - 84 years	551 (24.7%)	31451.6
≥85 years	61 (2.7%)	2768.3
Total	2230	134395.6

Note: Randomized Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, and ABI-PRO-3001.

Note: There were no patients <18 years of age.

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Table SIII.7: Exposure BY ETHNIC or RACIAL ORIGINS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
White	409 (68.5%)	38483.0
Black or African American	15 (2.5%)	1403.6
Asian	125 (20.9%)	13964.4
American Indian or Alaska Native	1 (0.2%)	160.1
Native Hawaiian or other Pacific Islander	0	0.0
Other[a]	43 (7.2%)	3621.1
Missing	4 (0.7%)	290.6
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
White	551 (78.8%)	35838.0
Black or African American	15 (2.1%)	1112.1
Asian	126 (18.0%)	2584.7
American Indian or Alaska Native	0	0.0
Native Hawaiian or other Pacific Islander	0	0.0
Other[a]	6 (0.9%)	332.1
Missing	1 (0.1%)	24.1
Total	699	39891.1
INDICATION: mCRPC Post-chemotherapy		
White	737 (78.9%)	29308.4
Black or African American	28 (3.0%)	1210.4
Asian	154 (16.5%)	5426.4
American Indian or Alaska Native	3 (0.3%)	140.3
Native Hawaiian or other Pacific Islander	0	0.0

Table SIII.7: Exposure BY ETHNIC or RACIAL ORIGINS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
Other[a]	11 (1.2%)	483.9
Missing	1 (0.1%)	12.1
Total	934	36581.6

[a] Reported as: American-Latin, Arabic, Asian-Indian, Black Caribbean, Brown, Caucasian, Dominican, Galilean Arab, Half-Caste, Hispanic, Indian, Italian, Maori, Mestizo, Mexican, Middle Eastern, Mixed Race, Scottish, and unknown.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302 and ABI-PRO-3002; mCRPC Post-chemotherapy includes Trials COU-AA-301, and ABI-PRO-3001.

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Table SIII.8: Exposure BY ETHNIC or RACIAL ORIGINS, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
White	1697 (76.1%)	103629.4
Black or African American	58 (2.6%)	3726.1
Asian	405 (18.2%)	21975.6
American Indian or Alaska Native	4 (0.2%)	300.4
Native Hawaiian or other Pacific Islander	0	0.0
Other[a]	60 (2.7%)	4437.1
Missing	6 (0.3%)	326.9
Total	2230	134395.6

[a] Reported as: American-Latin, Arabic, Asian-Indian, Black Caribbean, Brown, Caucasian, Dominican, Galilean Arab, Half-Caste, Hispanic, Indian, Italian, Maori, Mestizo, Mexican, Middle Eastern, Mixed Race, Scottish, and unknown.

Note: Randomized Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, and ABI-PRO-3001.

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Table SIII.9: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
Renal impairment at baseline	597	57922.9
Normal (CrCl ≥80 mL/min)	289 (48.4%)	28228.4
Mild (CrCl >50 to <80 mL/min)	270 (45.2%)	26470.7
Moderate (CrCl >30 to ≤50 mL/min)	36 (6.0%)	3008.4
Severe (CrCl ≤30 mL/min)	1 (0.2%)	114.1
Missing	1 (0.2%)	101.1
Liver function abnormality at baseline	597	57922.9
ALT		
≤ULN (normal)	530 (88.8%)	51523.0
>ULN to ≤2.5 x ULN	67 (11.2%)	6399.9
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0

Table SIII.9: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
Missing	0	0.0
AST		
≤ULN (normal)	543 (91.0%)	53037.3
>ULN to ≤2.5 x ULN	54 (9.0%)	4885.6
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	0	0.0
Bilirubin		
≤ULN (normal)	589 (98.7%)	57234.0
>ULN to ≤1.5 x ULN	8 (1.3%)	688.9
>1.5 to ≤3.0 x ULN	0	0.0
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	0	0.0
Alkaline phosphatase[a]		
≤ULN (normal)	NA	
>ULN to ≤2.5 x ULN	NA	
>2.5 to ≤5.0 x ULN	NA	
>5.0 to ≤20.0 x ULN	NA	
>20.0 x ULN	NA	
Missing	NA	
INDICATION: mCRPC Pre-chemotherapy		
Renal impairment at baseline	699	39891.1
Normal (CrCl ≥80 mL/min)	404 (57.8%)	25225.6
Mild (CrCl >50 to <80 mL/min)	233 (33.3%)	11333.1
Moderate (CrCl >30 to ≤50 mL/min)	56 (8.0%)	2982.1
Severe (CrCl ≤30 mL/min)	2 (0.3%)	59.3
Missing	4 (0.6%)	291.0
Liver function abnormality at baseline	699	39891.1
ALT		
≤ULN (normal)	635 (90.8%)	35985.1
>ULN to ≤2.5 x ULN	64 (9.2%)	3906.0
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	0	0.0
AST		
≤ULN (normal)	636 (91.0%)	36774.0
>ULN to ≤2.5 x ULN	62 (8.9%)	3075.7
>2.5 to ≤5.0 x ULN	1 (0.1%)	41.4
>5.0 to ≤20.0 x ULN	0	0.0

Table SIII.9: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
>20.0 x ULN	0	0.0
Missing	0	0.0
Bilirubin		
≤ULN (normal)	694 (99.3%)	39690.4
>ULN to ≤1.5 x ULN	5 (0.7%)	200.7
>1.5 to ≤3.0 x ULN	0	0.0
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	0	0.0
Alkaline phosphatase		
≤ULN (normal)	505 (72.2%)	30883.6
>ULN to ≤2.5 x ULN	140 (20.0%)	6968.9
>2.5 to ≤5.0 x ULN	35 (5.0%)	1482.7
>5.0 to ≤20.0 x ULN	18 (2.6%)	551.6
>20.0 x ULN	1 (0.1%)	4.4
Missing	0	0.0
INDICATION: mCRPC Post-chemotherapy		
Renal impairment at baseline[b]	791	31503.9
Normal (CrCl ≥80 mL/min)	502 (63.5%)	20289.4
Mild (CrCl >50 to <80 mL/min)	225 (28.4%)	8995.1
Moderate (CrCl >30 to ≤50 mL/min)	54 (6.8%)	1881.3
Severe (CrCl ≤30 mL/min)	4 (0.5%)	61.9
Missing	6 (0.8%)	276.1
Liver function abnormality at baseline	934	36581.6
ALT		
≤ULN (normal)	893 (95.6%)	35201.1
>ULN to ≤2.5 x ULN	34 (3.6%)	1250.4
>2.5 to ≤5.0 x ULN	5 (0.5%)	72.9
>5.0 to ≤20.0 x ULN	1 (0.1%)	0.9
>20.0 x ULN	0	0.0
Missing	1 (0.1%)	56.3
AST		
≤ULN (normal)	812 (86.9%)	33462.7
>ULN to ≤2.5 x ULN	105 (11.2%)	2928.6
>2.5 to ≤5.0 x ULN	14 (1.5%)	113.4
>5.0 to ≤20.0 x ULN	2 (0.2%)	20.6
>20.0 x ULN	0	0.0
Missing	1 (0.1%)	56.3
Bilirubin		
≤ULN (normal)	927 (99.3%)	36346.9
>ULN to ≤1.5 x ULN	4 (0.4%)	157.1
>1.5 to ≤3.0 x ULN	2 (0.2%)	21.3

Table SIII.9: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (by Indication)

	Persons n (%)	Person-weeks
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	1 (0.1%)	56.3
Alkaline phosphatase		
≤ULN (normal)	539 (57.7%)	23899.7
>ULN to ≤2.5 x ULN	237 (25.4%)	8074.7
>2.5 to ≤5.0 x ULN	112 (12.0%)	3350.7
>5.0 to ≤20.0 x ULN	41 (4.4%)	1151.6
>20.0 x ULN	4 (0.4%)	48.6
Missing	1 (0.1%)	56.3

[a] Alkaline phosphatase data were not collected in Trial 212082PCR3011.
[b] CrCl test results are not available for Trial ABI-PRO-3001.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302 and ABI-PRO-3002; mCRPC Post-chemotherapy includes Trials COU-AA-301 and ABI-PRO-3001.

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Table SIII.10: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
Renal impairment at baseline[a]	2087	129317.9
Normal (CrCl ≥80 mL/min)	1195 (57.3%)	73743.4
Mild (CrCl >50 to <80 mL/min)	728 (34.9%)	46799.0
Moderate (CrCl >30 to ≤50 mL/min)	146 (7.0%)	7871.9
Severe (CrCl ≤30 mL/min)	7 (0.3%)	235.3
Missing	11 (0.5%)	668.3
Liver function abnormality at baseline	2230	134395.6
ALT		
≤ULN (normal)	2058 (92.3%)	122709.3
>ULN to ≤2.5 x ULN	165 (7.4%)	11556.3
>2.5 to ≤5.0 x ULN	5 (0.2%)	72.9
>5.0 to ≤20.0 x ULN	1 (<0.1%)	0.9
>20.0 x ULN	0	0.0
Missing	1 (<0.1%)	56.3
AST		
≤ULN (normal)	1991 (89.3%)	123274.0
>ULN to ≤2.5 x ULN	221 (9.9%)	10889.9
>2.5 to ≤5.0 x ULN	15 (0.7%)	154.9
>5.0 to ≤20.0 x ULN	2 (0.1%)	20.6
>20.0 x ULN	0	0.0
Missing	1 (<0.1%)	56.3

Table SIII.10: Exposure BY SPECIAL POPULATIONS, Randomized Clinical Trials Population (Total)

	Persons n (%)	Person-weeks
Bilirubin		
≤ULN (normal)	2210 (99.1%)	133271.3
>ULN to ≤1.5 x ULN	17 (0.8%)	1046.7
>1.5 to ≤3.0 x ULN	2 (0.1%)	21.3
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	1 (<0.1%)	56.3
Alkaline phosphatase[b]	1633	76472.7
≤ULN (normal)	1044 (63.9%)	54783.3
>ULN to ≤2.5 x ULN	377 (23.1%)	15043.6
>2.5 to ≤5.0 x ULN	147 (9.0%)	4833.4
>5.0 to ≤20.0 x ULN	59 (3.6%)	1703.1
>20.0 x ULN	5 (0.3%)	53.0
Missing	1 (0.1%)	56.3

[a] CrCl test results are not available for Trial ABI-PRO-3001.
[b] Alkaline phosphatase data were not collected in Trial 212082PCR3011.

Note: Randomized Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, and ABI-PRO-3001.

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Exposure in All Clinical Trials Including Open Extensions

The all clinical trials population includes the following trials:

- mHNPC: Trial 212082PCR3011;
- mCRPC Pre-chemotherapy: Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002;
- mCRPC Post-chemotherapy: Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008;

The all clinical trials population includes subjects who were administered a starting dose of 1,000 mg/day abiraterone acetate (Table SIII.13).

In the all clinical trials population, 2,684 subjects (all men) received a dose of abiraterone acetate 1,000 mg/day (Table SIII.14).

Exposure to abiraterone acetate in all clinical trials population is summarized by duration, by dose, by age group, by ethnic or racial origin, and by baseline renal status and baseline hepatic status in Tables SIII.11, SIII.13, SIII.15, SIII.17, and SIII.19 by indication and in Tables SIII.12, SIII.14, SIII.16, SIII.18, and SIII.20 overall.

Table SIII.11: Exposure BY DURATION, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
Cumulative up to 12 weeks	25 (4.2%)	
Cumulative up to 24 weeks	59 (9.9%)	
Cumulative up to 36 weeks	99 (16.6%)	
Cumulative up to 48 weeks	130 (21.8%)	
Cumulative up to 60 weeks	172 (28.8%)	
Cumulative up to 72 weeks	203 (34.0%)	
Cumulative up to 84 weeks	235 (39.4%)	
Cumulative up to 96 weeks	258 (43.2%)	
Cumulative up to 108 weeks	316 (52.9%)	
Cumulative up to 120 weeks	355 (59.5%)	
Cumulative up to 132 weeks	424 (71.0%)	
Cumulative up to 144 weeks	481 (80.6%)	
Cumulative up to 156 weeks	525 (87.9%)	
Cumulative up to 168 weeks	556 (93.1%)	
Cumulative up to 180 weeks	585 (98.0%)	55725.1
Total person time	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
Cumulative up to 12 weeks	91 (11.6%)	
Cumulative up to 24 weeks	215 (27.4%)	
Cumulative up to 36 weeks	314 (39.9%)	
Cumulative up to 48 weeks	405 (51.5%)	
Cumulative up to 60 weeks	475 (60.4%)	
Cumulative up to 72 weeks	523 (66.5%)	
Cumulative up to 84 weeks	569 (72.4%)	
Cumulative up to 96 weeks	601 (76.5%)	
Cumulative up to 108 weeks	624 (79.4%)	
Cumulative up to 120 weeks	685 (87.2%)	
Cumulative up to 132 weeks	741 (94.3%)	
Cumulative up to 144 weeks	764 (97.2%)	
Cumulative up to 156 weeks	776 (98.7%)	
Cumulative up to 168 weeks	776 (98.7%)	
Cumulative up to 180 weeks	779 (99.1%)	44746.0
Total person time	786	46315.1
INDICATION: mCRPC Post-chemotherapy		
Cumulative up to 12 weeks	260 (20.0%)	
Cumulative up to 24 weeks	537 (41.3%)	
Cumulative up to 36 weeks	742 (57.0%)	
Cumulative up to 48 weeks	899 (69.1%)	

Table SIII.11: Exposure BY DURATION, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
Cumulative up to 60 weeks	987 (75.9%)	
Cumulative up to 72 weeks	1058 (81.3%)	
Cumulative up to 84 weeks	1150 (88.4%)	
Cumulative up to 96 weeks	1218 (93.6%)	
Cumulative up to 108 weeks	1264 (97.2%)	
Cumulative up to 120 weeks	1270 (97.6%)	
Cumulative up to 132 weeks	1276 (98.1%)	
Cumulative up to 144 weeks	1284 (98.7%)	
Cumulative up to 156 weeks	1289 (99.1%)	
Cumulative up to 168 weeks	1289 (99.1%)	
Cumulative up to 180 weeks	1290 (99.2%)	50134.4
Total person time	1301	52509.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002; mCRPC Post-chemotherapy includes Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.12: Exposure BY DURATION the All Clinical Trials Population[a] (Total)

	Persons n (%)	Person-weeks
All Clinical Trials		
Cumulative up to 12 weeks	376 (14.0%)	
Cumulative up to 24 weeks	811 (30.2%)	
Cumulative up to 36 weeks	1155 (43.0%)	
Cumulative up to 48 weeks	1434 (53.4%)	
Cumulative up to 60 weeks	1634 (60.9%)	
Cumulative up to 72 weeks	1784 (66.5%)	
Cumulative up to 84 weeks	1954 (72.8%)	
Cumulative up to 96 weeks	2077 (77.4%)	
Cumulative up to 108 weeks	2204 (82.1%)	
Cumulative up to 120 weeks	2310 (86.1%)	
Cumulative up to 132 weeks	2441 (90.9%)	
Cumulative up to 144 weeks	2529 (94.2%)	
Cumulative up to 156 weeks	2590 (96.5%)	
Cumulative up to 168 weeks	2621 (97.7%)	
Cumulative up to 180 weeks	2654 (98.9%)	150605.6

Table SIII.12: Exposure BY DURATION the All Clinical Trials Population[a] (Total)

	Persons n (%)	Person-weeks
Total person time	2684	156747.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

Note: All Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, ABI-PRO-3001, COU-AA-001/EXT, COU-AA-002, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.13: Exposure BY DOSE, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
1,000 mg/day	597 (100.0%)	57922.9
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
1,000 mg/day	786 (100.0%)	46315.1
Total	786	46315.1
INDICATION: mCRPC Post-chemotherapy		
1,000 mg/day	1301 (100.0%)	52509.0
Total	1301	52509.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002; mCRPC Post-chemotherapy includes Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.14: Exposure BY DOSE, the All Clinical Trials Population[a] (Total)

	Persons n (%)	Person-weeks
All Clinical Trials		
1,000 mg/day	2684 (100.0%)	156747.0
Total	2684	156747.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

Note: All Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, ABI-PRO-3001, COU-AA-001/EXT, COU-AA-002, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

[RMP12B.RTF] [JNJ-212082\Z_RMP\DBR_M1RMP_2016\RE_M1RMP_2016\PROD\RMP12B.SAS] 31JAN2017, 07:25

Table SIII.15: Exposure BY AGE GROUP, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
<50 years	11 (1.8%)	1115.7
50 - 64 years	210 (35.2%)	20441.0
65 - 74 years	253 (42.4%)	24862.7
75 - 84 years	114 (19.1%)	10881.0
≥85 years	9 (1.5%)	622.4
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
<50 years	8 (1.0%)	404.4
50 - 64 years	187 (23.8%)	11081.0
65 - 74 years	325 (41.3%)	20107.4
75 - 84 years	232 (29.5%)	13162.3
≥85 years	34 (4.3%)	1560.0
Total	786	46315.1
INDICATION: mCRPC Post-chemotherapy		
<50 years	26 (2.0%)	862.9
50 - 64 years	356 (27.4%)	14085.9
65 - 74 years	567 (43.6%)	23171.3
75 - 84 years	322 (24.8%)	13247.9
≥85 years	30 (2.3%)	1141.1
Total	1301	52509.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002; mCRPC Post-chemotherapy includes Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

Note: There were no patients <18 years of age

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Table SIII.16: Exposure BY AGE GROUP, the All Clinical Trials Population[a] (Total)

	Persons n (%)	Person-weeks
All Clinical Trials		
<50 years	45 (1.7%)	2383.0
50 - 64 years	753 (28.1%)	45607.9
65 - 74 years	1145 (42.7%)	68141.4
75 - 84 years	668 (24.9%)	37291.1
≥85 years	73 (2.7%)	3323.6
Total	2684	156747.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

Note: All Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, ABI-PRO-3001, COU-AA-001/EXT, COU-AA-002, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

Note: There were no patients <18 years of age.

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Table SIII.17: Exposure BY ETHNIC or RACIAL ORIGINS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
White	409 (68.5%)	38483.0
Black or African American	15 (2.5%)	1403.6
Asian	125 (20.9%)	13964.4
American Indian or Alaska Native	1 (0.2%)	160.1
Native Hawaiian or other Pacific Islander	0	0.0
Other[b]	43 (7.2%)	3621.1
Missing	4 (0.7%)	290.6
Total	597	57922.9
INDICATION: mCRPC Pre-chemotherapy		
White	632 (80.4%)	41948.7
Black or African American	18 (2.3%)	1291.6
Asian	127 (16.2%)	2593.7
American Indian or Alaska Native	0	0.0
Native Hawaiian or other Pacific Islander	0	0.0
Other[b]	8 (1.0%)	457.0
Missing	1 (0.1%)	24.1
Total	786	46315.1

Table SIII.17: Exposure BY ETHNIC or RACIAL ORIGINS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mCRPC Post-chemotherapy		
White	1004 (77.2%)	40592.1
Black or African American	33 (2.5%)	1297.1
Asian	239 (18.4%)	9620.9
American Indian or Alaska Native	4 (0.3%)	152.1
Native Hawaiian or other Pacific Islander	0	0.0
Other[b]	20 (1.5%)	834.6
Missing	1 (0.1%)	12.1
Total	1301	52509.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

[b] Reported as: American-Latin, Arabic, Asian-Indian, Black Caribbean, Brown, Caucasian, Dominican, Egyptian, Galilean Arab, Greek, Half-Caste, Hispanic, Indian, Italian, Maori, Mestizo, Mexican, Middle Eastern, Mixed Race, Scottish, South Asian, and unknown.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002; mCRPC Post-chemotherapy includes Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.18: Exposure BY ETHNIC or RACIAL ORIGINS, the All Clinical Trials Population[a] (Total)

	Persons n (%)	Person-weeks
Randomized Clinical Trials		
White	2045 (76.2%)	121023.9
Black or African American	66 (2.5%)	3992.3
Asian	491 (18.3%)	26179.0
American Indian or Alaska Native	5 (0.2%)	312.3
Native Hawaiian or other Pacific Islander	0	0.0
Other[b]	71 (2.6%)	4912.7
Missing	6 (0.2%)	326.9
Total	2684	156747.0

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

[b] Reported as: American-Latin, Arabic, Asian-Indian, Black Caribbean, Brown, Caucasian, Dominican, Egyptian, Galilean Arab, Greek, Half-Caste, Hispanic, Indian, Italian, Maori, Mestizo, Mexican, Middle Eastern, Mixed Race, Scottish, South Asian, and unknown.

Note: All Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, ABI-PRO-3001, COU-AA-001/EXT, COU-AA-002, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.19: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mHNPC		
Renal impairment at baseline[b]	597	57922.9
Normal (CrCl ≥80 mL/min)	289 (48.4%)	28228.4
Mild (CrCl >50 to <80 mL/min)	270 (45.2%)	26470.7
Moderate (CrCl >30 to ≤50 mL/min)	36 (6.0%)	3008.4
Severe (CrCl ≤30 mL/min)	1 (0.2%)	114.1
Missing	1 (0.2%)	101.1
Liver function abnormality at baseline	597	57922.9
ALT		
≤ULN (normal)	530 (88.8%)	51523.0
>ULN to ≤2.5 x ULN	67 (11.2%)	6399.9
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	0	0.0
AST		
≤ULN (normal)	543 (91.0%)	53037.3
>ULN to ≤2.5 x ULN	54 (9.0%)	4885.6
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	0	0.0
Bilirubin		
≤ULN (normal)	589 (98.7%)	57234.0
>ULN to ≤1.5 x ULN	8 (1.3%)	688.9
>1.5 to ≤3.0 x ULN	0	0.0
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	0	0.0
Alkaline phosphatase[c]		
≤ULN (normal)	NA	
>ULN to ≤2.5 x ULN	NA	
>2.5 to ≤5.0 x ULN	NA	
>5.0 to ≤20.0 x ULN	NA	
>20.0 x ULN	NA	
Missing	NA	

Table SIII.19: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mCRPC Pre-chemotherapy		
Renal impairment at baseline[b]	741	43150.4
Normal (CrCl ≥80 mL/min)	429 (57.9%)	27282.9
Mild (CrCl >50 to <80 mL/min)	239 (32.3%)	11528.4
Moderate (CrCl >30 to ≤50 mL/min)	56 (7.6%)	2982.1
Severe (CrCl ≤30 mL/min)	2 (0.3%)	59.3
Missing	15 (2.0%)	1297.7
Liver function abnormality at baseline	786	46315.1
ALT		
≤ULN (normal)	712 (90.6%)	41311.3
>ULN to ≤2.5 x ULN	73 (9.3%)	4750.3
>2.5 to ≤5.0 x ULN	0	0.0
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	1 (0.1%)	253.6
AST		
≤ULN (normal)	714 (90.8%)	42517.4
>ULN to ≤2.5 x ULN	70 (8.9%)	3502.7
>2.5 to ≤5.0 x ULN	1 (0.1%)	41.4
>5.0 to ≤20.0 x ULN	0	0.0
>20.0 x ULN	0	0.0
Missing	1 (0.1%)	253.6
Bilirubin		
≤ULN (normal)	763 (97.1%)	44707.0
>ULN to ≤1.5 x ULN	12 (1.5%)	550.1
>1.5 to ≤3.0 x ULN	0	0.0
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	11 (1.4%)	1058.0
Alkaline phosphatase		
≤ULN (normal)	556 (70.7%)	34639.9
>ULN to ≤2.5 x ULN	157 (20.0%)	8286.3
>2.5 to ≤5.0 x ULN	41 (5.2%)	1758.6
>5.0 to ≤20.0 x ULN	20 (2.5%)	568.0
>20.0 x ULN	1 (0.1%)	4.4
Missing	11 (1.4%)	1058.0

Table SIII.19: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
INDICATION: mCRPC Post-chemotherapy		
Renal impairment at baseline[b]	873	35452.1
Normal (CrCl ≥80 mL/min)	529 (60.6%)	21639.9
Mild (CrCl >50 to <80 mL/min)	268 (30.7%)	11042.4
Moderate (CrCl >30 to ≤50 mL/min)	66 (7.6%)	2431.9
Severe (CrCl ≤30 mL/min)	4 (0.5%)	61.9
Missing	6 (0.7%)	276.1
Liver function abnormality at baseline	1301	52509.0
ALT		
≤ULN (normal)	1236 (95.0%)	49966.6
>ULN to ≤2.5 x ULN	54 (4.2%)	2297.7
>2.5 to ≤5.0 x ULN	6 (0.5%)	82.9
>5.0 to ≤20.0 x ULN	1 (0.1%)	0.9
>20.0 x ULN	0	0.0
Missing	4 (0.3%)	161.0
AST		
≤ULN (normal)	1088 (83.6%)	46377.9
>ULN to ≤2.5 x ULN	183 (14.1%)	5661.1
>2.5 to ≤5.0 x ULN	24 (1.8%)	288.4
>5.0 to ≤20.0 x ULN	2 (0.2%)	20.6
>20.0 x ULN	0	0.0
Missing	4 (0.3%)	161.0
Bilirubin		
≤ULN (normal)	1283 (98.6%)	51788.6
>ULN to ≤1.5 x ULN	11 (0.8%)	451.9
>1.5 to ≤3.0 x ULN	2 (0.2%)	21.3
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	5 (0.4%)	247.3
Alkaline phosphatase		
≤ULN (normal)	733 (56.3%)	33813.4
>ULN to ≤2.5 x ULN	334 (25.7%)	11708.9
>2.5 to ≤5.0 x ULN	156 (12.0%)	4819.6

Table SIII.19: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a] (by Indication)

	Persons n (%)	Person-weeks
>5.0 to ≤20.0 x ULN	68 (5.2%)	1904.3
>20.0 x ULN	5 (0.4%)	64.6
Missing	5 (0.4%)	198.3

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.
[b] CrCl test results are only available for 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, COU-AA-001/EXT, and PCR2007.
[c] Alkaline phosphatase data were not collected in Trial 212082PCR3011.

Note: mHNPC includes Trial 212082PCR3011; mCRPC Pre-chemotherapy includes Trials COU-AA-302, ABI-PRO-3002, COU-AA-001/EXT, and COU-AA-002; mCRPC Post-chemotherapy includes Trials COU-AA-301, ABI-PRO-3001, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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Table SIII.20: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a](Total)

	Persons n (%)	Person-weeks
All Clinical Trials		
Renal impairment at baseline[b]	2211	136525.4
Normal (CrCl ≥80 mL/min)	1247 (56.4%)	77151.1
Mild (CrCl >50 to <80 mL/min)	777 (35.1%)	49041.6
Moderate (CrCl >30 to ≤50 mL/min)	158 (7.1%)	8422.4
Severe (CrCl ≤30 mL/min)	7 (0.3%)	235.3
Missing	22 (1.0%)	1675.0
Liver function abnormality at baseline	2684	156747.0
ALT		
≤ULN (normal)	2478 (92.3%)	142800.9
>ULN to ≤2.5 x ULN	194 (7.2%)	13447.9
>2.5 to ≤5.0 x ULN	6 (0.2%)	82.9
>5.0 to ≤20.0 x ULN	1 (<0.1%)	0.9
>20.0 x ULN	0	0.0
Missing	5 (0.2%)	414.6
AST		
≤ULN (normal)	2345 (87.4%)	141932.6
>ULN to ≤2.5 x ULN	307 (11.4%)	14049.4
>2.5 to ≤5.0 x ULN	25 (0.9%)	329.9
>5.0 to ≤20.0 x ULN	2 (0.1%)	20.6
>20.0 x ULN	0	0.0
Missing	5 (0.2%)	414.6
Bilirubin		
≤ULN (normal)	2635 (98.2%)	153729.6
>ULN to ≤1.5 x ULN	31 (1.2%)	1690.9

Table SIII.20: Exposure BY SPECIAL POPULATIONS, the All Clinical Trials Population[a](Total)

	Persons n (%)	Person-weeks
>1.5 to ≤3.0 x ULN	2 (0.1%)	21.3
>3.0 to ≤10.0 x ULN	0	0.0
>10.0 x ULN	0	0.0
Missing	16 (0.6%)	1305.3
Alkaline phosphatase[c]	2087	98824.1
≤ULN (normal)	1289 (61.8%)	68453.3
>ULN to ≤2.5 x ULN	491 (23.5%)	19995.1
>2.5 to ≤5.0 x ULN	197 (9.4%)	6578.1
>5.0 to ≤20.0 x ULN	88 (4.2%)	2472.3
>20.0 x ULN	6 (0.3%)	69.0
Missing	16 (0.8%)	1256.3

[a] Subjects with a dose of 1,000 mg/day abiraterone acetate.

[b] CrCl test results are only available for Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, COU-AA-001/EXT, and PCR2007.

[c] Alkaline phosphatase data were not collected in Trial 212082PCR3011.

Note: All Clinical Trials includes Trials 212082PCR3011, COU-AA-302, ABI-PRO-3002, COU-AA-301, ABI-PRO-3001, COU-AA-001/EXT, COU-AA-002, COU-AA-003/EXT, COU-AA-004, COU-AA-BE, COU-AA-BMA, COU-AA-006, COU-AA-015, PCR2007, and PCR2008.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Hypersensitivity to the active substance or to any of the excipients**
Reason for being an exclusion criterion	Subjects with known hypersensitivity to the active substance or to any of the excipients of the test compound were excluded from clinical trials to avoid possible severe and life-threatening hypersensitivity reactions.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	It is standard practice to exclude all subjects from trials who have known hypersensitivity to either the active substance or excipients and to add it as a contraindication to labeling. In SmPC Section 4.3, ZYTIGA is contraindicated for patients with a hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC.
Criterion 2	**Abnormal liver transaminase test values concentrations consisting of any of the following:** • **Serum bilirubin ≥1.5 × ULN (except for subjects with documented Gilbert's disease).** • **AST or ALT ≥2.5 × ULN (for subjects with known liver metastasis, AST or ALT ≤5 × ULN allowed).**
Reason for being an exclusion criterion	Abnormal LFTs, particularly elevated transaminases, have been reported in association with ADT. A 'stable' selected population was required for the clinical trials at baseline so a subject with abnormal liver transaminase test values was excluded.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	A subset of the exclusion criteria for the trials is included in the SmPC. Severe hepatic impairment (Child-Pugh Class C) is a contraindication (SmPC Section 4.3). ZYTIGA should not be used in patients with severe hepatic impairment (SmPC Section 4.4) and use of ZYTIGA should be cautiously assessed in patients with moderate hepatic impairment in whom the benefit clearly should outweigh the possible risk (SmPC Section 4.4). Serum transaminases should be measured prior to starting treatment, every 2 weeks for the first 3 months and monthly there after (SmPC Sections 4.2 and 4.4). Guidelines are

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

	given in the SmPC for severe hepatotoxicity ie, if ALT or AST is 20 ULN treatment should be discontinued and patients should not be retreated (SmPC Sections 4.2 and 4.4).
Criterion 3	**Subjects who had partners of childbearing potential who were not willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the Principal Investigator and Sponsor**
Reason for being an exclusion criterion	Studies on abiraterone in animals have shown reproductive toxicity. The abiraterone acetate clinical development program included only male patients, and it is not known whether abiraterone or its metabolites are present in semen. Therefore, subjects with partners of childbearing potential who were not willing to use birth control with adequate barrier protection were excluded in order to prevent exposure of women of childbearing potential to abiraterone.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	ZYTIGA is contraindicated in women who are or may potentially be pregnant (SmPC Sections 4.3 and 4.6). It is not known if ZYTIGA or its metabolites are present in semen and thus a condom is required along with another effective contraceptive method (SmPC Section 4.6). Animal studies have shown reproductive toxicity (see SmPC Sections 4.6 and 5.3).
Criterion 4	**Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg). Subjects with a history of hypertension were allowed provided BP was controlled by antihypertensive therapy**
Reason for being an exclusion criterion	A ‘stable’ selected population was required for the clinical trials at baseline so a subject with uncontrolled hypertension was excluded (controlled hypertension was allowed).
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Warning in SmPC Section 4.4 for uncontrolled hypertension: before treatment, an echocardiogram is suggested and hypertension should be controlled before treatment and monitored regularly during treatment.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 5	**Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class II, III, or IV heart disease or cardiac ejection fraction measurement of <50% at baseline**
Reason for being an exclusion criterion	It is common clinical practice to exclude subjects with severe and potentially life-threatening cardiac conditions from trials on anticancer therapy, because they potentially place subjects with these comorbidities at increased risk for adverse events and additionally may confound the interpretation of safety data. A 'stable' selected population was required for the clinical trial population at baseline (to reduce any confounding factors) so a subject with clinically significant heart disease was excluded.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	A stable or decreasing reporting trend has been observed with abiraterone acetate for all types of cardiovascular diseases and no new safety signals have been identified over 11 years of postmarketing surveillance. The SmPC (Sections 4.2 and 4.4) provides sufficient information to address and mitigate the risk to patients with a history of heart disease or at risk of congestive heart failure (eg, a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischemic heart disease).
Criterion 6	**Active or symptomatic viral hepatitis or chronic liver disease**
Reason for being an exclusion criterion	Common clinical practice is to control active or symptomatic viral hepatitis or chronic liver disease before starting long-term anticancer therapy. In addition, a 'stable' selected population was required for the clinical trial population (to reduce any confounding factors) at baseline so a subject with uncontrolled active or symptomatic viral hepatitis or chronic liver disease was excluded.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	The SmPC Sections 4.4 and 4.8 provide the clinical trial exclusion criterion and it is stated in Section 4.4 that there are no data to support treatment in this population. There is no mechanism of action whereby ZYTIGA could exacerbate viral hepatitis or chronic liver disease.

Table SIV.1: Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 7	**Serum potassium <3.5 mmol/L**
Reason for being an exclusion criterion	A 'stable' selected population was required for the clinical trial population at baseline (to reduce any confounding factors) so a clinically normal potassium was required at baseline.
Considered to be included as missing information: Yes/No	No
Rationale (if not included as missing information)	Warning in SmPC Section 4.4 for hypokalemia: to correct and control hypokalemia before treatment and to monitor and correct during treatment.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions or those caused by prolonged exposure.

Adverse reactions due to cumulative effects are considered not applicable. Abiraterone has a half-life of about 12 to 14 hours. As a result, no cumulative effects are expected. No additional adverse cumulative effects have been seen during exposure to ZYTIGA. In addition, adverse reactions that have a long latency are considered not applicable. Abiraterone is a CYP17 inhibitor and expected effects from CYP17 inhibition are seen within the first 2 weeks in clinical trials.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	**Exposure**
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Population with relevant different ethnic origin	In the All Clinical Trials population, abiraterone acetate-treated subjects included the following (see Table SIII.17): • In mHNPC, 68.5% of subjects were white (n=409; 38,483.0 person-weeks), 20.9% were Asian (n=125; 13,964.4 person-weeks), 2.5% were black or African American (n=15; 1,403.6 person-weeks), and 7.2% were of other racial or ethnic origin (n=43; 3,621.1 person-weeks). • In mCRPC pre-chemotherapy, 80.4% of subjects were white (n=632; 41,948.7 person-weeks), 16.2% were Asian (n=127; 2,593.7 person-weeks), 2.3% were black or African American (n=18; 1291.6 person-weeks), and 1.0% were of other racial or ethnic origin (n=8; 457.0 person-weeks).

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	• In mCRPC post-chemotherapy, 77.2% of subjects were white (n=1,004; 40,592.1 person-weeks), 18.4% were Asian (n=239; 9,620.9 person-weeks), 2.5% were black or African American (n=33; 1,297.1 person-weeks), and 1.5% were of other racial or ethnic origin (n=20; 834.6 person-weeks).
Subpopulations carrying relevant genetic polymorphisms	Not applicable.
Other: Children	Not included in the clinical development program.
Other: Elderly	The All Clinical Trials population (see Table SIII.15) included the following elderly populations treated with abiraterone acetate: • In mHNPC, the majority of subjects were ≥65 years: – 42.4% of subjects were aged 65 to 74 years (n=253; 24,862.7 person-weeks), – 19.1% of subjects were aged 75 to 84 years (n=114; 10,881.0 person-weeks), and – 1.5% of subjects were aged ≥85 years (n=9; 622.4 person-weeks). • In mCRPC pre-chemotherapy, the majority of subjects were ≥65 years: – 41.3% of subjects were aged 65 to 74 years (n=325; 20,107.4 person-weeks), – 29.5% of subjects were aged 75 to 84 years (n=232; 13,162.3 person-weeks), and – 4.3% of subjects were aged ≥85 years (n=34; 1,560.0 person-weeks). • In mCRPC post-chemotherapy, the majority of subjects were ≥65 years: – 43.6% of subjects were aged 65 to 74 years (n=567; 23,171.3 person-weeks), – 24.8% of subjects were aged 75 to 84 years (n=322; 13247.9 person-weeks), and – 2.3% of subjects were aged ≥85 years (n=30; 11,41.1 person-weeks).
Patients with relevant co-morbidities:	
Patients with hepatic impairment	Exposure in subjects with liver function abnormality at baseline in the All Clinical Trials population is shown in Table SIII.19 and Table SIII.20. In Trial COU-AA-011, the safety profile of abiraterone acetate was assessed in non-cancer subjects with mild and moderate hepatic

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	impairment, as defined by Child-Pugh Classifications A and B, respectively, and in control subjects with normal hepatic function. In this Phase 1 study, 8 subjects with mild hepatic impairment and 8 subjects with moderate hepatic impairment received a single 1,000 mg dose of abiraterone acetate. Use in non-cancer subjects with severe hepatic impairment defined by Child-Pugh Classification C was investigated in a trial (212082PCR1004) to determine the PK of abiraterone after a single oral administration (suspension formulation). In this Phase 1 study, 8 subjects with severe hepatic impairment received a single 125 mg dose of abiraterone acetate.
Patients with renal impairment	Exposure in subjects with renal impairment at baseline in the All Clinical Trials population (measured by CrCl; see Table SIII.19 and Table SIII.20) is summarized below: Mild impairment (CrCl >50 to <80 mL/min): • Total: n=777; 49,041.6 person-weeks • mHNPC: n=270; 26,470.7 person-weeks • mCRPC pre-chemotherapy: n=239; 11,528.4 person-weeks • mCRPC post-chemotherapy: n=268; 11,042.4 person-weeks Moderate impairment (CrCl >30 to ≤50 mL/min): • Total: n=158; 8,422.4 person-weeks • mHNPC: n=36; 3,008.4 person-weeks • mCRPC pre-chemotherapy: n=56; 2,982.1 person-weeks • mCRPC post-chemotherapy: n=66; 2,431.9 person-weeks Severe impairment (CrCl ≤30 mL/min): • Total: n=7; 235.3 person-weeks • mHNPC: n=1; 114.1 person-weeks • mCRPC pre-chemotherapy: n=2; 59.3 person-weeks • mCRPC post-chemotherapy: n=4; 61.9 person-weeks In Trial COU-AA-012, the safety profile of abiraterone acetate was assessed in non-cancer subjects with end-stage renal disease (ESRD) and in matched control subjects with normal renal function. In this Phase 1 study, 8 subjects with ESRD received a single 1,000 mg dose of abiraterone acetate.
Patients with cardiovascular impairment	Subjects with uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥95 mmHg) or clinically significant cardiac disease (as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class II, III, or IV heart disease or cardiac ejection fraction measurement of <50% at

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
	baseline) were excluded from clinical trials.
Immunocompromised patients	Not applicable.
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Not applicable.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the times a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure were based upon finished product. The defined daily dosage for ZYTIGA is 1 gram (two 500 mg tablets or four 250 mg tablets) as a single daily dose that must not be taken with food. These tablets should be taken at least 2 hours after eating and no food should be eaten for at least 1 hour after. Estimates of exposure are presented in person-time (person-days, person-weeks, and person-years) and it is assumed that 1 gram is equivalent to 1 person-day, 7 person-days is equivalent to 1 person-week, and 52 person-weeks is equivalent to 1 person-year.

SV.1.2. Exposure

Exposure to ZYTIGA worldwide is summarized in Table SV.1. Based on 220,712,400 grams of ZYTIGA distributed worldwide, the estimated postmarketing exposure for ZYTIGA from launch to 30 April 2022 is 220,712,400 person-days or 31,530,343 person-weeks or 604,692 person-years.

Table SV.1: Exposure Table by Region

Cumulative Postmarketing (Nonstudy) Exposure to ZYTIGA (Launch to 30 April 2022)				
Region	**Grams**	**Person-Days**	**Person-Weeks**	**Person-Years**
EU[a]	99,404,588	99,404,588	14,200,656	272,341
North America	55,475,419	55,475,419	7,925,059	151,988
Rest of World	65,832,393	65,832,393	9,404,628	180,363
Worldwide Total	**220,712,400**	**220,712,400**	**31,530,343**	**604,692**

[a] United Kingdom is no longer a part of the European Union and has been grouped under rest of the world from January 2021 onwards.

Additional Stratification

Additional stratifications are provided using IQVIA (formerly IMS MIDAS™) data where possible and appropriate. Market research sources for nonstudy exposure data are unavailable for breakdowns such as: usage in pregnant or breastfeeding women, usage in hepatic impairment population, or usage in renal impairment population.

Exposure by Age and Sex Presented as a Percentage of Prescription Sales

Prescription (Rx) sales stratified by age and sex are available from IQVIA and are presented below (as a percentage of total Rxs). See Table SV.2.

Further splits such as sex within age group are not provided since it is not appropriate to stratify to this level of detail based on Rx information available from IQVIA for these subcategories. Rx units are reported as absolute values.

Table SV.2: Exposure Table by Age Group and Sex

Postmarketing (Nonstudy) ZYTIGA Exposure by Age Group in Europe (01 January 2019 to 31 December 2021)

Age Groups (Years)[a]	EU[b] (292,347 Rx[c])
0 to 17	0.02%
18 to 35	0.02%
36 to 64	10.49%
≥65	89.27%
NR	0.2%

[a] Regional Rx data by age were only available for the last 3 moving annual total years ending December 2021.
[b] Data stratified by age are only available for France, Germany, and United Kingdom.
[c] Included retail channels.

Postmarketing (Nonstudy) ZYTIGA Exposure by Age Group Outside Europe (01 January 2019 to 31 December 2021)

Age Groups (Years)[a]	Non-EU[b] (2,591,697 Rx[c])
36 to 64	11.4%
≥65	87.94%
NR	0.66%

[a] Regional Rx data by age are only available for the last 3 moving annual total years ending December 2021.
[b] Data stratified by age were only available for Canada, Japan, and the United States.
[c] Included retail channels.

Postmarketing (Nonstudy) ZYTIGA Exposure by Sex (01 January 2019 to 31 December 2021)

Country[a]	Male[b]	Patient Sex Unidentified[b]
Canada	100.0%	0.00%
France	100.0%	0.00%
Germany	99.79%	0.21%
Japan	100.0%	0.00%
United Kingdom	100.0%	0.00%
United States	100.0%	0.00%

[a] Regional data by sex are only available for the last 3 moving annual total years ending December 2021.
[b] Data are only available for Canada, France, Germany, Japan, United Kingdom, and the United States.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

ZYTIGA is an antineoplastic agent, and has no abuse potential. The concern for potential illegal use is therefore unlikely. No cases reporting drug abuse/misuse for illegal purposes have been received.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification With a Submission of an Updated RMP

The list of safety concerns has been re-evaluated in line with the definitions provided in GVP Module V, Rev 2. As a result, all 13 safety concerns classified as Important Identified Risks (6), Important Potential Risks (3) and Missing Information (4) have been removed from the RMP. The rationale for removal for each safety concern is presented in the table below.

Safety Concern	Reason for Removal From the List of Safety Concerns
Important Identified Risks	
• Cardiac disorders • Hepatotoxicity • Increased exposure with food • Rhabdomyolysis/myopathy	These risks have no additional pharmacovigilance activities or additional risk minimization activities. The specific clinical measures recommended in the routine risk minimization activities for these risks are part of standard clinical practice. Reporting rates for these risks have been stable or decreasing over time.
• Osteoporosis including osteoporosis-related fractures • Allergic alveolitis	These risks have no additional pharmacovigilance activities, additional risk minimization activities, or routine risk minimization activities recommending specific clinical measures to address the risk. Reporting rates for these risks have been stable or decreasing over time.
Important Potential Risks	
• Anemia • Cataract	These risks have no additional pharmacovigilance activities, additional risk minimization activities, or routine risk minimization activities recommending specific clinical measures to address the risk. Reporting rates for these risks have been stable or decreasing over time and no new safety signals have been identified.
• Drug-drug interaction (CYP2D6)	This risk has no additional pharmacovigilance activities or additional risk minimization activities. The specific clinical measures recommended in the routine risk minimization activities for this risk are part of standard clinical practice. No

Safety Concern	Reason for Removal From the List of Safety Concerns
	new safety signals have been identified with regards to this risk.
Missing Information	
Use in patients with active or symptomatic viral hepatitis	This risk has no additional pharmacovigilance activities, additional risk minimization activities, or routine risk minimization activities recommending specific clinical measures to address the risk. No new safety signals have been identified with regards to these risks.
Use in patients with moderate/severe hepatic impairment and chronic liver disease Use in patients with severe renal impairment	These risks have no additional pharmacovigilance activities or additional risk minimization activities. The SmPC provides sufficient information to address and mitigate the risk to patients with hepatic and renal impairment, including Warnings and Precautions, specific clinical measures (Sections 4.2, 4.4, and 5.2), and contraindications (severe hepatic impairment; Section 4.3). No new safety signals have been identified over 11 years of postmarketing safety surveillance.
Use in patients with heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of <50%	This risk has no additional pharmacovigilance activities or additional risk minimization activities. There is no reasonable expectation that existing or future feasible pharmacovigilance activities could further characterize the risk. The SmPC provides sufficient information to address and mitigate the risk to patients with history of heart disease or at risk of congestive heart failure (eg, a history of cardiac failure, uncontrolled hypertension, or cardiac events such as ischemic heart disease), including Warnings and Precautions and specific clinical measures (Sections 4.2 and 4.4). No new safety signals have been identified over 11 years of postmarketing safety surveillance.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Not applicable.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	None

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns		
Safety Concern	**Purpose/Description**	
Not applicable.		
Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Not applicable.		

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

Not applicable.

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Not applicable.

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Not applicable as there are no important identified risks, important potential risks, or missing information for abiraterone acetate.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Not applicable.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for ZYTIGA (Abiraterone Acetate)

This is a summary of the risk management plan (RMP) for ZYTIGA. The risks associated with ZYTIGA are well characterized and managed with established routine risk minimization measures, therefore, there are no important risks or uncertainties (missing information) associated with this product.

ZYTIGA's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how ZYTIGA should be used.

This summary of the RMP for ZYTIGA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns will be included in updates of ZYTIGA's RMP.

I. The Medicine and What it is Used For

ZYTIGA, with prednisone or prednisolone, is authorized for the following (see SmPC for the full indication):

- the treatment of newly diagnosed high-risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT).
- the treatment of metastatic castration-resistant prostate cancer (mCRPC) in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.
- the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.

ZYTIGA contains abiraterone acetate as the active substance and it is given by orally by tablet or film-coated tablet.

Further information about the evaluation of ZYTIGA’s benefits can be found in ZYTIGA’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage: https://www.ema.europa.eu/en/medicines/human/EPAR/zytiga.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Not applicable, as there are no important identified risks or important potential risks for ZYTIGA.

II.A. List of Important Risks and Missing Information

There are no important identified risks, important potential risks, or missing information for ZYTIGA.

II.B. Summary of Important Risks

There are no important identified risks, important potential risks, or missing information for ZYTIGA.

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of ZYTIGA.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for ZYTIGA.

PART VII: ANNEXES

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.