European Union Risk Management Plan
niraparib/abiraterone acetate fixed-dose combination tablet

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PPD

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	2.1
Rationale for submitting an updated RMP (if applicable)	Type II variation to update the exposure and risk data based on the final analysis for the MAGNITUDE trial.
Summary of significant changes in this RMP:	Exposure and risk data have been updated based on the final analysis for the pivotal study (MAGNITUDE). Postmarketing exposure data have been added. The Part IV post-authorization efficacy study commitment has been completed.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
Not applicable.		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	1.4
Approved within procedure	EMEA/H/C/005932/0000
Date of approval (Competent authority opinion date)	19 April 2023 (EC Decision)

TABLE OF CONTENTS

TABLE OF CONTENTS 3

PART I: PRODUCT(S) OVERVIEW 5

PART II: SAFETY SPECIFICATION 7

MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S) 7

MODULE SII: NONCLINICAL PART OF THE SAFETY SPECIFICATION 11

MODULE SIII: CLINICAL TRIAL EXPOSURE 19
SIII.1. Brief Overview of Development 19
SIII.2. Clinical Trial Exposure 21

MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS 26
SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program 26
SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs 28
SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s) 28

MODULE SV: POSTAUTHORIZATION EXPERIENCE 31
SV.1. Postauthorization Exposure 31
SV.1.1. Method used to Calculate Exposure 31
SV.1.2. Exposure 31

MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION 32

MODULE SVII: IDENTIFIED AND POTENTIAL RISKS 33
SVII.1. Identification of Safety Concerns in the Initial RMP Submission 33
SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP 33
SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP 34
SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP 36
SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information 36
SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks 37
SVII.3.2. Presentation of the Missing Information 45

MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS 46

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POSTAUTHORIZATION SAFETY STUDIES) 47
III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection 47
III.2. Additional Pharmacovigilance Activities 47
III.3. Summary Table of Additional Pharmacovigilance Activities 48

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES 49

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES) 50
V.1. Routine Risk Minimization Measures 50
V.2. Additional Risk Minimization Measures 52
V.2.1. Removal of Additional Risk Minimization Activities 52
V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities 52

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN 56
I. The Medicine and What it is Used For 56
II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks 56

II.A. List of Important Risks and Missing Information 57
II.B. Summary of Important Risks 57
II.C. Postauthorization Development Plan 61
II.C.1. Studies Which are Conditions of the Marketing Authorization 61
II.C.2. Other Studies in Postauthorization Development Plan 61

PART VII: ANNEXES 63
Annex 4: Specific Adverse Drug Reaction Follow-up Forms 64
Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable) 65

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (international nonproprietary name [INN] or common name)	Niraparib and abiraterone acetate
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Antineoplastic agents, other antineoplastic agents (L01XK52)
Marketing Authorization Applicant	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	AKEEGA®
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** The chemical name for niraparib tosylate monohydrate is 2-[4-(3S)-3-piperidinylphenyl]-2H-indazole-7-carboxamide, 4-methylbenzenesulfonate hydrate (1:1:1). The chemical name for abiraterone acetate is (3β)-17-(3-pyridinyl)androsta-5,16-dien-3-yl acetate.
	Summary of mode of action AKEEGA is a combination of niraparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), and abiraterone acetate (a prodrug of abiraterone), a 17α-hydroxylase/C17,20-lyase (CYP17) inhibitor, targeting 2 oncogenic dependencies in patients with metastatic castration-resistant prostate cancer (mCRPC) and homologous recombination repair (HRR) gene mutations. Niraparib is an inhibitor of PARP enzymes, PARP-1 and PARP-2, which play a role in DNA repair. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis, and cell death. Abiraterone acetate is converted in vivo to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme CYP17. This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal, and prostatic tumor tissues. CYP17 catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, dehydroepiandrosterone and androstenedione, respectively, by 17α-hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals.

	Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with luteinizing hormone-releasing hormone analogues (or orchiectomy).	
	Important information about its composition Not applicable.	
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet	
Indication(s) in the EEA	**Current:** AKEEGA is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.	
	Proposed: Not applicable.	
Dosage in the EEA	**Current:** The recommended starting dose is 200 mg niraparib/1,000 mg abiraterone acetate (two 100-mg/500-mg tablets) that must be taken orally as a single daily dose at approximately the same time every day on an empty stomach. AKEEGA is used with 10 mg prednisone or prednisolone daily.	
	Proposed: Not applicable.	
Pharmaceutical form(s) and strengths	**Current:** AKEEGA is formulated as film-coated tablets, available in 2 strengths: • niraparib tosylate monohydrate equivalent to 50 mg of niraparib / 500 mg abiraterone acetate equivalent to 446 mg of abiraterone; yellowish orange to yellowish brown, oval, film-coated tablet debossed with “N 50 A” on one side and plain on the other side • niraparib tosylate monohydrate equivalent to 100 mg of niraparib / 500 mg abiraterone acetate equivalent to 446 mg of abiraterone; orange, oval, film-coated tablet debossed with “N 100 A” on one side and plain on the other side	
	Proposed: Not applicable.	
Is/will the product be subject to additional monitoring in the European Union (EU)?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

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

Indication

Treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Specific data for mCRPC is provided whenever available, but when not available, data for CRPC or prostate cancer is provided instead.

Incidence:

Worldwide, prostate cancer is the second most common cancer among men, with an estimated 1,414,259 new cases diagnosed in 2020 (approximately 7% of all incident cancer cases), for an age-standardized incidence rate of 30.7 per 100,000 population. In Europe, prostate cancer is the most common cancer in men, with 473,344 new cases, representing 20.2% of all cancers in men, in 2020 (IARC 2020). In the United States, prostate cancer is the most common noncutaneous cancer among men, with an estimated incidence of 248,530 new cases in 2021 (ACS 2021).

The table below shows the estimated incidence rate of prostate cancer in selected European regions in 2020 (IARC 2020).

Region	Age-standardized incidence rate per 100,000 population
Northern Europe	83.4
Western Europe	77.6
Southern Europe	59.1
Central & Eastern Europe	46.4

Prevalence:

In Europe, the 5-year prevalence of prostate cancer in 2020 was estimated to be 1,873,814 cases or 518.1 per 100,000 population. The table below shows the estimated 5-year prevalence per 100,000 population in selected European regions in 2020 (IARC 2020).

Region	5-year prevalence per 100,000 population
Northern Europe	735.4
Western Europe	723.0
Southern Europe	503.0
Central & Eastern Europe	300.3

In the United States, the prevalence for 2018 was estimated at 2.02% of the male population (SEER Explorer 2021).

In a systematic review of literature on CRPC that included a total of 71,179 patients observed for up to 12 years, 10% to 20% of prostate cancer patients developed CRPC within 5 years of follow-up from diagnosis and 16% of these patients showed no evidence of bone metastasis at the time of CRPC diagnosis (Kirby 2011). An analysis of claims data in the United States reported

that the prevalence of mCRPC was 1,140 per 100,000 prostate cancer patients and 20 per 100,000 enrolees in 2017 (Wallace 2021). In France, the age-standardized prevalence of mCRPC was estimated at 62 per 100,000 men aged ≥40 years in 2014 (Thurin 2020).

In addition to androgen receptor (AR) signaling as a growth driver, DNA repair anomalies have been identified in up to approximately 30% of patients with metastatic prostate cancer, (Dhawan 2016; Mateo 2017; Robinson 2015). One study reported that 16.2% of mCRPC patients had a germline HRR gene mutation, including BRCA2 (3.3%), ATM (1.9%), and BRCA1 (0.95%) (Shore 2021). Another study reported 23% of mCRPC patients had DNA repair aberrations (Chau 2020). HRR, and specifically BRCA1/2, gene mutations have been associated with worse oncologic outcomes and reduced overall survival (OS) (Castro-Marcos 2017).

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

Age:

Older men are predominately affected by mCRPC. An analysis of US claims data reported the lowest prevalence rate among men aged 18 to 44 years and the highest prevalence rate among men older than 75 years (148 per 100,000) (Wallace 2021). In France, less than 1 mCRPC case per 100,000 was observed among men aged 40 to 49 years and the highest incidence rate was observed in men aged 80 to 89 years (175 per 100,000) in 2014 (Thurin 2020).

Sex:

Metastatic castration-resistant prostate cancer affects only men.

Racial 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 (Bray 2018). In an analysis that spanned 2010 to 2012, African Americans had a higher lifetime risk of developing (18.2% vs 13.3%) and dying from (4.4% vs 2.4%) prostate cancer compared to Caucasian Americans (DeSantis 2016). Globally, in 2020, prostate cancer incidence rates were relatively high in certain less developed regions such as the Caribbean (75.8 per 100,000 population), Southern Africa (65.9 per 100,000 population), and South America (62.5 per 100,000 population). Incidence rates remain low in Asian populations, estimated at 6.3 per 100,000 population and 13.5 per 100,000 population in South-Central and South-Eastern Asia, respectively (IARC 2020).

An analysis of US claims data for mCRPC reported that 61% of patients were white, 2% were Asian, 10% were Black, and 27% were of other or unknown racial origin (George 2020).

Risk Factors for the Disease:

Risk factors specific to mCRPC are not available, but risk factors for prostate cancer have been identified.

Established risk factors for prostate cancer are advancing age, Black race, and a family history of this malignancy (Zhou 2016). Some research has shown that a greater body mass index in prostate cancer patients is associated with higher rates of prostate-specific antigen (PSA) recurrence after prostatectomy (Amling 2004, Freedland 2004). Prostate cancer is thought to have a strong ethnic propensity, and there is a higher prevalence among Europeans and African Americans (Gunderson 2011). Inherited mutations in BRCA1 and BRCA2 have been reported to confer an increased risk of developing prostate cancer and a worse outcome (Athie 2019).

Environmental factors and exogenous factors have also been found to increase risk. A diet high in red meat or high-fat dairy products, or low in fruits and vegetables may be associated with increased risk (Brawley 2012).

Main Existing Treatment Options:

Patients with HRR gene mutations have historically been managed in the same manner as other patients with mCRPC who do not harbor an HRR mutation. Therapies targeting the AR-axis (AAP and enzalutamide), which are considered standard of care, have been associated with significant radiographic progression-free survival and survival benefits and improved quality of life for patients with mCRPC; however, patients with HRR gene alterations, particularly those patients with BRCA1 and BRCA2 gene alterations, have a worse prognosis and do not respond as well to these treatments as those without HRR gene mutations (Castro 2019; Annala 2017, 2018, Olmos 2023).

Based on the results from the Sponsor's MAGNITUDE Study (64091742PCR3001), niraparib/abiraterone acetate FDC (AKEEGA®) plus prednisone/prednisolone has been approved in the US, EU/EEA, and other regions for the treatment of patients with mCRPC and BRCA gene alterations (AKEEGA SmPC/USPI 2023).

Additionally, 2 other PARP inhibitors—olaparib (Lynparza®) and talazoparib (Talzenna®)—have also been approved in combination with AR-targeted therapies for the treatment of mCRPC with the following labelled indications: Lynparza® is approved in the US in combination with AAP for the treatment of adult patients with deleterious or suspected deleterious BRCA-mutated mCRPC (Lynparza USPI 2023) and in the EU in combination with AAP for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (Lynparza SmPC 2023). Talzenna® is approved in the US in combination with enzalutamide for the treatment of adult patients with HRR gene-mutated mCRPC (Talzenna USPI 2023) and in the EU in combination with enzalutamide for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (Talzenna SmPC 2024).

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

Natural history:

Patients with mCRPC generally have an unfavorable prognosis, but the clinical course may vary with some patients quickly progressing to widespread metastatic disease and others experiencing a more indolent disease. Most mCRPC patients present with bone metastases with or without

lymph node involvement (72.8%), followed by visceral disease (20.8%), and lymph node-only disease (6.4%) (Halabi 2016). Bone metastases, which can manifest as pain and debilitating skeletal events such as pathologic fractures and spinal cord compression, and are the primary cause of disability, reduced quality of life, and death (Body 2015). The long-term prognosis for patients with mCRPC is poor, with a relatively short OS, although survival varies highly depending on individual disease characteristics (Henríquez 2021). Several lines of evidence suggest HRR gene mutations act as second oncogenic drivers in men with prostate cancer and are shown to be associated with worse oncologic outcomes in these patients (Annala 2017, 2018; Castro 2013, 2015, 2019; Edwards 2010; Na 2017; Nyberg 2020). BRCA2 or ATM gene mutations are significant predictors of shorter time to PSA progression after second-line therapy (hazard ratio = 2.68; 95% confidence interval [CI]: 1.58-4.54) (Chi 2017), and patients with mCRPC and HRR gene mutations have a shorter life expectancy compared to patients with mCRPC and no HRR gene mutations (median OS from mCRPC of 28.5 versus 36 months, respectively) (Castro-Marcos 2017). Specifically, BRCA2 mutations have significantly worse cause-specific survival compared to subjects without an HRR mutation (17.4 versus 33.2 months, respectively; p=0.027) (Castro 2019).

Mortality:

Worldwide, there were an estimated 375,304 deaths due to prostate cancer in 2020 for an age-standardized risk of 7.7 per 100,000 population, and prostate cancer is the fifth leading cause of death from cancer in men. In Europe, the age-standardized mortality rate for prostate cancer in 2020 was estimated at 11.1 per 100,000 population (IARC 2020).

While patients with localized prostate cancer may be cured with surgery, radiation or other local modalities/interventions, development of metastases heralds a lethal disease. Despite advances in the treatment of men with mCRPC, the median OS in these patients is less than 3 years (Ryan 2015).

Important Comorbidities:

Prevalent comorbidities in patients with mCRPC include cardiovascular disease and diabetes (Chowdhury 2020). Comorbidities among CRPC patients in general include hypertension, dyspnea, cardiac disease (including ischemic heart disease/angina), renal failure/impairment, diabetes mellitus, peripheral edema, hypotension, urinary disorders, anemia, digestive disorders, and respiratory infections (Hirst 2012).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical data discussed in the table below are derived from the development programs of the individual active substances, niraparib and abiraterone acetate. Consistent with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S9 guidance on nonclinical evaluation for anticancer pharmaceuticals, nonclinical safety studies with the combination of niraparib and abiraterone acetate were not conducted. A nonclinical safety assessment was performed based on the mechanism of action of niraparib (PARP inhibitor) and abiraterone acetate (androgen biosynthesis inhibitor) and the animal toxicity data for the individual drugs. Other than the toxicities that are known from the individual active substances, this safety assessment did not indicate a relevant cause for concern for its use in the intended patient population. The combination of niraparib and abiraterone acetate was well tolerated when evaluated in 2 in vivo pharmacology studies in mice (mice VCaP xenograft tumor model and LuCAP BRCA2-mutant prostate tumor model) as assessed by animal weights during treatment.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Niraparib Results from repeat-dose oral toxicity studies up to 3 months in rats and dogs indicated that the bone marrow and the testes are the target organs of niraparib in both species. These target organ toxicities were observed at exposure levels below those observed in patients receiving 300 mg niraparib. Bone marrow suppression affected cells of both white and red lineages. It was often heralded by early decreases in reticulocytes, followed by adverse decreases of circulating white and red cells. In rats, infections and septicemia were considered to have resulted from the depletion of leukocytes (mainly neutrophils). The effect on the spermatogenic epithelium was characterized by a decreased amount of spermatogenic epithelium in dogs and testicular germ cell depletion in rats. Extension of dosing from 1 month to 3 months did not lower the no observed adverse effect level (NOAEL) in either species. In a 3-month study, NOAEL for dogs was 4.5 mg/kg/day and NOAEL for rats was 10 mg/kg/day. All findings were found to be reversible in both species.	Niraparib and abiraterone acetate The nature of toxicity of niraparib and abiraterone acetate is comparable across species and is related to the pharmacological activity of niraparib (ie, PARP inhibition) and abiraterone (ie, decrease in androgens resulting from CYP17 inhibition). Hematological toxicities were observed in nonclinical studies with niraparib and were confirmed by clinical data. In a review of the animal toxicity profiles of niraparib and abiraterone acetate, testicular atrophy and a decrease in red blood cells were observed with both drugs. No other overlapping toxicities have been observed in animals. In animal studies, male fertility was reduced with niraparib or abiraterone acetate but these effects were reversible following treatment cessation. Since testicular atrophy is a common side effect of background androgen deprivation therapy (ADT) with a gonadotropin-releasing hormone (GnRH) analogue in prostate cancer patients, it is not considered a relevant risk for the niraparib/abiraterone acetate fixed-dose combination (FDC) tablet.

Key Safety Findings	Relevance to Human Usage
Abiraterone acetate Repeat-dose toxicity studies of 28 days in mice, 13 and 26 weeks in rats, and 13 and 39 weeks in monkeys were conducted to characterize the chronic toxicity of abiraterone acetate when administered orally. The majority of toxicities were related to interference of abiraterone (acetate) with steroid metabolism and affected the testes (atrophy and reduced spermatogenesis) and other reproductive organs, including the accessory organs and mammary glands. Associated findings included adrenocortical hypertrophy and hypertrophy/hyperplasia of the pituitary gland (rat only). After a 4-week recovery period, full or partial reversibility was noted for the findings above. A minimal decrease in red blood cell mass was seen in studies in mice and rats and generally correlated with increased reticulocyte counts. 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).	
Hepatotoxicity Niraparib There were no observations on liver or liver function in the repeat-dose oral toxicity studies up to 3 months in rats and dogs. Abiraterone acetate 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 alkaline phosphatase (ALP) and total bilirubin. Bile duct/oval cell hyperplasia, observed from 13 weeks of treatment, partially reversed after 4 weeks in monkeys but not in rats. Hepatocellular hypertrophy (rat only) was fully reversible.	Niraparib and abiraterone acetate The niraparib/abiraterone acetate FDC tablet has the potential to affect liver function based on findings from animal studies with abiraterone acetate. Nonclinical data on niraparib revealed no special hazard for humans. The niraparib/abiraterone acetate FDC tablet is contraindicated in patients with severe hepatic impairment.

Key Safety Findings	Relevance to Human Usage
Reproductive toxicity	
Niraparib No fertility toxicity studies were conducted for niraparib. In the general toxicity studies, as described above, reversible findings were observed on spermatogenesis. There were no adverse findings caused by niraparib in the female reproductive tract. Abiraterone acetate Fertility studies were performed in male and female rats. In male rats, a reduction in organ weights of the reproductive system; decrease in sperm counts, motility, and altered sperm morphology; and a 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.	Niraparib and abiraterone acetate In animal studies, male fertility was reduced with niraparib or abiraterone acetate but these effects were reversible following treatment cessation. Findings in animals are consistent with the pharmacological activity of niraparib (ie, PARP inhibition) and abiraterone (ie, decrease in androgens resulting from CYP17 inhibition). The niraparib/abiraterone acetate FDC tablet is not for use in women and is contraindicated in women who are or may become pregnant.
Developmental toxicity	
Niraparib No embryo-fetal developmental toxicity studies were performed for niraparib. In mice, PARP-1 and PARP-2 double knock-out mutant embryos are not viable and die around the onset of gastrulation, demonstrating that the expression of both PARP-1 and PARP-2 is essential during early embryogenesis (Ménissier de Murcia 2003). Abiraterone acetate In an oral developmental toxicity study in rats, 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.	Niraparib and abiraterone acetate The niraparib/abiraterone acetate FDC tablet has the potential to cause fetal harm based on the mechanism of action of niraparib and abiraterone acetate and findings from animal studies with abiraterone acetate. The niraparib/abiraterone acetate FDC tablet is not for use in women and is contraindicated in women who are or may become pregnant.

Key Safety Findings	Relevance to Human Usage
Genotoxicity	
Niraparib Niraparib was negative in microbial mutagenesis assays (Ames test) and is not considered mutagenic. Niraparib was genotoxic in in vitro and in vivo mammalian systems and is considered to be clastogenic. Abiraterone acetate Abiraterone acetate and abiraterone were neither mutagenic in an in vitro microbial mutagenesis (Ames) assay nor clastogenic in an in vitro cytogenetic assay using primary human lymphocytes or an in vivo rat micronucleus assay.	Niraparib and abiraterone acetate The clastogenicity of niraparib is consistent with its ability to inhibit DNA repair (Bailey 1999; Simbulan-Rosenthal 1999) and observations from other members of this class and indicates genotoxic potential for niraparib/abiraterone acetate FDC tablet use in humans. Nonclinical data on abiraterone acetate revealed no special hazard for humans.
Carcinogenicity	
Niraparib No carcinogenicity studies were performed for niraparib. Abiraterone acetate A 6-month carcinogenicity study was performed in Tg.ras.H2 mice 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. A 2-year carcinogenicity study was performed in Crl:CD (Sprague Dawley) 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. Abiraterone acetate was not carcinogenic in female rats.	Niraparib and abiraterone acetate A potential risk for drug-related malignancies cannot be excluded for the niraparib/abiraterone acetate FDC tablet because niraparib is genotoxic. The increased incidence of interstitial cell neoplasms in the testes observed in the rat carcinogenicity study with abiraterone acetate was considered rat-specific and of no concern for use in humans.
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
Niraparib Niraparib inhibited human ether-*á-go-go*-related	Niraparib and abiraterone acetate No relevant risk for QT/QTc prolongation has been

Key Safety Findings	Relevance to Human Usage
gene (hERG) potassium current with a 50% maximum inhibitory concentration (IC_{50}) value of 15 µM in a Good Laboratory Practice (GLP) assay, similar to an IC_{50} of 10 µM observed in the previous non-GLP assay. In a GLP cardiovascular safety pharmacology study using a Latin square crossover design, dogs (4/sex/group) received single doses of niraparib at 0, 3, 6, or 15 mg/kg via oral gavage. Transient and slight increases in blood pressure (BP) (systolic, diastolic, and mean arterial pressures) were noted within 7 hours post dose at 15 mg/kg in male and female dogs. These effects were consistent with those observed in a non-GLP cardiovascular study. In that study, 3 anesthetized, vagotomized male dogs received 3 consecutive ascending doses of niraparib (1, 3, and 10 mg/kg) over 30-minute intravenous infusion periods. Niraparib had no effect on QT/corrected QT interval (QTc) up to and including the highest dose of 10 mg/kg. At that dose, the peak average plasma concentration measured during infusion in dogs was 15.3±1.1 µM (4,902 ng/mL total bound and unbound). Peak average plasma concentrations (total bound and unbound) measured during infusion of the 1 and 3 mg/kg doses were 1.2 µM (384 ng/mL) and 3.9 µM (1,250 ng/mL), respectively. Niraparib increased the heart rate in a dose-dependent fashion (+5%, +9%, and +17%). A dose-independent increase (+16% to +21%) in mean arterial pressure was observed from 1 mg/kg. Abiraterone acetate 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 hERG potassium current. Abiraterone acetate inhibited hERG 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	identified in the in vitro hERG assays and in vivo cardiovascular safety studies with either niraparib and abiraterone acetate. Based on the nonclinical data, the risk of cardiac disorders for the niraparib/abiraterone acetate FDC tablet is considered low. Hypertension was observed in nonclinical studies with niraparib and severe hypertension is considered an important identified risk for the niraparib/abiraterone acetate FDC tablet.

Key Safety Findings	Relevance to Human Usage
arrhythmias was considered limited based on the fact that there were no abnormalities in the electrocardiogram (ECG) recording at the end of the treatment period, and in most cases they 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 telemetered monkeys 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	
Niraparib In the initial in vitro screening assays, niraparib showed binding to the dopamine transporter (DAT) with IC_{50} of <5 µM. In the subsequent in vitro assays, niraparib inhibited the uptake of dopamine and norepinephrine with IC_{50} values of 24 and 130 nM in human Chinese hamster ovary (CHO)-K1 cells expressing DAT and in human Madin-Darby canine kidney (MDCK) cells expressing norepinephrine transporter, respectively. Data from studies in mice indicated that niraparib does not result in behavioral or neurochemical effects consistent with enhanced dopamine availability in the central nervous system (CNS), nor does it occupy the dopamine reuptake transporter at plasma levels which have been shown to cause antitumor activity. Similarly, in a CNS safety pharmacology study, niraparib had no effect on neurological function, including general behavior, neural reflexes, or spontaneous activity during the 24-hour post-dose period. Abiraterone acetate Abiraterone acetate had no effects on the CNS in an oral toxicity study with integrated Irwin observations.	Niraparib and abiraterone acetate Nonclinical data on abiraterone acetate revealed no special hazard for humans. In vitro, niraparib inhibited DAT at concentration levels below human exposure levels but no effect on behavioral and/or neurological parameters has been observed in repeat-dose toxicity studies in rats and dogs at exposure levels similar to or below the expected therapeutic exposure levels. The clinical relevance for the niraparib/abiraterone acetate FDC tablet is not known.
Other toxicity-related information or data	
Phototoxicity	
Niraparib Niraparib absorbs in the ultraviolet (UV) spectrum 193-311 nm. In an in vitro screening assay using BALB/c 3T3 mouse fibroblasts, UV light increased the cytotoxicity caused by niraparib. However, based on the inhibitory	Niraparib and abiraterone acetate Nonclinical data with niraparib and abiraterone acetate as individual active substances do not indicate phototoxic potential for niraparib/abiraterone acetate FDC tablet use in

Key Safety Findings	Relevance to Human Usage
action of niraparib on DNA repair, the increase of cytotoxicity is most likely due to the inability of the cell to repair the DNA damage caused by UV light. The results from an in vivo phototoxicity study using Long Evans pigmented rats showed no evidence of cutaneous or ocular phototoxicity after a 3-day oral administration of niraparib at doses as high as 100 mg/kg/day, demonstrating that niraparib does not have phototoxicity. Abiraterone acetate No phototoxicity assessments were performed for abiraterone acetate. Abiraterone acetate and abiraterone show limited absorption of light between 290 and 700 nm.	humans.
Cataract Niraparib There were no observations of cataract in the repeat-dose oral toxicity studies up to 3 months in rats and dogs. Abiraterone acetate 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 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.	Niraparib and abiraterone acetate Nonclinical data on niraparib revealed no special hazard for humans. The mechanism for cataract as observed in nonclinical studies with abiraterone acetate 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. 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. Based on absence of ocular findings in monkeys and mice following similar or longer durations of treatment at comparable exposures or higher exposure, 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 for niraparib/abiraterone acetate FDC tablet use in humans.

Key Safety Findings	Relevance to Human Usage
Drug metabolism and pharmacokinetics	
Mechanisms for drug interactions	
Niraparib No major drug-drug interactions are anticipated for niraparib. Abiraterone acetate Abiraterone acetate showed potent inhibition of cytochrome P450 (CYP)2D6, CYP1A2, and CYP2C8 in vitro in human liver microsomes.	Niraparib and abiraterone acetate Clinical drug-drug interaction trials with abiraterone acetate (COU-AA-015 and 212082PCR1011) confirmed lack of drug-drug interaction for CYP1A2. However, significant interaction (200% increase in exposure) was observed for dextromethorphan, a substrate of CYP2D6. In the drug-drug interaction Trial 212082PCR1011, the area under the concentration-time curve (AUC) of pioglitazone (ie, CYP2C8 substrate) was minimally increased (46%) when given with a single dose of abiraterone acetate.

Summary of Nonclinical Safety Concerns

Important identified risks	Severe hypertension
Important potential risks	None
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The niraparib/abiraterone acetate FDC tablet with prednisone or prednisolone has been developed by the marketing authorization applicant for the treatment of patients with mCRPC with HRR gene mutations. The marketing authorization application specifically includes patients with mCRPC with BRCA1/2 mutations (germline and/or somatic), which is the target population for this RMP. The combination tablet consists of 2 authorized individual active substances, niraparib and abiraterone acetate.

The marketing authorization applicant in-licensed niraparib from GlaxoSmithKline (marketing authorization holder for Zejula®) in April 2016, for worldwide (excluding Japan) development for the treatment of prostate cancer only. GlaxoSmithKline is responsible for the development of niraparib for all other indications and is the marketing authorization holder for the individual active substance niraparib.

Niraparib, a PARP-1 and PARP-2 inhibitor, is authorized in the European Union for certain populations with epithelial ovarian, fallopian tube, or primary peritoneal cancer (Zejula Summary of Product Characteristics [SmPC] 2022).

Abiraterone acetate (ZYTIGA®), an androgen biosynthesis inhibitor, in combination with prednisone or prednisolone (AAP) is authorized in the European Union for the treatment of men with metastatic prostate cancer (ZYTIGA SmPC 2022).

For patients with mCRPC, targeting the AR-axis continues to be an important therapeutic approach. However, for up to approximately 30% of patients with mCRPC who have HRR gene mutations (Dhawan 2016; Mateo 2017; Robinson 2015), there may be a second oncogenic driver, which could be treated with a PARP inhibitor. For such patients, antitumor activity with a PARP inhibitor has been consistently demonstrated in multiple studies (Abida 2020; de Bono 2020; Smith 2019). Additionally, preliminary clinical data have indicated that combining a PARP inhibitor with AR-targeted therapy may provide an additional clinical efficacy benefit in these patients (Clarke 2018; Hussain 2018).

In the clinical development of the niraparib and AAP combination, the 200-mg dose of niraparib was selected as the optimal dose to be combined with AAP based on achieving maximum observed analyte concentration and AUC values within the efficacious target combination ranges, no dose-limiting toxicity, an overall tolerable safety profile, and no drug-drug interaction detected between niraparib and AAP (Trial 64091742PCR1001, see below) (Saad 2021). The niraparib/abiraterone acetate FDC tablet is developed to simplify the combination regimen by reducing the pill burden from up to 6 pills per day plus prednisone to 2 tablets per day plus prednisone. FDC development is supported by a bioavailability (BA) / bioequivalence (BE) trial (Trial 67652000PCR1001, see below).

The safety of the niraparib/abiraterone acetate FDC tablet in the mCRPC patient population is supported by data from the following 3 clinical trials, which are included in the risk management plan (RMP):

- **Ongoing Phase 3 Trial 64091742PCR3001** (hereafter referred to as MAGNITUDE) is a randomized, placebo-controlled, multicenter, double-blind trial to assess the efficacy and safety of niraparib in combination with AAP in men with mCRPC who previously received no prior treatment for mCRPC except <4 months of AAP. Subjects with HRR gene mutations (Cohort 1) and subjects without HRR gene mutations (Cohort 2) received 200 mg niraparib and AAP (1,000 mg/10 mg) or placebo and AAP as single-agent combination (SAC). As no additional benefit was observed in subjects without HRR gene mutations in the combination of niraparib with AAP compared to AAP alone, based upon a pre-planned futility analysis in Cohort 2, enrollment into Cohort 2 was stopped. In Cohort 3, subjects with HRR gene mutations received open-label niraparib and abiraterone acetate as an FDC tablet to obtain clinical experience with the FDC.
- **Ongoing Phase 1b/2 Trial 64091742PCR2002** (hereafter referred to as QUEST) is an open-label, dose-selection and dose-expansion trial to evaluate the safety and antitumor effect of niraparib in combination with other agents for the treatment of men with mCRPC who progressed on 1 prior line of novel AR-targeted therapy for mCRPC. The recommended Phase 2 dose (RP2D) for niraparib plus AAP was previously established in Trial 64091742PCR1001; therefore, Combination 2 explored the safety and efficacy of subjects with HRR gene mutations receiving 200 mg niraparib and AAP (1,000 mg/10 mg) daily as SAC and is included in the RMP.
- **Completed Phase 1b Trial 64091742PCR1001** (hereafter referred to as BEDIVERE) was an open-label, dose-selection and dose-expansion trial to determine the safety and RP2D of niraparib in combination with AR-targeted therapy in men with mCRPC previously treated with ≥1 line of taxane-based chemotherapy and ≥1 line of AR-targeted therapy. Subjects with or without HRR gene mutations who received 200 mg niraparib and AAP (1,000 mg/10 mg) are included in the RMP.

MAGNITUDE Cohort 1 provides blinded, randomized, and controlled data in the indicated population. This is considered the pivotal safety data. MAGNITUDE Cohort 3 provides supportive safety information on the clinical experience with the niraparib/abiraterone acetate FDC tablet in the indicated population. Additional supportive data is based on data from all subjects who received the proposed registration dose regimen as SAC in MAGNITUDE Cohort 2, QUEST Combination 2, and BEDIVERE.

Data from the Phase 1 Trial 67652000PCR1001 (BA/BE) in which the bioavailability and bioequivalence between niraparib/abiraterone acetate FDC formulations and the SAC of niraparib and abiraterone acetate was assessed and from the Phase 2 Trial 64091742PCR2001 (GALAHAD), which provided preliminary safety and efficacy data of 300 mg niraparib in subjects with mCRPC and DNA-repair anomalies, are not included in the RMP. Due to their design, these trials do not contribute to the safety evaluation of the niraparib/abiraterone acetate FDC tablet.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 1 trial, ie, MAGNITUDE (pivotal Cohort 1).

Exposure to niraparib and AAP as SAC in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.3 for all subjects by duration, by age group, and by variable stratifications relevant to the product (eg, ethnicity, race, renal impairment at baseline, hepatic impairment at baseline).

Table SIII.1: Exposure by Duration: Randomized Clinical Trials Population

	Patients	Person-months
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) pivotal Cohort 1		
Duration of exposure (months)		
0 - <3 months	16	24.7
3 - <6 months	14	66.7
6 - <9 months	18	135.1
9 - <12 months	18	187.9
12 - <15 months	18	244.6
15 - <18 months	16	266.9
18 - <21 months	12	239.8
21 - <24 months	15	335.2
24 - <27 months	15	376.1
27 - <30 months	17	483.5
≥30 months	53	1,972.3
Total	212	4,332.8

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Table SIII.2: Exposure by Age: Randomized Clinical Trials Population

	Patients	Person-months
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) pivotal Cohort 1		
Age group (years)		
18-64	61	1,192.0
65-74	88	2,017.2
75-84	56	1,052.5
≥85	7	71.1
Total	212	4,332.8

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Table SIII.3: Exposure by Special Populations: Randomized Clinical Trials Population (eg, Ethnicity, Race, Renal Impairment at Baseline, Hepatic Impairment at Baseline)

	Patients	Person-months
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) pivotal Cohort 1		
Ethnicity		
Hispanic or Latino	26	556.6
Not Hispanic or Latino	166	3,361
Not Reported[a]	20	415.1
Total	212	4,332.7
Race		
White	160	3,264.5
Black or African American	5	87.2
Asian	29	653
American Indian or Alaska Native	1	23.4
Not Reported[a]	17	304.7
Total	212	4,332.7
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	96	2,184.2
Mild (CrCl 60 to <90 mL/min)	86	1,654.4
Moderate (CrCl 30 to <60 mL/min)	30	494.1
Severe (CrCl <30 mL/min)	0	0
Missing	0	0
Total	212	4,332.7
Hepatic impairment at baseline[b]		
Normal	182	3,943.3
Mild	30	389.5
Moderate	0	0
Severe	0	0
Missing	0	0
Total	212	4,332.7

[a] Includes Unknown and missing values.
[b] Normal (per NCI Organ Dysfunction criteria): Total bilirubin ≤ULN and AST ≤ULN; Mild: (total bilirubin ≤ULN and AST >ULN) or (ULN <total bilirubin ≤1.5x ULN); Moderate: 1.5x ULN <total bilirubin ≤3x ULN; Severe: total bilirubin >3x ULN.
AST=aspartate aminotransferase; CrCl=creatinine clearance; NCI=National Cancer Institute; ULN=upper limit of normal.

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Exposure in All Clinical Trials

The all clinical trials population includes 3 trials:

- MAGNITUDE (Cohorts 1, 2, and 3)
- QUEST (Combination 2; referred to as Combo 2 in tables)
- BEDIVERE

Exposure to niraparib and AAP as SAC and to the niraparib/abiraterone acetate FDC tablet plus prednisone or prednisolone in the all clinical trials population is summarized in Tables SIII.4 through SIII.6 for all subjects by duration, by age group, and by variable stratifications relevant to the product (eg, ethnicity, race, renal impairment at baseline, hepatic impairment at baseline).

Table SIII.4: Exposure by Duration: All Clinical Trials Populations

	Patients	Person-months
Indication: mCRPC, cumulative safety data from 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2, and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE)		
Duration of exposure (months)		
0 - <3 months	51	85.4
3 - <6 months	47	204.9
6 - <9 months	45	338.1
9 - <12 months	51	550.2
12 - <15 months	76	1,012.5
15 - <18 months	31	508.5
18 - <21 months	26	515.4
21 - <24 months	36	815.7
24 - <27 months	37	940.1
27 - <30 months	20	567.3
≥30 months	53	1,972.3
Total	473	7,510.3
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) Cohort 3 FDC		
Duration of exposure (months)		
0 - <3 months	10	15.2
3 - <6 months	12	52.3
6 - <9 months	9	69.7
9 - <12 months	5	52
12 - <15 months	4	53.4
15 - <18 months	4	66.2
18 - <21 months	12	236.8
21 - <24 months	17	392.2
24 - <27 months	20	513.9
27 - <30 months	2	54.8
Total	95	1,506.4

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Table SIII.5: Exposure by Age: All Clinical Trials Populations

	Patients	Person-months
Indication: mCRPC, cumulative safety data from 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2, and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE)		
Age group (years)		
18-64	118	1,856.1
65-74	218	3,750.4
75-84	122	1,787.1
≥85	15	116.8
Total	473	7,510.3
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) Cohort 3 FDC		
Age group (years)		
18-64	25	371.5
65-74	48	876.2
75-84	19	241.1
≥85	3	17.6
Total	95	1,506.4

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Table SIII.6: Exposure by Special Populations: All Clinical Trials Populations (eg, Ethnicity, Race, Renal Impairment at Baseline, Hepatic Impairment at Baseline)

	Patients	Person-months
Indication: mCRPC, cumulative safety data from 64091742PCR3001(MAGNITUDE, Cohorts 1, 2, and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE)		
Ethnicity		
Hispanic or Latino	49	887.2
Not Hispanic or Latino	393	6,031.1
Not Reported[a]	31	592.1
Total	473	7,510.3
Race		
White	340	5,398.6
Black or African American	13	190.4
Asian	88	1,376.4
American Indian or Alaska Native	2	45.7
Native Hawaiian or Other Pacific Islander	1	11.1
Not Reported[a]	29	488.2
Total	473	7,510.3
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	205	3,419.4
Mild (CrCl 60 to <90 mL/min)	198	3,168.7
Moderate (CrCl 30 to <60 mL/min)	67	908.1
Severe (CrCl <30 mL/min)	2	10.4
Missing	1	3.7
Total	473	7,510.3
Hepatic impairment at baseline[b]		
Normal	419	6,869.9
Mild	53	638.2
Moderate	1	2.3
Severe	0	0
Missing	0	0
Total	473	7,510.3
Indication: mCRPC: 64091742PCR3001 (MAGNITUDE) Cohort 3 FDC		
Ethnicity		
Hispanic or Latino	12	208.2
Not Hispanic or Latino	77	1,176.1
Not Reported[a]	6	122.1
Total	95	1,506.4
Race		
White	70	1,085.3
Black or African American	3	44.8
Asian	14	233.9
American Indian or Alaska Native	1	22.3
Native Hawaiian or Other Pacific Islander	0	0
Not Reported[a]	7	120.2
Total	95	1,506.4
Renal impairment at baseline		
Normal (CrCl ≥90 mL/min)	38	589.9
Mild (CrCl 60 to <90 mL/min)	45	733.5
Moderate (CrCl 30 to <60 mL/min)	11	182.5
Severe (CrCl <30 mL/min)	1	0.6
Missing	0	0

Table SIII.6: Exposure by Special Populations: All Clinical Trials Populations (eg, Ethnicity, Race, Renal Impairment at Baseline, Hepatic Impairment at Baseline)

	Patients	Person-months
Total	95	1,506.4
Hepatic impairment at baseline[b]		
Normal	84	1,362.8
Mild	11	143.6
Moderate	0	0
Severe	0	0
Missing	0	0
Total	95	1,506.4

[a] Includes Unknown and missing values.
[b] Normal (per NCI Organ Dysfunction criteria): total bilirubin ≤ULN and AST ≤ULN; Mild: (total bilirubin ≤ULN and AST >ULN) or (ULN <total bilirubin ≤1.5x ULN); Moderate: 1.5x ULN <total bilirubin ≤3x ULN; Severe: total bilirubin >3x ULN.
AST=aspartate aminotransferase; CrCl=creatinine clearance; NCI=National Cancer Institute; ULN=upper limit of normal.
Trials included: subjects receiving Niraparib+AAP from Trials 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2 and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE).

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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

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**History or current diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), or other prior malignancy (exceptions: adequately treated basal cell or squamous cell skin cancer, superficial bladder cancer, or any other cancer in situ currently in complete remission) ≤2 years prior to randomization, or malignancy that currently requires active systemic therapy.**
Reason for being an exclusion criterion	Inclusion of subjects with these conditions could confound the safety and efficacy evaluation. The exact mechanism(s) contributing to or driving the occurrence of secondary malignancies have not been identified. It is possible that DNA-repair deficiencies resulting from PARP inhibition and/or breast cancer gene (BRCA) mutations may be involved.
Considered to be included as missing information	No
Rationale (if not included as missing information)	MDS/AML and second primary malignancies (SPM) other than MDS and AML are important potential risks.
Criterion 2	**Patients in poor medical condition due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, myocardial infarction or arterial thrombotic events in the past 6 months, severe or unstable angina, New York Heart Association (NYHA) Class II, III, or IV heart disease, or any psychiatric disorder that prohibits obtaining informed consent.**
Reason for being an exclusion criterion	It is common clinical practice to exclude patients with severe and potentially life-threatening conditions from clinical trials on anticancer therapy and/or to treat these severe and potentially life-threatening conditions before starting anticancer therapy.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

	Considering the treatment may cause certain cardiovascular toxicities (hypertension for both components and abiraterone-related mineralocorticoid excess, which may cause hypertension, hypokalemia, and fluid retention volume overload) only patients with stable and well controlled cardiovascular disorders were allowed.
Considered to be included as missing information	Yes (Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%)
Rationale (if not included as missing information)	Not applicable
Criterion 3	**Uncontrolled hypertension (systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension were allowed provided BP was controlled by antihypertensive therapy**
Reason for being an exclusion criterion	Inclusion of subjects with uncontrolled hypertension could confound the safety evaluation. As hypertension is associated with the use of niraparib and of abiraterone acetate, hypertension could be exacerbated after combination treatment of niraparib and abiraterone acetate.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Severe hypertension is an important identified risk.
Criterion 4	**Active or symptomatic viral hepatitis or chronic liver disease (as evidenced by ascites, encephalopathy, or bleeding disorders secondary to hepatic dysfunction)**
Reason for being an exclusion criterion	It is common clinical practice to control active or symptomatic viral hepatitis or chronic liver disease before starting long-term anticancer therapy. Inclusion of subjects with uncontrolled active or symptomatic viral hepatitis or chronic liver disease could confound the safety evaluation.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	The niraparib/abiraterone acetate FDC tablet is contraindicated in patients with severe hepatic impairment.
Criterion 5	**Allergies, hypersensitivity, or intolerance to the active substance or to any of the excipients**
Reason for being an exclusion criterion	Niraparib and abiraterone acetate are contraindicated for patients with a hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of their respective SmPCs. Therefore, the use of the niraparib/abiraterone acetate FDC tablet is contraindicated in patients with hypersensitivity to any of the components to avoid possible severe and life-threatening allergic/hypersensitivity reactions.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Hypersensitivity to the active substances or to any of the excipients of its final commercial formulation is a contraindication to niraparib/abiraterone acetate FDC tablet use.

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, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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	The niraparib/abiraterone acetate FDC tablet is not for use in women and is contraindicated in women who are or may become pregnant.
Breastfeeding women	The niraparib/abiraterone acetate FDC tablet is not for use in women.

Type of Special Population	Exposure
Population with relevant different racial and/or ethnic origin	Of the 473 adult subjects in the all clinical trials population, 340 (72%) subjects were white, 88 (19%) were Asian, 13 (3%) were Black or African American, 2 (<1%) were American Indian or Alaska Native, and 1 (<1%) was Native Hawaiian or Other Pacific Islander. For 29 (6%) subjects, race was not reported. The majority of the subjects (393 [83%]) were not Hispanic or Latino; 49 (10%) subjects were Hispanic or Latino and ethnicity was not reported for 31 (7%) subjects.
Subpopulations carrying relevant genetic polymorphisms	Of the 212 adult subjects exposed to niraparib+AAP in MAGNITUDE Cohort 1, 12 (6%) had BRCA1, 86 (41%) had BRCA2, and 16 (8%) had co-occurring BRCA gene mutations. Other HRR gene mutations occurred in 98 (46%) subjects (ATM, CHEK2, PALB2, CDK12, FANCA, BRIP1, HDAC2, and co-occurring non-BRCA gene mutations).
Elderly patients	Of the 473 adult subjects in the all clinical trials population, 355 (75%) subjects were ≥65 years of age and 137 (29%) subjects were ≥75 years of age.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Subjects with active or symptomatic viral hepatitis or chronic liver disease were excluded from clinical trials. Of the 473 adult subjects in the all clinical trials population, 53 (11%) subjects had mild (total bilirubin ≤upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or ULN <total bilirubin ≤1.5x ULN) and 1 (<1%) subject had moderate (1.5x ULN <total bilirubin ≤3x ULN) hepatic impairment at baseline.
Patients with renal impairment	Of the 473 adult subjects in the all clinical trials population, 198 (42%) subjects had mild (creatinine clearance [CrCl] 60 to <90 mL/min), 67 (14%) subjects had moderate (CrCl 30 to <60 mL/min), and 2 (<1%) subjects had severe (CrCl <30 mL/min) renal impairment at baseline.
Patients with cardiovascular impairment	Subjects with clinically significant heart disease were excluded from clinical trials.
Immunocompromised patients	Subjects with active, uncontrolled infection were not included in the clinical development program.
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

Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method used to Calculate Exposure

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. In order to do this, estimates were made as to how much medication equals 1 person-month of exposure. The recommended dose is 200 mg niraparib/1000 mg abiraterone acetate daily, therefore 60 grams niraparib/300 grams abiraterone acetate equals 1 person month, assuming 30 days per month.

Estimates of exposure are presented in person-time (person-day, person-month, and person-year) and it is assumed that 2 tablets are equivalent to 1 person-day, 60 tablets (30 person-days) are equivalent to 1 person month, and 12 person months is equivalent to 1 person-year..

SV.1.2. Exposure

Table 1: Exposure to Niraparib/AA FDC (Launch to 31 October 2023)

Regions	Units	Person-Days	Person-Months	Person-Years
European Union	1,568	784	26	2
North America	24,876	12,438	415	35
Worldwide Total	**26,444**	**13,222**	**441**	**37**

Key: AA=Abiraterone Acetate; FDC=Fixed Dose Combination

Based on the 26,444 tablets distributed worldwide, the estimated post-marketing exposure for niraparib/AA FDC from launch to 31 October 2023 is 13,222 person-days or 441 person-months or 37 person-years.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

The niraparib/abiraterone acetate FDC tablet is an antineoplastic agent which will be prescribed under medical supervision and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

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

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

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Risk 1: urinary tract infection, pneumoniae, nasopharyngitis, bronchitis, conjunctivitis
Risk 2: hypertriglyceridaemia
Risk 3: insomnia, depression, anxiety, confusional state
Risk 4: dizziness, headache, dysgeusia
Risk 5: back pain, arthralgia, myalgia
Risk 6: haematuria
Risk 7: dyspnoea, cough, pneumonitis, epistaxis
Risk 8: decreased appetite, constipation, nausea, vomiting, abdominal pain[a], dyspepsia, diarrhoea, abdominal distention, stomatitis, dry mouth
Risk 9: fatigue, asthenia, oedema peripheral, mucosal inflammation
Risk 10: rash[b], photosensitivity
Risk 11: weight decreased, blood creatinine increased
Risk 12: cataract
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Risk 1: pulmonary embolism
Risk 2: Urosepsis

Risks not Included in the List of Safety Concerns in the RMP
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered to by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Risk 1: drug-drug interaction (CYP2C8), drug-drug interaction (CYP2D6)
Risk 2: fractures[c]
Risk 3: allergic alveolitis
Risk 4: increased exposure with food
Risk 5: anemia, thrombocytopenia, neutropenia, leukopenia, lymphopenia
Risk 6: hypokalaemia, tachycardia, palpitations, atrial fibrillation, cardiac failure[d], myocardial infarction, angina pectoris[e], QT prolongation
Risk 7: hepatitis[f], acute hepatic failure, alkaline phosphatase increased, AST increased, ALT increased, gamma-glutamyl transferase increased
Known risks that do not impact the risk-benefit profile:
Not applicable
Other reasons for considering the risks not important:
Not applicable

[a] Includes abdominal pain upper
[b] Includes rash, erythema, dermatitis, rash maculo-papular, rash pruritic
[c] Includes osteoporosis and osteoporosis-related fractures
[d] Includes cardiac failure congestive, cor pulmonale, left ventricular dysfunction
[e] Includes coronary artery disease, acute coronary syndrome
[f] Includes hepatitis acute, fulminant, hepatic cytolysis, hepatotoxicity

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

Safety Concerns for Inclusion in the RMP	**Risk-Benefit Impact**
Important identified risks	
Severe hypertension	Hypertension is an important identified risk for niraparib. Hypertension was reported in clinical trials with niraparib and in the postmarketing setting. Hypertension was also reported in clinical trials with abiraterone acetate and is an adverse reaction for abiraterone acetate. Cases of severe (grade 3 or higher) and serious hypertension have been reported in subjects treated with the combination of niraparib and abiraterone acetate during the clinical development program. Therefore, severe

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
	hypertension is considered an important identified risk with the use of the niraparib/abiraterone acetate FDC tablet. Although severe (ie, grade 3 or higher) hypertension occurred in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program, only 1 subject experienced a grade 4, serious event of hypertensive crisis. The SmPC and package leaflet (PL) provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.
Important potential risks	
Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	MDS/AML is a safety concern for niraparib monotherapy in ovarian cancer. MDS/AML, including cases with fatal outcome, have been reported in ovarian cancer trials among patients previously treated with platinum-based chemotherapy and who received 300 mg of niraparib, and in the postmarketing setting. Therefore, MDS/AML is considered an important potential risk with the use of the niraparib/abiraterone acetate FDC tablet. No cases of MDS/AML have been observed in patients with prostate cancer treated with niraparib or with the combination of niraparib (200 mg) and abiraterone acetate during the clinical development program. The only case of AML observed in the clinical development program of the combination of niraparib and abiraterone acetate, occurred in a subject who received placebo and abiraterone acetate. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.
Second primary malignancies (SPM) other than MDS and AML	SPM other than MDS and AML is an important potential risk for niraparib. SPM other than MDS and AML were reported in clinical trials with niraparib. Therefore, SPM other than MDS and AML is considered an important potential risk with the use of the niraparib/abiraterone acetate FDC tablet. Although SPM other than MDS and AML occurred in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program, the observed incidence was low. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.
Missing information	
Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous thrombotic events in the past 6 months,	Subjects with clinically significant heart disease were excluded from clinical trials. The niraparib/abiraterone acetate FDC tablet should be used with caution in patients with a history of cardiovascular disease. Patients with a history of cardiac failure should be clinically optimized and appropriate management of symptoms instituted. If there is a clinically significant decrease in cardiac function, discontinuation of treatment with the

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of <50%	niraparib/abiraterone acetate FDC tablet should be considered.

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

Not applicable.

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

The important identified and potential risks for the niraparib/abiraterone acetate FDC tablet are based on well-established risks of the niraparib and abiraterone acetate individual active substances, and on the development program on which they relied. The safety analysis of the MAGNITUDE[1], QUEST, and BEDIVERE trials did not reveal any unexpected findings or additional important risks.

Important identified risks

1. Severe hypertension

Important potential risks

1. Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
2. Second primary malignancies (SPM) other than MDS and AML

Missing Information:

1. Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%

MedDRA version 24.0 was used to classify the clinical trials adverse event (AE) information that is summarized in this section.

[1] Note that the enrollment for MAGNITUDE Cohort 3 began after enrollment for Cohorts 1 and 2 was complete, resulting in a shorter treatment duration in this grouping, as compared with the niraparib+AAP arm of Cohort 1.

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

Important Identified Risk: Severe hypertension

Potential Mechanisms:

The mechanism by which niraparib and abiraterone acetate are associated with hypertension is unknown.

Primary hypertension results from a complex interaction of genes and environmental factors. In most people with established hypertension, increased resistance to blood flow (total peripheral resistance) accounts for the high pressure while cardiac output remains normal. Most evidence implicates either disturbances in the kidneys' salt and water handling and/or abnormalities of the sympathetic nervous system. These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of primary hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may contribute to increased peripheral resistance and vascular damage in hypertension (Oparil 2003).

Evidence Source(s) and Strength of Evidence:

Hypertension is an important identified risk for niraparib. Hypertension was observed in nonclinical studies with niraparib and was reported in clinical trials with niraparib and in the postmarketing setting.

Hypertension was also reported in clinical trials with abiraterone acetate and is an adverse reaction for abiraterone acetate.

Cases of severe (grade 3 or higher) and serious hypertension have been reported in subjects treated with the combination of niraparib and abiraterone acetate during the clinical development program.

Characterization of the Risk:

Note: Although the important identified risk is severe hypertension, all adverse events identified by the SMQ (narrow) of hypertension are captured in the following table, independent of their severity.

Frequency, Seriousness, Outcomes, and Severity of Hypertension

	Randomized Clinical Trial (Magnitude Cohort 1 SAC)		Magnitude Cohort 3 FDC	All Clinical Trials[a]
	Niraparib+AAP	Placebo+AAP/Comparator	Niraparib+AAP	Niraparib+AAP
Cumulative for all indications				
Number of subjects treated	212	211	95	473
Frequency	73 (34.4%)	52 (24.6%)	29 (30.5%)	155 (32.8%)
Seriousness				
Was serious	0	0	0	1 (0.2%)
Outcomes				
Fatal	0	0	0	0
Not recovered/Not Resolved	46 (21.7%)	21 (10%)	8 (8.4%)	85 (18%)
Recovering/Resolving	3 (1.4%)	1 (0.5%)	3 (3.2%)	6 (1.3%)

Frequency, Seriousness, Outcomes, and Severity of Hypertension

	Randomized Clinical Trial (Magnitude Cohort 1 SAC)		Magnitude Cohort 3 FDC	All Clinical Trials[a]
	Niraparib+AAP	Placebo+AAP/Comparator	Niraparib+AAP	Niraparib+AAP
Recovered/Resolved with sequelae	2 (0.9%)	1 (0.5%)	0	2 (0.4%)
Recovered/Resolved	22 (10.4%)	29 (13.7%)	18 (18.9%)	62 (13.1%)
Unknown	0	0	0	0
Severity (toxicity grade)				
Worst grade=1	6 (2.8%)	7 (3.3%)	3 (3.2%)	11 (2.3%)
Worst grade=2	30 (14.2%)	14 (6.6%)	9 (9.5%)	60 (12.7%)
Worst grade=3	37 (17.5%)	31 (14.7%)	16 (16.8%)	82 (17.3%)
Worst grade=4	0	0	1 (1.1%)	2 (0.4%)
Worst grade=5	0	0	0	0
Missing grade	0	0	0	0

Includes all subjects who had one or more occurrences of an adverse event meeting the search criteria (see Annex 7); the subject is counted only once regardless of the number of events or the number of occurrences.
Adverse event outcome is based on the worst adverse event outcome in the risk category (in the hierarchy order of "Fatal", "Not recovered/Not Resolved", "Recovering/Resolving", "Recovered/Resolved with sequelae", "Recovered/Resolved", "Unknown") reported by each subject for the specified risk.
[a]All Clinical Trials included: subjects receiving Niraparib+AAP from Trials 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2 and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE).
AAP=abiraterone acetate plus prednisone or prednisolone; FDC=fixed-dose combination; SAC=single-agent combination

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In MAGNITUDE Cohort 1, the incidence of Grade 3 events was similar between the treatment arms (17.5% vs 14.7%). There were no Grade 4 events or SAEs and there were no reports of hypertensive crisis or posterior reversible encephalopathy syndrome (PRES) in either treatment arm. There were no treatment discontinuations due to hypertension.

In the all clinical trials population, there was 1 subject who had an event of hypertensive crisis, which was Grade 4, serious, but did not lead to discontinuation of treatment.

Medication can normalize BP. Changes in life style risk factors, for example reducing salt intake, smoking cessation, and reducing alcohol consumption can all improve increased BP values.

Considering antihypertensive therapy and relatively short treatment duration, the long-term outcome of hypertension in patients treated with niraparib or abiraterone acetate is currently not known. In the general population, patients are typically asymptomatic and the hypertension is treatable. However, if left untreated, hypertension can progress to serious complications including long-term comorbidities and in some cases events with potentially fatal outcomes, such as hypertensive crisis and PRES.

Complications of hypertension include heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease.

No new safety information pertaining to this risk has emerged from post-marketing experience. .

Risk Factors and Risk Groups:

There are multiple risk factors for hypertension in the general population including lifestyle factors (excess salt intake, excess body weight, smoking, alcohol), renal disease, endocrine disease, and family history (Oparil 2003).

Preventability:

Specific guidance is provided in the SmPC Sections 4.2, 4.4, and 4.8 to minimize and manage the risk of severe hypertension. Pre-existing hypertension should be adequately controlled before treatment initiation. Blood pressure should be monitored during treatment with AKEEGA and a monitoring schedule be in place. Treatment interruption is instructed in patients who develop Grade ≥3 adverse reactions and appropriate medical management should be provided. In case of PRES, treatment should be permanently discontinued and appropriate medical management should be instituted.

Impact on the Risk-Benefit Balance of the Product:

Although severe (ie, grade 3 or higher) hypertension occurred in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program, only 1 subject experienced a grade 4, serious event of hypertensive crisis. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.

Public Health Impact:

Only one event of hypertensive crisis was reported in clinical trials with the combination of niraparib and abiraterone acetate and this event did not lead to treatment discontinuation. The usage of the niraparib/abiraterone acetate FDC tablet will be limited due to the small number of patients in the target population and all usage will be carefully monitored by the healthcare professional. Therefore, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Hypertension (SMQ)

Important Potential Risk: Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)

Potential Mechanisms:

The mechanism(s) contributing to or driving the occurrence of secondary malignancies have not been identified. It is possible that DNA-repair deficiencies resulting from PARP inhibition and/or BRCA mutations may be involved.

Evidence Source(s) and Strength of Evidence:

MDS is a hematological malignancy of the bone marrow, which could result in anemia, increased risk of infection, and easy bleeding. Symptoms include weakness, feeling tired, fever, weight loss, frequent infections, bruising, bleeding easily, breathlessness, and blood in urine or stools. MDS can progress to AML, a cancer of the blood and bone marrow. Both MDS and AML are serious conditions, which can result in death.

MDS/AML is a safety concern for niraparib monotherapy in ovarian cancer. MDS/AML, including cases with fatal outcome, have been reported in ovarian cancer trials among patients previously treated with platinum-based chemotherapy and who received 300 mg of niraparib, and in the postmarketing setting (Zejula SmPC 2022).

No cases of MDS/AML have been observed in patients with prostate cancer treated with niraparib or with the combination of niraparib (200 mg) and abiraterone acetate during the clinical development program.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of MDS/AML

	Randomized Clinical Trial (Magnitude Cohort 1 SAC)		Magnitude Cohort 3 FDC	All Clinical Trials[a]
	Niraparib+AAP	Placebo+AAP/ Comparator	Niraparib+AAP	Niraparib+AAP
Cumulative for all indications				
Number of subjects treated	212	211	95	473
Frequency	0	1 (0.5%)	0	0
Seriousness				
Was serious	0	1 (0.5%)	0	0
Outcomes				
Fatal	0	0	0	0
Not recovered/Not Resolved	0	1 (0.5%)	0	0
Recovering/Resolving	0	0	0	0
Recovered/Resolved with sequelae	0	0	0	0
Recovered/Resolved	0	0	0	0
Unknown	0	0	0	0
Severity (toxicity grade)				
Worst grade=1	0	0	0	0
Worst grade=2	0	0	0	0
Worst grade=3	0	0	0	0
Worst grade=4	0	1 (0.5%)	0	0
Worst grade=5	0	0	0	0
Missing grade	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of MDS/AML

	Randomized Clinical Trial (Magnitude Cohort 1 SAC)		Magnitude Cohort 3 FDC	All Clinical Trials[a]
	Niraparib+AAP	Placebo+AAP/ Comparator	Niraparib+AAP	Niraparib+AAP

Includes all subjects who had one or more occurrences of an adverse event meeting the search criteria (see Annex 7); the subject is counted only once regardless of the number of events or the number of occurrences.
Adverse event outcome is based on the worst adverse event outcome in the risk category (in the hierarchy order of "Fatal", "Not recovered/Not Resolved", "Recovering/Resolving", "Recovered/Resolved with sequelae", "Recovered/Resolved", "Unknown") reported by each subject for the specified risk.
[a]All Clinical Trials included: subjects receiving Niraparib+AAP from Trials 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2 and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE).
AAP=abiraterone acetate plus prednisone or prednisolone; FDC=fixed-dose combination; SAC=single-agent combination

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AEs of MDS or AML were neither reported in subjects in the niraparib+AAP arm in MAGNITUDE Cohort 1 nor in the all clinical trials population. There was 1 subject with a Grade 4 event of AML in the placebo+AAP arm of MAGNITUDE Cohort 1.

Reversibility of MDS/AML is unlikely in all patient populations. Remission is less likely in AML following myelodysplasia.

MDS/AML in a patient population already experiencing a primary malignancy is a serious debilitating condition and fatal outcomes have been reported in the niraparib clinical development program.

No new safety information pertaining to this risk has emerged from post-marketing experience.

Risk Factors and Risk Groups:

Risk factors include:

- Increased age.
- Previous cancer therapy including radiotherapy, platinum-based chemotherapy, alkylating agents, epipodophyllotoxins, topoisomerase II inhibitors, or colony-stimulating factors used to stimulate marrow function during chemotherapy (Hershman 2007; Hijiya 2009; Morton 2019).
- Prolonged use of alkylator therapy for other illnesses, eg, rheumatological disease.
- Environmental toxins, especially benzene and other organic solvents, smoking, petroleum products, fertilizers, semi-metal, stone dusts, and cereal dusts. Exposure to benzene can produce aplastic anemia and pancytopenia, which can progress to AML.
- Other genetically associated diseases, eg, Schwachman-Diamond syndrome, Fanconi's anemia, and neurofibromatosis type 1 (Fenaux 2021).
- Antecedent hematological disorders including MDS predispose patients to AML (Catenacci 2005).
- Genetic risk factors such as p53 or BRCA mutations.

Preventability:

Information about the possible occurrence of MDS/AML and specific guidance on how to manage the risk is provided in SmPC Section 4.4. There are no specific recommendations to prevent MDS/AML; however, patients with suspected MDS/AML or with prolonged hematological toxicity that has not resolved with treatment interruption or dose reduction should be referred to a hematologist for further evaluation. If MDS and/or AML is confirmed, treatment with AKEEGA should be permanently discontinued and the patient should be treated appropriately.

Impact on the Risk-Benefit Balance of the Product:

No cases of MDS/AML were reported in patients with prostate cancer who received the combination of niraparib and abiraterone acetate. The only case of AML observed in the clinical development program of the combination of niraparib and abiraterone acetate, occurred in a subject who received placebo and abiraterone acetate. The SmPC and PL provide information on how to manage the risk. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.

Public Health Impact:

No cases of MDS/AML were reported in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program. The usage of the niraparib/abiraterone acetate FDC tablet will be limited due to the small number of patients in the target population and all usage will be carefully monitored by the healthcare professional. Therefore, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Myelodysplastic syndrome (SMQ)

Important Potential Risk: Second primary malignancies (SPM) other than MDS and AML

Potential Mechanisms:

Second primary cancers are linked to treatment with DNA-damaging agents, such as platinum-based chemotherapy, radiotherapy, or topoisomerase II inhibitors. The accumulation of DNA damage in some cells could create genomic instability, which could contribute to the development of second primary cancers. A PARP inhibitor does not directly cause DNA damage but reduces the ability of cells to repair DNA damage, leading to the accumulation of unrepaired double strand breaks, especially in the cells that have a deficient homologous recombination pathway, such as cells with BRCA mutation.

Evidence Source(s) and Strength of Evidence:

SPM other than MDS and AML is an important potential risk for niraparib. SPM other than MDS and AML were reported in clinical trials with niraparib.

SPM other than MDS and AML have been reported in subjects treated with the combination of niraparib and abiraterone acetate during the clinical development program.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of SPM Other Than MDS and AML

	Randomized Clinical Trial (Magnitude Cohort 1 SAC)		Magnitude Cohort 3 FDC	All Clinical Trials[a]
	Niraparib+AAP	Placebo+AAP/ Comparator	Niraparib+AAP	Niraparib+AAP
Cumulative for all indications				
Number of subjects treated	212	211	95	473
Frequency	10 (4.7%)	4 (1.9%)	0	12 (2.5%)
Seriousness				
Was serious	3 (1.4%)	2 (0.9%)	0	5 (1.1%)
Outcomes				
Fatal	0	0	0	0
Not recovered/Not Resolved	5 (2.4%)	1 (0.5%)	0	6 (1.3%)
Recovering/Resolving	0	0	0	0
Recovered/Resolved with sequelae	0	0	0	0
Recovered/Resolved	5 (2.4%)	3 (1.4%)	0	5 (1.1%)
Unknown	0	0	0	1 (0.2%)
Severity (toxicity grade)				
Worst grade=1	1 (0.5%)	1 (0.5%)	0	1 (0.2%)
Worst grade=2	4 (1.9%)	2 (0.9%)	0	5 (1.1%)
Worst grade=3	2 (0.9%)	1 (0.5%)	0	3 (0.6%)
Worst grade=4	3 (1.4%)	0	0	3 (0.6%)
Worst grade=5	0	0	0	0
Missing grade	0	0	0	0

Includes all subjects who had one or more occurrences of an adverse event meeting the search criteria (see Annex 7); the subject is counted only once regardless of the number of events or the number of occurrences.
Adverse event outcome is based on the worst adverse event outcome in the risk category (in the hierarchy order of "Fatal", "Not recovered/Not Resolved", "Recovering/Resolving", "Recovered/Resolved with sequelae", "Recovered/Resolved", "Unknown") reported by each subject for the specified risk.
[a]All Clinical Trials included: subjects receiving Niraparib+AAP from Trials 64091742PCR3001 (MAGNITUDE, Cohorts 1, 2 and 3), 64091742PCR2002 (QUEST, Combo 2), and 64091742PCR1001 (BEDIVERE).
AAP=abiraterone acetate plus prednisone; FDC=fixed-dose combination; SAC=single-agent combination

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In MAGNITUDE Cohort 1, AEs of an SPM other than MDS or AML were reported in 4.7% of subjects in the niraparib+AAP arm and in 1.9% of subjects in the placebo+AAP arm. None of the reported PTs occurred in more than 1% of subjects in either treatment arm.

A Swedish study based on the National Prostate Cancer Register concluded that about 17% of all prostate cancer occurred in combination with another primary cancer (before or after prostate cancer diagnosis). Overall, there were increased standardized incidence ratios for almost all cancer types. (Van Hemelrijck 2012)

Mehtälä et al. found that the incidence rate of SPM per 1,000 person-years was 81.8 (78.8–85.0) for metastatic prostate cancer and 115.6 (95.1–140.7) for mCRPC (Mehtälä 2020).

In another study, 28.1% of patients diagnosed with metastatic prostate cancer, regardless of treatment, had a synchronous SPM, of which colorectal (9.1%), stomach (7.3%), and lung (7.1%) cancers were the most prevalent types (Koo 2015). Although the incidence of SPM in this study is much higher when compared to MAGNITUDE, the types of SPM seen in MAGNITUDE seem to resemble literature data.

No new safety information pertaining to this risk has emerged from post-marketing experience.Risk Factors and Risk Groups:

The use of prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies (Livraghi 2015).

The risk factors for MDS and AML are also applicable to the other SPM (see risk factors described for the important potential risk of MDS/AML). Regardless of type of treatment, population-based studies in several tumor types, including prostate cancer, have shown that patients with metastatic disease are at increased risk for the development of SPM. The risk of SPM also increases with age and over time since primary cancer diagnosis.

Preventability:

There are no specific recommendations to prevent the occurrence of SPM other than MDS/AML.

Impact on the Risk-Benefit Balance of the Product:

Although SPM other than MDS and AML occurred in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program, the observed incidence was low. Overall, the risk-benefit balance for the product is positive considering the severity of the disease treated and the potential efficacy for patients treated with the niraparib/abiraterone acetate FDC tablet.

Public Health Impact:

The observed incidence of SPM other than MDS and AML was low in subjects who received the combination of niraparib and abiraterone acetate in the clinical development program. The usage of the niraparib/abiraterone acetate FDC tablet will be limited due to the small number of patients

in the target population and all usage will be carefully monitored by the healthcare professional. Therefore, the impact on public health is expected to be low.

Annex 1 MedDRA Term:

Malignancies (SMQ)

SVII.3.2. Presentation of the Missing Information

Missing information: Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%
Evidence source: Subjects with clinically significant heart disease were excluded from clinical trials.
Anticipated risk/consequence of the missing information: The niraparib/abiraterone acetate FDC tablet should be used with caution in patients with a history of cardiovascular disease. Patients with a history of cardiac failure should be clinically optimized and appropriate management of symptoms instituted. If there is a clinically significant decrease in cardiac function, discontinuation of treatment with the niraparib/abiraterone acetate FDC tablet should be considered.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Severe hypertension
Important Potential Risks	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
	Second primary malignancies (SPM) other than MDS and AML
Missing Information	Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%

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

Additional Pharmacovigilance Activities	
Study	
Study name and title	Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA
Rationale and study objectives	MDS/AML risk is well characterized in the ovarian cancer population treated with PARP inhibitors, particularly among those who have been heavily pretreated with myelotoxic chemotherapy. Although MDS/AML has not been observed in prostate cancer trials with either niraparib monotherapy or in combination settings, population-based studies in several tumor types including prostate cancer show that patients with metastatic disease are at an increased risk for SPM. This study therefore seeks to characterize the risk of SPM and MDS/AML among metastatic prostate cancer patients exposed to AKEEGA. Specific objectives are as follows: • **Primary:** To estimate the incidence rate of SPM, including MDS/AML, in patients with mCRPC treated with AKEEGA. • **Secondary:** To evaluate the distribution of SPM/MDS/AML events across different risk factors such as age, prior chemotherapy, and other relevant factors.
Safety concern(s) addressed	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML

Additional Pharmacovigilance Activities	
Study design	Series of retrospective database analyses to monitor the incidence and risk factors for MDS/AML and SPM other than MDS/AML among multiple real world databases. Potential data sources include: US based administrative claims databases such as Optum, Inc., Oncology electronic health record databases such as Flatiron, and existing registries such as linked registries in the Nordic countries.
Study population	Men of 18 years and older with a diagnosis of metastatic prostate cancer and exposure to AKEEGA, identified in US and EU based real world databases and registries.
Milestones	• Feasibility: within 3 months of the Committee for Medicinal Products for Human Use (CHMP) opinion. • Draft protocol: within 6 months of CHMP opinion. • Interim reports: provided annually. • Final report of study results: 5 years following study initiation.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA Planned	• **Primary:** To estimate the incidence rate of SPM, including MDS/AML, in patients with mCRPC treated with AKEEGA. • **Secondary:** To evaluate the distribution of SPM/MDS/AML events across different risk factors such as age, prior chemotherapy, and other relevant factors.	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML	Feasibility	Within 3 months of CHMP opinion
			Draft protocol	Within 6 months of CHMP opinion
			Interim reports	Provided annually
			Final report of study results	5 years following study initiation

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

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Severe hypertension	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations to adequately control pre-existing hypertension before starting AKEEGA treatment, to monitor BP during treatment in accordance with a monitoring schedule, and to correct and control hypertension are provided in SmPC Sections 4.2, 4.4, and 4.8, and PL Section 2. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • An instruction to permanently discontinue AKEEGA and to institute appropriate medical management in patients developing PRES is provided in SmPC Section 4.4. • Patients who experience a sudden increase in BP, which may be a medical emergency that could lead to organ damage or can be life-threatening, should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status

Safety Concern	Routine Risk Minimization Activities
Important Potential Risks	
Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	**Routine risk communication:** • SmPC Section 4.4 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Instructions to refer the patient to a hematologist for further evaluation in case of suspected MDS/AML or prolonged hematological toxicity that has not resolved with treatment interruption or dose reduction, to permanently discontinue AKEEGA treatment if MDS or AML is confirmed, and to treat the patient appropriately are provided in SmPC Section 4.4 and PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Legal status
Second primary malignancies (SPM) other than MDS and AML	**Routine risk communication:** • None **Routine risk minimization activities recommending specific clinical measures to address the risk:** • None **Other routine risk minimization measures beyond the Product Information:** • Legal status
Missing Information	
Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Advice to use AKEEGA with caution in patients with a history of cardiovascular disease is provided in SmPC Section 4.4. • A recommendation to optimize cardiac function and treatment for cardiac risk factors before starting treatment with AKEEGA is provided in SmPC Section 4.4 and PL Section 2.

Safety Concern	Routine Risk Minimization Activities
	• A recommendation to monitor patients during treatment for signs and symptoms of cardiac dysfunction in accordance with a monitoring schedule and to correct abnormalities is provided in SmPC Section 4.4. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • A recommendation to consider treatment discontinuation in case of a clinically significant decrease in cardiac function is provided in SmPC Section 4.4. • Patients who experience muscle weakness, muscle twitches, or a pounding heart beat (palpitations) should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Activity 1	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

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

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Severe hypertension	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• PL Section 4 • Recommendations to adequately control pre-existing hypertension before starting AKEEGA treatment, to monitor BP during treatment in accordance with a monitoring schedule, and to correct and control hypertension are provided in SmPC Sections 4.2, 4.4, and 4.8, and PL Section 2. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • An instruction to permanently discontinue AKEEGA and to institute appropriate medical management in patients developing PRES is provided in SmPC Section 4.4. • Patients who experience a sudden increase in BP, which may be a medical emergency that could lead to organ damage or can be life-threatening, should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status **Additional risk minimization measures:** • None	
Important Potential Risks		
Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	**Routine risk minimization measures:** • SmPC Section 4.4 • PL Section 2 • Instructions to refer the patient to a hematologist for further evaluation in case of suspected MDS/AML or prolonged hematological toxicity that has not resolved with treatment	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	interruption or dose reduction, to permanently discontinue AKEEGA treatment if MDS or AML is confirmed, and to treat the patient appropriately are provided in SmPC Section 4.4 and PL Section 2. • Legal status **Additional risk minimization measures:** • None	exposed to AKEEGA (final report of study results: 5 years following study initiation)
Second primary malignancies (SPM) other than MDS and AML	**Routine risk minimization measures:** • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA (final report of study results: 5 years following study initiation)
Missing Information		
Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Advice to use AKEEGA with caution in patients with a history of cardiovascular disease is provided in SmPC Section 4.4.	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• A recommendation to optimize cardiac function and treatment for cardiac risk factors before starting treatment with AKEEGA is provided in SmPC Section 4.4 and PL Section 2. • A recommendation to monitor patients during treatment for signs and symptoms of cardiac dysfunction in accordance with a monitoring schedule and to correct abnormalities is provided in SmPC Section 4.4. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • A recommendation to consider treatment discontinuation in case of a clinically significant decrease in cardiac function is provided in SmPC Section 4.4. • Patients who experience muscle weakness, muscle twitches, or a pounding heart beat (palpitations) should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status **Additional risk minimization measures:** • None	

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for AKEEGA (niraparib/abiraterone acetate fixed-dose combination tablet)

This is a summary of the risk management plan (RMP) for AKEEGA. The RMP details important risks of AKEEGA, how these risks can be minimized, and how more information will be obtained about AKEEGA 's risks and uncertainties (missing information).

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

This summary of the RMP for AKEEGA 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 or changes to the current ones will be included in updates of AKEEGA's RMP.

I. The Medicine and What it is Used For

AKEEGA is authorized with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated (see SmPC for the full indication). It contains niraparib and abiraterone acetate as the active substances and it is given as film-coated tablets for oral administration (50 mg niraparib/500 mg abiraterone acetate or 100 mg niraparib/500 mg abiraterone acetate).

Further information about the evaluation of AKEEGA's benefits can be found in AKEEGA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

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

Important risks of AKEEGA, together with measures to minimize such risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of AKEEGA is not yet available, it is listed under 'missing information' below.

II.A. List of Important Risks and Missing Information

Important risks of AKEEGA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of AKEEGA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Severe hypertension
Important potential risks	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML
Missing information	Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class III or IV heart disease or cardiac ejection fraction measurement of <50%

II.B. Summary of Important Risks

Important Identified Risk: Severe hypertension	
Evidence for linking the risk to the medicine	Hypertension is an important identified risk for niraparib. Hypertension was observed in nonclinical studies with niraparib and was reported in clinical trials with niraparib and in the postmarketing setting. Hypertension was also reported in clinical trials with abiraterone acetate and is an adverse reaction for abiraterone acetate. Cases of severe (grade 3 or higher) and serious hypertension have been reported in subjects treated with the combination of niraparib and abiraterone acetate during the clinical development program.
Risk factors and risk groups	There are multiple risk factors for hypertension in the general population including lifestyle factors (excess salt intake, excess body weight, smoking, alcohol), renal disease, endocrine disease, and family history.

Important Identified Risk: Severe hypertension	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations to adequately control pre-existing hypertension before starting AKEEGA treatment, to monitor blood pressure (BP) during treatment in accordance with a monitoring schedule, and to correct and control hypertension are provided in SmPC Sections 4.2, 4.4, and 4.8, and PL Section 2. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • An instruction to permanently discontinue AKEEGA and to institute appropriate medical management in patients developing posterior reversible encephalopathy syndrome (PRES) is provided in SmPC Section 4.4. • Patients who experience a sudden increase in BP, which may be a medical emergency that could lead to organ damage or can be life-threatening, should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status Additional risk minimization measures: • None

Important Potential Risk: Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	
Evidence for linking the risk to the medicine	MDS/AML is a safety concern for niraparib monotherapy in ovarian cancer. MDS/AML, including cases with fatal outcome, have been reported in ovarian cancer trials among patients previously treated with platinum-based chemotherapy and who received 300 mg of niraparib, and in the postmarketing setting. No cases of MDS/AML have been observed in patients with prostate cancer treated with niraparib or with the combination of niraparib (200 mg) and abiraterone acetate during the clinical development program.
Risk factors and risk groups	Risk factors include: • Increased age. • Previous cancer therapy including radiotherapy, platinum-based chemotherapy, alkylating agents, epipodophyllotoxins,

Important Potential Risk: Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	
	topoisomerase II inhibitors, or colony-stimulating factors used to stimulate marrow function during chemotherapy. • Prolonged use of alkylator therapy for other illnesses, eg, rheumatological disease. • Environmental toxins, especially benzene and other organic solvents, smoking, petroleum products, fertilizers, semi-metal, stone dusts, and cereal dusts. Exposure to benzene can produce aplastic anemia and pancytopenia, which can progress to AML. • Other genetically associated diseases, eg, Schwachman-Diamond syndrome, Fanconi's anemia, and neurofibromatosis type 1. • Antecedent hematological disorders including MDS predispose patients to AML. • Genetic risk factors such as p53 or breast cancer gene (BRCA) mutations.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.4 • PL Section 2 • Instructions to refer the patient to a hematologist for further evaluation in case of suspected MDS/AML or prolonged hematological toxicity that has not resolved with treatment interruption or dose reduction, to permanently discontinue AKEEGA treatment if MDS or AML is confirmed, and to treat the patient appropriately are provided in SmPC Section 4.4 and PL Section 2. • Legal status Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA (final report of study results: 5 years following study initiation) See Section II.C of this summary for an overview of the postauthorization development plan.

Important Potential Risk: Second primary malignancies (SPM) other than MDS and AML	
Evidence for linking the risk to the medicine	SPM other than MDS and AML is an important potential risk for niraparib. SPM other than MDS and AML were reported in clinical trials with niraparib. SPM other than MDS and AML have been reported in subjects treated with the combination of niraparib and abiraterone acetate during the clinical development program.
Risk factors and risk groups	The use of prior DNA-damaging chemotherapeutic drugs represents a risk factor for development of new malignancies. The risk factors for MDS and AML are also applicable to the other SPM (see risk factors described for the important potential risk of MDS/AML). Regardless of type of treatment, population-based studies in several tumor types, including prostate cancer, have shown that patients with metastatic disease are at increased risk for the development of SPM. The risk of SPM also increases with age and over time since primary cancer diagnosis.
Risk minimization measures	Routine risk minimization measures: • Legal status Additional risk minimization measures: • None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA (final report of study results: 5 years following study initiation) See Section II.C of this summary for an overview of the postauthorization development plan.

Missing Information: Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous 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%	
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Advice to use AKEEGA with caution in patients with a history of cardiovascular disease is provided in SmPC Section 4.4. • A recommendation to optimize cardiac function and treatment for cardiac risk factors before starting treatment with AKEEGA is provided in SmPC Section 4.4 and PL Section 2. • A recommendation to monitor patients during treatment for signs and symptoms of cardiac dysfunction in accordance with a monitoring schedule and to correct abnormalities is provided in SmPC Section 4.4. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • A recommendation to consider treatment discontinuation in case of a clinically significant decrease in cardiac function is provided in SmPC Section 4.4. • Patients who experience muscle weakness, muscle twitches, or a pounding heart beat (palpitations) should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

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

Not applicable.

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

Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA.

Purpose of the study:

- **Primary:** To estimate the incidence rate of SPM, including MDS/AML, in patients with mCRPC treated with AKEEGA.
- **Secondary:** To evaluate the distribution of SPM/MDS/AML events across different risk factors such as age, prior chemotherapy, and other relevant factors.

PART VII: ANNEXES

Table of Contents

Annex 4 Specific Adverse Drug Reaction Follow-up Forms

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

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Table of Contents

Specific Adverse Drug Reaction Follow-up Questionnaires	
Safety Concern	Purpose/Description
Not applicable.	

Follow-up Forms

Not applicable.

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

Not applicable.