PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAKEEGA™

Niraparib and abiraterone acetate tablets

100 mg niraparib (as niraparib tosylate)/500 mg abiraterone acetate,

50 mg niraparib (as niraparib tosylate)/500 mg abiraterone acetate

Oral administration

Antineoplastic agent/Androgen biosynthesis inhibitor

PrAKEEGA™ (niraparib and abiraterone acetate), indicated for:

- The treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) metastatic castration resistant prostate cancer (mCRPC), who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patients must have confirmation of *BRCA* mutation before AKEEGA™ treatment is initiated.

has been issued market authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for PrAKEEGA™ please refer to Health Canada's Notice of Compliance with conditions - drug products web site: https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/notice-compliance/conditions.html"

Janssen Inc.
Toronto, Ontario
M3C 1L9

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What is a Notice of Compliance with Conditions (NOC/c)?

An NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention, or diagnosis of a serious, life-threatening, or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

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Sections or subsections that are not applicable at the time of authorization are not listed

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

PrAKEEGA™ (niraparib and abiraterone acetate) is indicated with prednisone or prednisolone for:

The treatment of adult patients with deleterious or suspected deleterious *BRCA* mutated (germline and/or somatic) metastatic castration resistant prostate cancer (mCRPC), who are asymptomatic/mildly symptomatic , and in whom chemotherapy is not clinically indicated. Patients must have confirmation of *BRCA* mutation before AKEEGA™ treatment is initiated.

- Marketing authorization with conditions issued based on radiographic progression-free survival, time to symptomatic progression and time to cytotoxic chemotherapy (See 14 CLINICAL TRIALS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in subsequent analyses.

The efficacy of AKEEGA™ in patients with visceral metastases is uncertain (See 14 CLINICAL TRIALS)

1.1 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics (≥65 years of age)

No overall differences in safety and efficacy of niraparib and abiraterone acetate combination therapy were observed between these patients and younger patients, however, greater sensitivity of some older individuals cannot be ruled out (see 7 WARNINGS AND PRECAUTIONS).

2 CONTRAINDICATIONS

AKEEGA™ is contraindicated in:

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

Serious Warnings and Precautions

- AKEEGA™ may cause hypertension, hypokalemia, and fluid retention due to mineralocorticoid excess (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- AKEEGA™ should be used with caution in patients with a history of cardiovascular disease (see 7 WARNINGS AND PRECAUTIONS, Cardiovascular)
- AKEEGA™ should not be given to patients with moderate to severe hepatic impairment (see 7 WARNINGS AND PRECAUTIONS, Hepatic Impairment)
- MDS/AML has been reported with PARP inhibitor treatment (see 7 WARNINGS AND PRECAUTIONS)

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

AKEEGA™ is a fixed-dose dual combination of niraparib and abiraterone acetate. Confirm presence of a *BRCA* mutation using a validated test prior to initiation of AKEEGA™ (see 14 CLINICAL TRIALS).

4.2 Recommended Dose and Dosage Adjustment

The recommended dosage of AKEEGA™ is 200 mg niraparib and 1000 mg abiraterone acetate (two 100 mg/500 mg tablets), as a single daily dose that **must be taken on an empty stomach** at approximately the same time every day (see 4 DOSAGE AND ADMINISTRATION, Administration). For dose reduction to 100 mg niraparib and 1000 mg abiraterone acetate, a low strength tablet (two 50 mg/ 500 mg tablets) is recommended (see 4 DOSAGE AND ADMINISTRATION, Dose Modification). If further dose reduction below 100 mg/day niraparib is required, discontinue AKEEGA.

Dosage of Prednisone or Prednisolone

AKEEGA™ is used with 10 mg prednisone or prednisolone daily.

Treatment Withdrawal

Treatment should be continued until disease progression, unequivocal clinical progression, or unacceptable toxicity.

Dose Modification

Hematologic Adverse Reactions

The dose adjustment recommendations for anemia, thrombocytopenia and neutropenia are listed in Table 1 and in Table 2.

Table 1: Dose Adjustment Recommendations for Anemia

Grade 1	No change, consider weekly monitoring.
Grade 2	At least weekly monitoring for 28 days, if baseline anemia was Grade ≤ 1.
Grade ≥ 3	Withhold AKEEGA™[1] and switch to single agent AAP. Provide supportive management with monitoring at least weekly until recovered to Grade ≤ 2. Consider resuming AKEEGA™ at one dose-level reduction [**two low strength (50 mg/500 mg) tablets**] if anemia persists based on clinical judgment.
Second occurrence ≥ Grade 3	Withhold AKEEGA™ and switch to single agent AAP. Provide supportive management and monitor at least weekly until recovered to Grade ≤ 2. Further treatment with AKEEGA™ should restart at one dose-level reduction [**two low strength (50 mg/500 mg) tablets].** Weekly monitoring is recommended for 28 days after resuming treatment with **AKEEGA™**. If

	patient was already on a reduced dose [two **low strength (50 mg/500 mg) tablets],** consider treatment discontinuation.
Third occurrence ≥ Grade 3	Consider discontinuing treatment with AKEEGA™ based on clinical judgment.

[1] During AKEEGA™ treatment interruption, physician may consider giving abiraterone acetate and prednisone to maintain daily dose of abiraterone acetate (see abiraterone acetate product monograph).

Table 2: Dose Adjustment Recommendations for Thrombocytopenia and Neutropenia

Grade 1	No change, consider weekly monitoring
Grade 2	At least weekly monitoring and consider withholding AKEEGA™ and switch to single agent abiraterone acetate plus prednisone (AAP) combination until recovery to Grade 1 or baseline.[1] Resume AKEEGA™ with recommendation of weekly monitoring for 28 days after restart.
First occurrence ≥ Grade 3[2]	Withhold AKEEGA™ and switch to single agent AAP combination. Monitor at least weekly) until platelets and neutrophils recover to Grade 1 or baseline.[1] Then resume AKEEGA™ or, if warranted, at one dose-level reduction [two **low strength** (50 mg/500 mg) tablets]. Weekly monitoring of blood counts is recommended for 28 days after restarting dose.
Second occurrence ≥ Grade 3	Withhold AKEEGA™ and switch to single agent AAP combination. Monitor at least weekly until platelets and/or neutrophils recover to Grade 1. Further treatment with AKEEGA™ should restart at one dose-level reduction [two **low strength** (50 mg/500 mg) tablets]. Weekly monitoring is recommended for 28 days after resuming treatment with AKEEGA™. If patient was already on a reduced dose [two **low strength** (50 mg/500 mg) tablets], consider treatment discontinuation.
Third occurrence ≥ Grade 3	Permanently discontinue AKEEGA™ and switch to single agent AAP combination

[1] During AKEEGA™ treatment interruption related to hematological toxicities, abiraterone acetate plus prednisone or prednisolone should be generally continued by the physician (see abiraterone acetate product monograph)

[2] If patient requires platelet transfusion or has neutropenic fever or neutropenia requiring granulocyte-colony stimulating factor for Grade ≥3 AE deemed to be related to AKEEGA™ toxicity, interrupt study drug and restart at 1 dose-level reduction after resolution to Grade 1 or baseline. If AKEEGA™ was previously dose-reduced for the same hematologic toxicity, discontinue AKEEGA™

Non-Hematologic Adverse Reactions

For drug-related ≥Grade 3 toxicities, if the toxicity cannot be definitively attributed to either niraparib or abiraterone acetate only, then AKEEGA™ should be interrupted. Treatment with AKEEGA™ must not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline. To resume treatment, initiate treatment with single AAP combination first. If there is continued resolution of the toxicity to baseline/Grade 1, then switch to treatment with AKEEGA™ at least 7 days after restarting AAP.

If a patient was on a reduced dose of AKEEGA™ (100mg/1000mg), AKEEGA™ must be discontinued for a Grade ≥ 3 treatment-related adverse reaction lasting more than 28 days.

Permanently discontinue AKEEGA™ for treatment-related hypertensive crisis.

Hepatotoxicity

For patients who develop ≥ Grade 3 hepatotoxicity (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above five times the upper limit of normal [ULN]), treatment with AKEEGA™ should be interrupted and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level of one regular strength AKEEGA™ tablet (equivalent to 100 mg niraparib and 500 mg abiraterone acetate).For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 100 mg/500 mg daily (1 tablet), treatment with AKEEGA™ should be discontinued.

Permanently discontinue AKEEGA™ for patients who develop severe hepatotoxicity (ALT or AST 20 times the ULN). Permanently discontinue AKEEGA™ for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation (see 7 WARNINGS AND PRECAUTIONS).

Recommended Monitoring

See 7 WARNINGS AND PRECAUTIONS for required monitoring prior to, and during treatment with AKEEGA™.

Special Populations

Pediatrics (<18 years of age) Health Canada has not authorized an indication for pediatric use.

Geriatrics (≥65 years of age)

No dose adjustment is necessary for elderly patients (see 10.3 Pharmacokinetics).

Hepatic Impairment

No dose adjustment is necessary for patients with mild hepatic impairment (AST or ALT ≤ 3 x ULN or serum total bilirubin ≤ 1.5 x ULN). AKEEGA™ should not be used in patients with moderate to severe hepatic impairment (see SERIOUS WARNINGS AND PRECAUTIONS BOX; 10.3 Pharmacokinetics).

Renal Impairment

No dose adjustment is necessary for patients with mild to moderate renal impairment (see 10.3 Pharmacokinetics). AKEEGA™ has not been studied in patients with severe renal impairment (Creatinine clearance <30mL/min).

Reconstitution

Not applicable

4.3 Administration

AKEEGA™ must be taken on an empty stomach. AKEEGA™ must be taken at least two hours after eating and food must not be eaten for at least one hour after taking AKEEGA™. The tablets must be swallowed whole with water (see 10.3 Pharmacokinetics–Absorption). Do not break, crush, or chew tablets.

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

4.4 Missed Dose

If a dose of either AKEEGA™, prednisone or prednisolone is missed, it should be resumed the next day with the usual daily dose and normal daily schedule. Extra tablets must not be taken to make up for the missed dose.

5 OVERDOSAGE

There is no specific treatment in the event of AKEEGA™ overdose. In the event of an overdose, physicians should follow general supportive measures and treat patients symptomatically.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form Strength/Composition	Non-medicinal Ingredients
oral	tablets Regular strength: 100 mg niraparib (as niraparib tosylate)/500 mg abiraterone acetate Low strength: 50 mg niraparib (as niraparib tosylate)/500 mg abiraterone acetate	Colloidal anhydrous silica, crospovidone, glycerol monocaprylocaprate, hypromellose, iron oxide (E172), iron oxide red (E172), iron oxide yellow (E172), lactose monohydrate, magnesium stearate, polyvinyl alcohol, silicified microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide (E171)

AKEEGA™ tablets are available as regular strength (100 mg niraparib (as niraparib tosylate) and500 mg abiraterone acetate) and low-dose strength (50 mg niraparib (as niraparib tosylate) and500 mg abiraterone acetate):

AKEEGA™ 100 mg niraparib (as niraparib tosylate) and 500 mg abiraterone acetate tablets: Orange, oval, tablets (22 mm x 11 mm), debossed with "N 100 A" on one side, and plain on the other side.

AKEEGA™ 50 mg niraparib (as niraparib tosylate) and 500 mg abiraterone acetate tablets: Yellowish orange to yellowish brown, oval, tablets (22 mm x 11 mm), debossed with "N 50 A" on one side, and plain on the other side.

AKEEGA™ tablets of both strengths will be available in 150 ml high-density polyethylene (HDPE) bottles with 60 tablets each.

7 WARNINGS AND PRECAUTIONS

Please see 3 SERIOUS WARNINGS AND PRECAUTIONS BOX.

General

AKEEGA™ is used with 10 mg prednisone or prednisolone daily. Gonadotropin releasing hormone (GnRH) agonists must be taken during treatment with AKEEGA™ or patients must have been previously treated with orchiectomy.

AKEEGA™ must be taken on an empty stomach. AKEEGA™ must be taken at least two hours after eating and food must not be eaten for at least one hour after taking AKEEGA™. The tablets must be swallowed whole with water (see 4 DOSAGE AND ADMINISTRATION and 10.3 Pharmacokinetics-Absorption)

Lactose Intolerance

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose galactose malabsorption should not take this medicine.

Carcinogenesis and Mutagenesis

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML)

MDS/AML, including cases with fatal outcome, have been reported in ovarian, fallopian tube or primary peritoneal cancer trials among patients who received niraparib monotherapy (see ZEJULA PM).

In the MAGNITUDE study Cohort 1 (see 8 ADVERSE REACTIONS), with a median duration of follow-up of 26.8 months in the niraparib+AAP arm and 26.9 months in the placebo+AAP arm respectively, AML was reported in 0 subjects in the niraparib +AAP arm and 1 subject (0.5%) in the placebo+AAP arm.

For suspected MDS/AML or prolonged hematological toxcities that has not resolved with treatment interruption or dose reduction, the patient should be referred to a hematologist for

further evaluation. If MDS and/or AML is confirmed, treatment with AKEEGA™ should be permanently discontinued.

Cardiovascular

AKEEGA™ should be used with caution in patients with a history of cardiovascular disease. Before and during treatment of patients with a significant risk for congestive heart failure (e.g., a history of cardiac failure, or cardiac events such as ischemic heart disease), cardiac failure should be treated, and cardiac function optimized. Symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter. The safety of AKEEGA™ in patients with clinically significant heart disease, as evidenced by myocardial infarction, arterial and venous thrombotic events in the past six months, severe or unstable angina, or NYHA Class II to IV heart failure or cardiac ejection fraction measurement of < 50%, is unknown as these patients were excluded from the MAGNITUDE study.

Hypertension

AKEEGA™ may cause hypertension. Pre-existing hypertension should be adequately controlled before starting AKEEGA™ treatment. Blood pressure should be monitored at least weekly for two months, monthly afterwards for the first year and every other month thereafter during treatment with AKEEGA™.

Hypokalemia, Fluid retention

AKEEGA™ may cause hypokalemia and fluid retention (see 8 ADVERSE REACTIONS) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see 10.2 Pharmacodynamics). Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by hypokalemia. QT prolongation has been observed in patients experiencing hypokalemia in association with AKEEGA™ treatment. Hypokalemia and fluid retention should be corrected and controlled.

Fluid retention (weight gain, peripheral edema) should be monitored every two weeks for three months, then monthly thereafter and abnormalities corrected).

Venous Thromboembolic Events

Venous thromboembolic events (VTE), including pulmonary embolism, have occurred in patients treated with AKEEGA™ (see 8 ADVERSE REACTIONS). Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate.

Driving and Operating Machinery

Patients who take AKEEGA™ may experience asthenia, fatigue, dizziness. AKEEGA™ may influence the ability to drive or use machines. Patients should use caution when driving or operating a vehicle or potentially dangerous machinery.

Endocrine and Metabolism

Hypoglycemia

Cases of hypoglycemia have been reported when abiraterone acetate plus prednisone or prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (see 9 DRUG INTERACTIONS); therefore, blood sugar should be monitored in patients with diabetes.

Hematologic

Hematologic Adverse Reactions

Hematologic adverse reactions (anemia, neutropenia and thrombocytopenia) have been reported in patients treated with niraparib monotherapy and combination therapy (see 8 ADVERSE REACTIONS).

In the MAGNITUDE study, the overall incidence of Grade ≥3 anemia, neutropenia and thrombocytopenia was 29.7%, 6.6% and 6.6% respectively, in Cohort 1 patients receiving niraparib+AAP.

Testing complete blood counts weekly for the first month, bi-weekly for the next two months, followed by monthly monitoring for the first year and then every other month for the remainder of treatment is recommended (see 4 DOSAGE AND ADMINISTRATION).

Based on individual laboratory values, weekly monitoring for the second month may be warranted. If a patient develops severe persistent hematologic toxicity including pancytopenia that does not resolve within 28 days following interruption, AKEEGA™ should be discontinued. Due to the risk of thrombocytopenia, other medicinal products known to reduce platelet counts should be used with caution in patients taking AKEEGA™.

Hepatic/Biliary/Pancreatic

Hepatic Impairment

There are no data on the clinical safety and efficacy of AKEEGA™ administered to patients with moderate or severe hepatic impairment (aspartate aminotransferase [AST] and alanine aminotransferase [ALT] ≤3 x ULN or Child-Pugh Class B or C). AKEEGA™ should not be used in patients with moderate to severe hepatic impairment (see 3 SERIOUS WARNINGS AND PRECAUTIONS, 4 DOSAGE AND ADMINISTRATION, and 10.3 Pharmacokinetic Properties).

Hepatotoxicity

Marked increases in liver enzymes leading to treatment interruption or discontinuation occurred in clinical studies with abiraterone acetate, including in the MAGNITUDE study, (2 % of patients experienced a dose modification, one patient (0.5%) discontinued treatment in Cohort 1)-(see 8 ADVERSE REACTIONS). Severe hepatotoxicity (including fatal outcomes) has been reported during post-marketing experience with abiraterone acetate monotherapy (see ZYTIGA PM).

Serum aminotransferase and total bilirubin levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If

clinical symptoms or signs suggestive of hepatotoxicity develop, serum aminotransferases and bilirubin should be measured immediately. If at any time the ALT or AST rises above five times the upper limit of normal (ULN) or bilirubin rises 3 times the ULN, treatment with AKEEGA™ should be interrupted and liver function closely monitored. Permanently discontinue AKEEGA™ for patients who develop a concurrent elevation of ALT greater than 3 x ULN and total bilirubin greater than 2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

Retreatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level (See 4 DOSAGE AND ADMINISTRATION) If patients develop severe hepatotoxicity (ALT or AST twenty times the ULN) anytime while on therapy, treatment with AKEEGA™ should be permanently discontinued. Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of AKEEGA™ in this population.

Immune

In patients treated with abiraterone acetate monotherapy, cases of anaphylactic reactions requiring rapid medical interventions have been reported during post-marketing experience (see ZYTIGA PM).

Monitoring and Laboratory Tests

- Complete blood counts should be obtained prior to starting treatment, weekly for the first month, bi-weekly for the next two months, followed by monthly monitoring for the first year and then every other month for the remainder of treatment (see 4 DOSAGE AND ADMINISTRATION).
- Serum aminotransferases and total bilirubin should be measured prior to starting treatment, every two weeks for the first three months of treatment and monthly thereafter for the first year and then every other month for the duration of treatment.
- Serum potassium should be monitored monthly for the first year and then every other month for the duration of treatment.
- Blood pressure should be monitored at least weekly for two months, monthly afterwards for the first year and every other month thereafter during treatment with AKEEGA™.
- In patients who develop hypokalemia whilst being treated with AKEEGA™, consider maintaining the patient's potassium level at ≥ 4.0 mM (see 4 DOSAGE AND ADMINISTRATION
- Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If AKEEGA™ is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess. In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Musculoskeletal

Increased Fractures and Mortality in Combination with Radium dichloride

Treatment with AKEEGA™ in combination with radium dichloride is not recommended. In a randomized clinical trial of patients with asymptomatic or mildly symptomatic bone-predominant metastatic castration resistant prostate cancer with bone metastases, the addition of radium 223 dichloride to abiraterone plus prednisone/prednisolone showed an increase in mortality and an increased rate of fracture (see ZYTIGA PM).

Myopathy/Rhabdomyolysis

Cases of myopathy/rhabdomyolysis have been reported in patients treated with abiraterone acetate monotherapy (see ZYTIGA PM). Caution is recommended in patients concomitantly treated with drugs known to be associated with myopathy/rhabdomyolysis.

Neurologic

Posterior Reversible Encephalopathy Syndrome (PRES)

Posterior Reversible Encephalopathy Syndrome (PRES) is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI).

There have been reports of PRES in patients receiving niraparib as a monotherapy in the ovarian, fallopian tube or primary peritoneal cancer population (see ZEJULA PM).

In case of PRES, treatment with AKEEGA™ should be permanently discontinued and appropriate medical management should be instituted.

Reproductive Health: Female and Male Potential

It is not known whether components of AKEEGA™ or their metabolites are present in semen. If the patient is engaged in sex with a pregnant woman or a woman of childbearing potential, a condom is required along with another highly effective contraceptive method during treatment and for three months after the last dose of AKEEGA™.

Studies in animals have shown reproductive toxicity See 2 CONTRAINDICATIONS and 7.1.1 Pregnant Women.

- **Fertility**

  There are no clinical data on fertility with AKEEGA™. In animal studies, male fertility was reduced with niraparib or abiraterone acetate, but these effects were reversible following treatment cessation (see 16 NON-CLINICAL TOXICOLOGY).

- **Teratogenic Risk**

  AKEEGA™ has the potential to cause fetal harm based on the mechanism of action of both components and findings from animal studies with abiraterone acetate (see

2 CONTRAINDICATIONS and 16 NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

AKEEGA™ is not authorized for use in women (see 10.3 Pharmacokinetics).

There are no data of the use of AKEEGA™ in pregnant women. AKEEGA™ has the potential to cause fetal harm based on the mechanism of action of both components and findings from animal studies with abiraterone acetate. Animal developmental and reproductive toxicology studies were not conducted with niraparib (see 16 NON-CLINICAL TOXICOLOGY– Reproductive and Developmental Toxicology).

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

7.1.2 Breast-feeding

AKEEGA™ is not authorized for use in women.

7.1.3 Pediatrics (<18 years of age)

No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics (≥65 years of age)

In MAGNITUDE Cohort 1, 70.9% of subjects were aged ≥65 years and 26.5% were aged ≥75 years. No overall differences in safety and efficacy of niraparib and abiraterone acetate combination therapy were observed between these patients and younger subjects. However, greater sensitivity of older individuals ≥ 75 years cannot be ruled out. Increased vigilance in older individuals (≥75 years) could be recommended.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety profile of AKEEGA™ is based on data from a Phase 3, randomized, double-blind, placebo-controlled study, MAGNITUDE cohort 1 (HRR positive) who received niraparib plus abiraterone acetate and prednisone (AAP) (n=212) or placebo plus AAP (n=211) as single agent combinations orally once daily (see 14 CLINICAL TRIALS). The median duration of exposure to niraparib plus AAP was 13.8 months (range: 0- 29) . The baseline and disease characteristics were median age of 69 years (range 43-100) , the racial distribution was 74% Caucasian, 16.5% Asian, and 1.2% Black, and others or not reported (8.3%); Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0: 66%, ECOG PS1: 34% . At study entry, 83.5% of patients had bone involvement and 21.3% had visceral disease. All patients who had not received prior orchiectomy continued background androgen deprivation therapy with a GnRH analogue .

Serious adverse events occurred in 36% of subjects treated with niraparib plus AAP and 25% of subjects treated with placebo plus AAP. Anemia (5.7%) was the serious adverse reaction reported in ≥2% of subjects who received niraparib plus AAP.

Fatal adverse events occurred in 5.7% of subjects treated with niraparib plus AAP and 3.3% of subjects treated with placebo plus AAP. Fatal adverse reactions due to pneumonia occurred in 0.5 % of subjects who received niraparib plus AAP and none of the subjects who received placebo plus AAP.

The most common adverse reactions of all Grades, occurring in >20% of patients in MAGNITUDE Cohort 1 were anemia, hypertension, constipation, fatigue, nausea and thrombocytopenia. The most frequently observed Grade≥3 adverse reactions were anemia, hypertension, thrombocytopenia, neutropenia and blood alkaline phosphatase increased.

Dose interruptions of any component of combination therapy due to an adverse event occurred in 43% of subjects treated with niraparib plus AAP and 23% of patients treated with placebo plus AAP. 22% of subjects in Cohort 1 needed dose interruptions of niraparib and use of single agent abiraterone acetate. The median length of treatment with single agent abiraterone acetate was 102 days (range: 6; 518). The most common adverse reactions leading to dose interruption in the niraparib plus AAP arm were anemia (22%), thrombocytopenia (9%) and neutropenia (7%). All other TEAEs leading to dose interruption occurred with <5% frequency.

Dose reductions due to an adverse event occurred in 27% of patients in the niraparib plus AAP arm and 9.5% of subjects in the patients plus AAP arm in Cohort 1. The most common adverse reactions leading to dose reduction in the niraparib plus AAP arm were anemia (13%), thrombocytopenia (3%) and fatigue (2%).

Permanent discontinuation due to an adverse event occurred in 10.8% of patients treated with niraparib plus AAP and 6.2% of subjects treated with placebo plus AAP in Cohort 1. The most common adverse events leading drug discontinuation in the niraparib plus AAP arm were COVID-19/COVID-19 pneumonia (2.8 %) and anemia (2.4%).

Overall, the safety and tolerability profile of AKEEGA™ was in line with the known safety profile of its 2 single agents, with no new safety signals identified.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use. The safety of niraparib plus AAP and AKEEGA™ in mCRPC patients with HRR mutations was assessed in the MAGNITUDE study, Cohorts 1 and 3 respectively (Table 3).

Table 3: Adverse Drug Reactions in mCRPC Patients with HRR Gene Mutations, Cohort 1 (≥2% Increase in Frequency in niraparib+AAP Compared to Placebo +AAP)

System/Organ Class	Niraparib+ AAP N=212			Placebo + AAP N=211		
Adverse Reaction	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Blood and lymphatic system disorders						
Anemia	46.2	28.3	1.4	20.4	7.6	0
Thrombocytopenia	21.2	2.8	3.8	8.5	2.4	0
Neutropenia	13.7	5.2	1.4	5.7	1.4	0
Leukopenia	10.4	1.9	0	2.4	0.5	0
Lymphopenia	9.0	3.3	0.5	1.9	0.5	0.5
Infections and infestations						
Urinary tract infection	9.4	3.3	0	6.2	1.9	0
Metabolism and nutrition disorders						
Decreased appetite	14.2	0.5	0	6.2	0.5	0
Hypokalemia	13.7	2.8	0	9.5	2.8	0
Psychiatric disorders						
Insomnia	10.4	0	0	3.8	0	0
Nervous system disorders						
Dizziness	11.3	0.5	0	5.7	0	0
Cardiac disorders						
Arrhythmia[a]	12.7	2.4	0	5.7	1.4	0
Venous Thromboembolism[b]	8.0	5.2	0	3.3	1.4	0
Vascular disorders						
Hypertension	31.1	14.6	0	20.9	12.3	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	16.0	1.9	0	5.7	0.9	0
Cough	7.1	0	0	4.7	0	0
Pneumonitis	2.4	0	0	0	0	0
Gastrointestinal disorders						
Constipation	30.7	0	0	13.7	0	0
Nausea	23.6	0.5	0	13.7	0	0
Vomiting	13.2	0.5	0	6.6	0.5	0
Dyspepsia	6.1	0	0	2.8	0	0
Abdominal Pain Upper	4.7			2.8		
Abdominal distention	3.8	0	0	0.5	0	0
Musculoskeletal and connective tissue disorders						
Arthralgia	13.2	0.5	0	9.5	0.5	0
Renal and urinary disorders						
Hematuria	6.6	0.9	0	3.8	0.5	0
Dysuria	4.7	0	0	1.9	0	0
General disorders and administration site conditions						
Fatigue	26.4	3.3	0	16.6	4.3	0
Asthenia	15.6	0.5	0	9.0	0.5	0
Investigations						
Blood alkaline phosphatase increased	9.9	4.2	0.9	6.6	2.4	0

System/Organ Class	Niraparib+ AAP N=212			Placebo + AAP N=211		
Adverse Reaction	All Grades %	Grade 3 %	Grade 4 %	All Grades %	Grade 3 %	Grade 4 %
Weight decreased	9.0	0.9	0	2.4	0	0
Blood creatinine increased	9.0	1.4	0	3.8	0	0.5

*CTCAE=Common Terminology Criteria for Adverse Events version 5.0

[a]Grouped terms for arrhythmia: tachcardia, palpitations, atrial fibrillations,sinus tachycardia, supraventricular extrasystoles, atrial tachycardia, cardio-respiratory arrest, ventricular extrasystoles, atrial flutter, bradycardia, heart rate increased, ventricular tachycardia

[b]Grouped terms for thromboembolism (venous): embolism, pulmonary embolism, thrombosis, deep vein thrombosis, venous thrombosis

Hematological Toxicities

Hematological toxicities (anemia, thrombocytopenia, and neutropenia) including laboratory findings are the most frequent adverse reactions attributable to niraparib. These toxicities generally occurred within the first two months of treatment.

In the MAGNITUDE study, the following hematologic parameters were inclusion criteria: absolute neutrophil count (ANC) ≥ 1,500 cells/µL; platelets ≥ 100,000 cells/µL and hemoglobin ≥ 9 g/dL.

- ***Anemia***

Anemia was the most frequent adverse reaction (46.2%) and most observed Grade ≥ 3 event (28.3%) in the MAGNITUDE study. Anemia generally occurred early during therapy (median time to onset of 57 days, range: 1; 636 days), however, 50% of these patients had ongoing, low-grade persistent anemia. Dose interruptions occurred in 22.2% of patients and dose reductions in 13%. Twenty-six percent of patients received at least one anemia related transfusion. Anemia caused treatment discontinuation in 2.4% of subjects.

- ***Thrombocytopenia***

In the MAGNITUDE study, 21.2% of treated patients reported thrombocytopenia while 6.6% of patients experienced Grade 3-4 thrombocytopenia. Median time from first dose to first onset was 43 days. Thrombocytopenia was managed with dose modification (interruption 9.4% and reduction in 2.8%) and platelet transfusion (2.4%) where appropriate. Discontinuation occurred in 0.5% of patients and 1.4% of patients experienced a concurrent bleeding event.

- ***Neutropenia***

In the MAGNITUDE study, 14% of patients experienced neutropenia with Grade 3-4 neutropenia reported in 6.6% of patients. Median time from first dose to first report of neutropenia was 50 days. Neutropenia led to treatment interruption in 6.6% of patients and dose reduction in 1.4%. In the MAGNITUDE study, 0.9% of patients had a concurrent infection.

Non-Hematologic Adverse Reactions

Hypertension

Hypertension is an adverse reaction for both components of AKEEGA™ and patients with uncontrolled hypertension (persistent systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥100 mmHg) were excluded in all combination trials. Hypertension was reported in 31% of patients of whom 15% had Grade ≥ 3. The median time to onset of hypertension was 56 days.

Cardiac Events

In the MAGNITUDE study, the most frequent major adverse cardiovascular events [MACE (Ischemic Heart Disease, Cardiac Failure)] were ischemic heart disease (1.9%) and Cardiac failure was also reported in 1.9% of patients. Additionally, arrythmias were reported in 12.7% of patients.

Hepatotoxicity

Hepatotoxicity had been recognized as important identified risk for abiraterone acetate. Patients with moderate and severe hepatic impairment (NCI classification) and patients with Child-Turcotte-Pugh Class B and C were excluded from AKEEGA™ combination studies.

In the MAGNITUDE study, patients with baseline hepatitis or significant abnormalities of liver function tests were excluded (Serum total bilirubin ≤1.5× ULN or direct bilirubin ≤1 x ULN and AST or ALT ≤3 × ULN).

The overall incidence of hepatotoxicity in the MAGNITUDE study was 12% in both arms. Grade 3 events occurred in 1.4% of patients and a Grade 4 event occurred in only one patient (0.5%). The incidence of SAEs was 0.9%. The median time to onset of hepatotoxicity in the MAGNITUDE study was 30 days. Hepatotoxicity was managed with dose interruptions in 1.4% and dose reduction in 0.9% of patients. One patient (0.5%) in the MAGNITUDE study discontinued treatment due to hepatotoxicity.

8.3 Less Common Clinical Trial Adverse Reactions

The following are selected clinically significant adverse reactions reported in less than 1% of patients receiving niraparib plus AAP or AKEEGA™ and with higher incidences reported than with placebo +AAP:

Cardiac disorders: QT Prolongation
Infections and Infestations: Urosepsis, Conjunctivitis
Investigations: Gamma-glutamyl transferase increased
Metabolism and nutrition disorders: Hypertriglyceridemia
Skin and Subcutaneous tissue disorders: Photosensitivity

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 4 presents hematology and chemistry laboratory abnormalities worsening from baseline from the placebo-controlled Cohort 1 in the MAGNITUDE study.

Table 4: Summary of Laboratory Abnormalities Worsening From Baseline in Niraparib plus AAP Treated Patients at a Higher Incidence than Placebo +AAP; Cohort 1 All HRR Safety Analysis Set (MAGNITUDE)

	Placebo + AAP	Niraparib + AAP	Placebo + AAP	Niraparib + AAP
	Grade 1-4	Grade 1-4	Grade 3-4	Grade 3-4
Analysis set: safety	211	212	211	212
CHEMISTRY				
Alkaline Phosphatase Increased	56 (26.5%)	73 (34.4%)	2 (0.9%)	7 (3.3%)
Blood Bilirubin Increased	17 (8.1%)	22 (10.4%)	2 (0.9%)	0
Creatinine Increased	31 (14.7%)	61 (28.8%)	3 (1.4%)	1 (0.5%)
Hyperkalemia	45 (21.3%)	53 (25.0%)	5 (2.4%)	5 (2.4%)
Hypokalemia	38 (18.0%)	47 (22.2%)	6 (2.8%)	9 (4.2%)
HEMATOLOGY				
Anemia	102 (48.3%)	147 (69.3%)	14 (6.6%)	56 (26.4%)
Hemoglobin Increased	0	1 (0.5%)	0	0
Lymphocyte Count Decreased	49 (23.2%)	98 (46.2%)	20 (9.5%)	37 (17.5%)
Neutrophil Count Decreased	31 (14.7%)	60 (28.3%)	5 (2.4%)	15 (7.1%)
Platelet Count Decreased	40 (19.0%)	77 (36.3%)	4 (1.9%)	15 (7.1%)
White Blood Cell Decreased	30 (14.2%)	83 (39.2%)	2 (0.9%)	10 (4.7%)

Key: AAP = abiraterone acetate plus prednisone.

8.5 Post-Market Adverse Reactions

At the time of authorization, no post-market findings were identified.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No clinical trial evaluating drug interactions has been performed using AKEEGA™. Interactions that have been identified in studies with individual components of AKEEGA™ (niraparib or abiraterone acetate) determine the interactions that may occur with AKEEGA™.

Niraparib (see ZEJULA PM for Drug Interaction Overview)
No formal drug interaction studies have been performed with niraparib.

In Vitro Studies
Substrate of CYPs: Niraparib is a substrate of carboxylesterases (CEs) and UDP-glucuronosyltransferases (UGTs) *in vivo*.

Inhibition of CYPs: Neither niraparib nor the major primary metabolite M1 is an inhibitor of CYP1A1/2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. The potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Therefore, caution is recommended when niraparib is combined with active substances with CYP3A4-dependent metabolism.

Induction of CYPs: Neither niraparib nor M1 is a CYP3A4 inducer in vitro. Niraparib weakly induces CYP1A2 in vitro. Therefore, caution is recommended when niraparib is combined with active substances with CYP1A2-dependent metabolism.

Inhibition of UGTs: Niraparib did not exhibit inhibitory effect against the UGT isoforms (UGT1A1,UGT1A4, UGT1A9, and UGT2B7) up to 200 µM in vitro. Therefore, the potential for a clinically relevant inhibition of UGTs by niraparib is minimal.

Inhibition of transporter systems: Niraparib is a weak inhibitor of Breast Cancer Resistance Protein (BCRP) and P-glycoprotein (P-gp) with an IC_{50} = 5.8 µM and 161 µM, respectively, but does not inhibit bile salt export pump (BSEP). The M1 metabolite is not an inhibitor of P-gp, BCRP, BSEP, MRP2, or Multidrug And Toxin Extrusion (MATE)-1 or 2. Neither niraparib nor M1 is an inhibitor of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic anion transporter 1 (OAT1), 3 (OAT3), or organic cation transporter 2 (OCT2).

Niraparib is an inhibitor of MATE-1 and -2 with IC_{50} of 0.18 µM and ≤ 0.14 µM, respectively (see 9.4 Drug-Drug Interactions). In vitro, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC_{50} = 34.4 µM.
Caution is recommended when niraparib is combined with active substances that undergo uptake transport by OCT1.

Substrate of transporter systems: Niraparib is a substrate of P-gp and BCRP. Niraparib is not a substrate of BSEP, MRP2, or MATE-1 or 2. The metabolite M1 is not a substrate of P-gp, BCRP,

BSEP, or MATE-1 and 2. Neither niraparib nor M1 is a substrate of organic anion transport polypeptide 1B1 (OATP1B1), 1B3 (OATP1B3), or organic cation transporter 1 (OCT1), organic anion transporter 1 (OAT1), 3 (OAT3), or organic cation transporter 2 (OCT2).

Abiraterone Acetate (see ZYTIGA PM for Drug Interaction Overview)

In Vitro Studies

In vitro studies indicated that CYP3A4 (see 9.4 Drug-Drug Interactions) and sulfotransferase 2A1 (SULT2A1) are the major isoenzymes involved in the metabolism of abiraterone.

Inhibition of CYPs: Abiraterone is an inhibitor of the hepatic drug-metabolizing enzymes CYP2C8 and CYP2D6 (see 9.4 Drug-Drug Interactions). *In vitro* studies with human hepatic microsomes demonstrated that abiraterone was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5 (No clinical DDI studies have been performed to confirm these *in vitro* findings).

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

9.3 Drug-Behavioural Interactions

Photosensitivity has been observed in patients exposed to niraparib monotherapy (See ZEJULA PM) and as a combination therapy with AKEEGA™. Patients should be counselled to avoid sun exposure when possible while on treatment with AKEEGA™.

9.4 Drug-Drug Interactions

Potential for other medicinal ingredients to affect AKEEGA™

CYP3A4 inducers: Based on *in vitro* data, abiraterone is a substrate of CYP3A4. In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampicin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC_{∞} of abiraterone was decreased by 55%. Strong inducers of CYP3A4 during treatment with AKEEGA™ are to be avoided.

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

Potential for AKEEGA™ to affect other drugs

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

the active metabolite of dextromethorphan, increased by approximately 33%. Caution is advised when AKEEGA™ is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

CYP2C8 substrates: In a clinical pharmacokinetic interaction study in healthy subjects, the AUC of pioglitazone was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of the CYP2C8 substrate pioglitazone, each decreased by 10%, when a single dose of pioglitazone was given together with a single dose of 1000 mg abiraterone acetate. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with AKEEGA™.

The drugs listed in Table 5 are interactions for AKEEGA™.

Table 5: Established or Potential Drug-Drug Interactions

Common name	Source of Evidence	Effect	Clinical Comment
Drugs that may affect the exposure of AKEEGA™			
Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St. John's wort)	CT*	Decreased abiraterone exposure	Strong inducers of CYP3A4 during treatment with AKEEGA™ are to be avoided.
Strong CYP3A4 inhibitors (e.g., ketoconazole)	CT*	No clinically meaningful effect on the pharmacokinetics of abiraterone	No dose adjustment needed for AKEEGA™ when given with strong inhibitors of CYP3A4.
Drugs for which the exposure may be affected by AKEEGA™			
CYP2D6 substrates (e.g., metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol)	CT*	Inhibited metabolism of CYP2D6 substrates	Caution is advised when co-administering AKEEGA™ with medicinal products activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction should be considered.

Common name	Source of Evidence	Effect	Clinical Comment
CYP2C8 substrates: (e.g., pioglitazone and repaglinide)	CT*	Inhibited metabolism of CYP2C8 substrates	Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with AKEEGA™.
MATE-1 and -2 substrates (e.g. metformin)	T*	Inhibited metabolism of MATE-1 and -2 substrates	Monitoring of the clinical effects of MATE-1 and MATE-2 substrates with a narrow therapeutic index is recommended if used concomitantly with AKEEGA™.

CT*= Clinical trial with abiraterone acetate, T*=Theoretical

Drug interactions of AKEEGA™ with vaccines or immunosuppressant agents has not been studied.

The data on niraparib, in combination with cytotoxic medicinal products, are limited. Caution should be taken if AKEEGA™ is used in combination with vaccines, immunosuppressant agents or with other cytotoxic medicinal products. The safety of immunization during treatment with AKEEGA™ with live or live-attenuated vaccines and the response to immunization with any vaccine are unknown.

9.5 Drug-Food Interactions

AKEEGA™ must not be taken with food (see 4 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING and 10.3 Pharmacokinetics). Administration with food has the potential to result in increased and highly variable systemic exposures of AKEEGA™.

9.6 Drug-Herb Interactions

Concomitant use with St. John's wort (*Hypericum perforatum*) or products containing St. John's wort is to be avoided.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

The niraparib and abiraterone acetate tablet is a dual-action tablet combination of niraparib (an inhibitor of poly (ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role

in DNA repair) and the abiraterone prodrug (abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. This combination targets two oncogenic dependencies in patients with mCRPC and HRR gene alterations.

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. Increased niraparib-induced cytotoxicity was observed in tumour cell lines with or without deficiencies in *BRCA1/2*. Niraparib reduced tumour growth in mouse xenograft models of human cancer cell lines with defective *BRCA1/2* function and in patient-derived xenograft tumour models with homologous recombination deficiency that had either mutated or wild type *BRCA1/2*, and in tumours that are *BRCA* wild-type and without detectable homologous recombination deficiency.

Abiraterone acetate is converted *in vivo* to abiraterone that selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17). CYP17 enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal, and prostatic tumour tissues. CYP17 catalyzes the conversion of pregnenolone and progesterone into testosterone precursors, DHEA, and androstenedione, respectively, by 17αhydroxylation and cleavage of the C17,20 bond.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with GnRH agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with GnRH agonists (or orchiectomy).

In preclinical mouse models of prostate cancer, the combination of niraparib and abiraterone acetate demonstrated superior efficacy relative to either active substance administered alone. This was demonstrated in both the *BRCA*1/2 wild-type VCaP model, and the *BRCA*2 mutant LuCaP 96 model.

10.2 Pharmacodynamics

As niraparib and abiraterone acetate tablets contain niraparib and abiraterone acetate, the pharmacodynamic effects of each component should be considered.

Cardiac Electrophysiology

Niraparib (see ZEJULA PM for Pharmacodynamics)

The potential for QTc prolongation with niraparib was evaluated in a randomized, placebo-controlled study in cancer patients (367 patients on niraparib and 179 patients on placebo). No large changes in the mean QTc interval (>20 ms) were detected in the study following the treatment of niraparib 300 mg once daily.

Abiraterone Acetate (see ZYTIGA PM for Pharmacodynamics)

A multicentre, open-label, uncontrolled, single arm ECG assessment study was performed in 33 patients with metastatic castration-resistant prostate cancer who were medically (N=28) or surgically castrated (N=5). Patients had serial ECG recordings at baseline and on day 1 of the first

and second 28-day cycles of treatment with abiraterone acetate 1g/day plus prednisone 5 mg twice daily. At steady-state on day 1 of cycle 2, the QTc interval was significantly shortened at most time points, with a maximum decrease from baseline of mean -10.7 (90% CI -14.8, -6.5) ms at 24 h post-dosing.

Androgen deprivation is associated with QTc prolongation. In this study the QTc interval averaged 435−440 ms at baseline and 57.6% of subjects had baseline QTc values > 450 ms prior to initiation of abiraterone acetate. Because the subjects in this trial were already androgen-deprived, the results of this study cannot be extrapolated to non-castrated populations.

Cardiovascular Effects (see ZEJULA PM for Pharmacodynamics)

Niraparib (see ZEJULA PM for Pharmacodynamics)

Niraparib has the potential to cause effects on pulse rate and blood pressure in patients, which may be related to pharmacological inhibition of the dopamine transporter (DAT), norepinephrine transporter (NET), and serotonin transporter (SERT).

Based on the PRIMA study conducted in patients with advanced ovarian cancer (NCT02655016), mean pulse rate and blood pressure increased over baseline in the niraparib arm relative to the placebo arm at most on-study assessments. Mean greatest increases from baseline in pulse rate on treatment were 22.4 and 14.0 beats/min in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in systolic blood pressure on treatment were 24.4 and 19.6 mmHg in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in diastolic blood pressure on treatment were 15.9 and 13.9 mmHg in the niraparib and placebo arms, respectively.

Based on the NOVA study conducted in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer (NCT02354131), mean pulse rate and blood pressure increased over baseline in the niraparib arm relative to the placebo arm at all on-study assessments. Mean greatest increases from baseline in pulse rate on treatment were 24.1 and 15.8 beats/min in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in systolic blood pressure on treatment were 24.5 and 18.3 mmHg in the niraparib and placebo arms, respectively. Mean greatest increases from baseline in diastolic blood pressure on treatment were 16.5 and 11.6 mmHg in the niraparib and placebo arms, respectively.

Mineralocorticoid receptor antagonists

Patients in the pivotal clinical trial MAGNITUDE (64091742PCR3001) were not allowed to use the mineralocorticoid receptor antagonist spironolactone since spironolactone has the ability to bind and activate the androgen receptor, which could stimulate disease progression. The use of spironolactone with AKEEGA™ should be avoided.

10.3 Pharmacokinetics

Table 6: Summary of AKEEGA™ (200 mg niraparib and 1000 mg abiraterone acetate) Pharmacokinetic Parameters in mCRPC Patients

	$C_{max,ss}$ (ng/mL)	T_{max} (h)*	$T_{1/2}$ (h)	$AUC_{0-24h,ss}$ (ng·h/mL)	CL/F (L/h)	V_d/F (L)
Mean for niraparib	831	3.00	62.3	13616	16.7	1117
Mean for abiraterone	151	1.50	19.7	707	1673	25774

*Median for T_{max}

Co-administration of niraparib and abiraterone acetate has no impact on the exposure of the individual moieties. The AUC and C_{max} are comparable for niraparib and abiraterone when administered as a combination when compared to respective monotherapy exposures.

Absorption

In mCRPC patients, under fasted and modified fasted conditions, upon administration of multiple doses of niraparib and abiraterone acetate tablets, the maximum plasma concentration was achieved within a median of 3 hours for niraparib, and a median of 1.5 hours for abiraterone.

The food effect of the individual components has been extensively characterized. Given the normal variation in the content and composition of meals, taking niraparib and abiraterone acetate tablets with meals has the potential to result in increased and highly variable exposures of abiraterone. Niraparib and abiraterone acetate tablets must be taken at least two hours after eating and food must not be eaten for at least one hour after taking abiraterone acetate.

Distribution:

Based on population pharmacokinetic analysis, the apparent steady-state volume of distribution (Vss/F) of niraparib and abiraterone were 1,117 L and 25,774 L, respectively, indicative of extensive extravascular distribution. Niraparib was moderately protein-bound in human plasma (83 %), mainly with serum albumin. The plasma protein binding of ^{14}Cabiraterone in human plasma is >99%.

Metabolism:

Niraparib is metabolized primarily by carboxylesterases (CEs) to form a major inactive metabolite, M1. In a mass balance study, M1 and M10 (the subsequently formed M1 glucuronides) were the major circulating metabolites. Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone by a CYP independent pathway. Abiraterone undergoes metabolism including sulphation, hydroxylation, and oxidation primarily in the liver. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and Noxide abiraterone sulphate, each represent approximately 43% of total radioactivity. The formation of N-oxide abiraterone sulphate is predominantly catalyzed by CYP3A4 and SULT2A1 while the formation of abiraterone sulphate is catalyzed by SULT2A1.

Elimination

Based on population pharmacokinetic analysis in patients with mCRPC, the apparent clearance (CL/F) of niraparib and abiraterone were estimated to be 16.7 L/h and 1673 L/h, respectively. The mean t½ of niraparib and abiraterone when given in combination were approximately 62 hours and 20 hours, respectively.

Special Populations and Conditions

Pediatrics: No studies have been conducted to investigate the pharmacokinetics of AKEEGA™ in pediatric patients.

Geriatrics: Based on population pharmacokinetic analysis in patients with mCRPC, geriatric patients aged 75 to 90 years had 23% (90% CI of 16-30%) higher $AUC_{0\text{-}24h,ss}$ and 16% (90% CI of 10-22%) higher $C_{max,ss}$ of niraparib compared to patients aged 45 to 65 years.

Based on population pharmacokinetic analysis in patients with mCRPC, geriatric patients aged 75 to 90 years had 25% (90% CI of 16-34%) higher $AUC_{0\text{-}24h,ss}$ and 19% (90% CI of 1-40%) higher $C_{max,ss}$ of abiraterone compared to patients aged 43 to 65 years.

Body weight: Based on the population pharmacokinetic analysis, body weight did not have a clinically relevant impact on the exposure of niraparib (range: 43.3-165 kg) and abiraterone (range: 46.0-165 kg).

Ethnic Origin: Based on a population pharmacokinetic analysis that included 69% White, 11 % Asian, and 6% Hispanic patients, ethnicity does not have a clinically significant effect on the exposure to niraparib.

Based on a population pharmacokinetic analysis that included 67% White, 17 % Asian, and 7% Hispanic patients, ethnicity does not have a clinically significant effect on the exposure to abiraterone.

Hepatic Insufficiency: No hepatic impairment study was conducted using AKEEGA™.

Based on the population pharmacokinetic analysis of data from clinical studies where prostate cancer patients received niraparib alone or niraparib and abiraterone acetate in combination, mild hepatic impairment (NCI-ODWG criteria, n=231) did not affect the exposure of niraparib

In a clinical study of cancer patients using NCI-ODWG criteria to classify the degree of hepatic impairment, niraparib AUC_{inf} in patients with moderate hepatic impairment (n=8) was 1.56 (90% CI: 1.06 to 2.30) times the niraparib AUC_{inf} in patients with normal hepatic function (n=9) following administration of a single 300 mg dose.

The pharmacokinetics of abiraterone were examined in subjects with pre-existing mild (n = 8) or moderate (n = 8) hepatic impairment (Child-Turcotte-Pugh Class A and B, respectively) and in 8 healthy control subjects. Systemic exposure to abiraterone after a single oral 1,000 mg dose increased approximately 1.11-fold and 3.6-fold in subjects with mild and moderate pre-existing hepatic impairment, respectively.

There is no clinical experience using AKEEGA™ in patients with moderate or severe hepatic impairment.

No dose adjustment of AKEEGA™ is necessary for patients with preexisting mild hepatic impairment. AKEEGA™ should not be used in patients with moderate and severe hepatic impairment (see 4 DOSAGE AND ADMINISTRATION, 3 SERIOUS WARNINGS AND PRECAUTIONS BOX and 7 WARNINGS AND PRECAUTIONS).

For patients who develop hepatotoxicity during treatment, suspension of treatment and dose adjustment may be required (see 4 DOSAGE AND ADMINISTRATION and 7 WARNINGS AND PRECAUTIONS).

Renal Insufficiency: No renal impairment study was conducted using AKEEGA™.

Based on the population pharmacokinetic analysis of data from clinical studies where prostate cancer patients received niraparib alone or niraparib and abiraterone acetate in combination, mild renal impairment (CrCl: 60 to 90 mL/min, n=337) had no clinically significant effect on the pharmacokinetics of niraparib. Patients with moderate renal impairment (CrCl: 30 to 60 mL/min, n=114) had 33% higher $AUC_{0\text{-}24h,ss}$ and 25% higher $C_{max,ss}$ of niraparib compared to patients with normal renal function.

The pharmacokinetics of abiraterone were compared in patients with end-stage renal disease on a stable hemodialysis schedule (n=8) versus matched control subjects with normal renal function (n=8). Systemic exposure to abiraterone after a single oral 1,000 mg dose did not increase in subjects with end-stage renal disease on dialysis.

No dose adjustment for the niraparib and abiraterone acetate tablets is necessary for patients with mild to moderate renal impairment.

There is no clinical experience in patients with severe renal impairment.

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15-30°C) in original container.

12 SPECIAL HANDLING INSTRUCTIONS

Based on its mechanism of action, this medicinal product may harm a developing fetus; therefore, women who are or may become pregnant should not handle it without protection, e.g., gloves (see 4 CONTRAINDICATIONS, and 7.1.1 Pregnant Women).

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

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substances

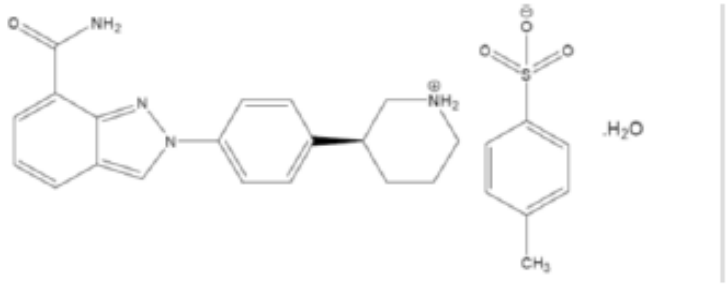
Proper/Common name: niraparib tosylate

Chemical name: 2-{4-[(3S)-piperidin-3-yl] phenyl}-2H-indazole 7-carboxamide 4-methylbenzenesulfonate hydrate (1:1:1)

Molecular formula: C19H20N4O. C7H8O3S.H2O

Molecular mass: 510.61

Structural formula:



Physicochemical properties: Niraparib tosylate monohydrate is a white to off-white, non-hygroscopic crystalline solid. Niraparib solubility is pH independent below the pKa of 9.95, with an aqueous free base solubility of 0.7 mg/mL to 1.1 mg/mL across the physiological pH range.

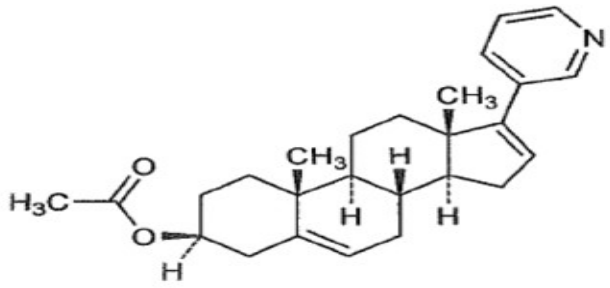
Proper name: abiraterone acetate

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

Molecular formula: $C_{26}H_{33}NO_2$

Molecular mass: 391.55

Structural formula:



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

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

The treatment of adult patients with deleterious *or suspected deleterious BRCA mutated (germline and/or somatic) metastatic castration-resistant prostate cancer (mCRPC), who are asymptomatic/mildly symptomatic, and in whom chemotherapy is not clinically indicated. Patients must have confirmation of BRCA mutation before AKEEGA™ treatment is initiated.*

Table 6: Summary of Patient Demographics for Clinical Trials in Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Mean age (Range)
64091742PCR3001 (MAGNITUDE)	Phase 3 Randomized, double-blind, placebo-controlled multicenter study with 3 Cohorts	**Cohort 1 and 2:** 200mg niraparib/placebo, 1000mg abiraterone as single agent combinations, and 10mg prednisone orally once daily. **Cohort 3:** 200mg niraparib, 1000mg abiraterone as fixed-dose combination tablets, and 10mg predinosone orally once Patients received concomitant background androgen deprivation therapy with a GnRH analogue if not surgically castrate.	Cohort 1 = 423 Cohort 2=247 Cohort 3=95	Cohort 1 = 69 (43-100 years) Cohort 2= 71 (52-87 years) Cohort 3=69.2 (47-90 years)

Study Design and Study Demographics (MAGNITUDE)

The efficacy of AKEEGA™ was established in MAGNITUDE (Study 64091742PCR3001), a randomized, double-blind, placebo-controlled multicenter Phase 3 clinical study to assess the efficacy of niraparib in combination with abiraterone acetate plus prednisone (AAP), compared with placebo plus AAP in metastatic castration-resistant prostate cancer (mCRPC) patients randomized in 3 Cohorts.

Key eligibility criteria included asymptomatic/mildy symptomatic patients with mCRPC who had not received prior systemic therapy in the mCRPC setting except for a short duration of prior AAP (up to four months in the absence of disease progression) and, an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, adequate hematological, hepatic, renal and cardiac function parameters (See Table 7 for Study Demographics). Asymptomatic/mildly symptomatic status was defined by a score of ≤3 on BPI-SF (Brief Pain Inventory Short Form), Question#3 worst pain over the past 24 hours at screening. Patients were required to have castrate levels of testosterone ≤50 ng/dL on a GnRHa or bilateral orchiectomy and continued background androgen deprivation therapy with a GnRH analogue if not surgically castrate. Subjects with active brain metastases, opiate use during screening, a history of adrenal dysfunction, history of current/prior AML/MDS, or prior AAP treatment outside mCRPC setting were excluded.

Patients were stratified by past taxane-based chemotherapy exposure in metastatic castration sensitive prostate cancer setting (24.4%), past AR-targeted therapy exposure (4.9%), prior AAP use up to four months (26.2%). In Cohort 1, Patients were further stratified by Homologous recombination repair (HRR) gene alteration status (*BRCA*1/2 vs. all non-*BRCA* HRRm).

Patients were prospectively screened for HRR alterations and then enrolled into either Cohort 1 and 3 (presence of HRR gene alterations) or Cohort 2 (absence of HRR gene alterations). Plasma, and/or tumor tissue (fresh or archival) samples for all patients were centrally tested with Foundation One® CDx or the Resolution CtDx HRD™ to determine HRR mutation status. These assays do not differentiate between germline and somatic mutations. Enrollment into the study based on local testing was infrequent. The same central tests were used to confirm HRR status for those subjects who enrolled based on local test results.

Cohort 1 consisted of 423 patients with mCRPC and 9 pre-specified HRR gene alterations (HRRm). Cohort 1 and 2 patients were randomized (1:1) to receive either niraparib plus abiraterone acetate and prednisone or prednisolone (AAP) orally at a dose of 200 mg/1,000 mg once daily or placebo plus AAP once daily as single agent combinations. Treatment was continued until disease progression, unequivocal clinical progression, unacceptable toxicity, or death.

Cohort 2 included 246 patients without HRR gene alterations. Since the pre-specified futility analysis for Cohort 2 was met, the independent data monitoring committee (IDMC) recommended unblinding and to stop enrolment in Cohort 2, with the unblinded patients allowed to remain on niraparib plus AAP or receive AAP alone.

Cohort 3 was a separate single-arm open-label cohort with no hypothesis testing, which enrolled patients after completion of enrollment into Cohort 1 and 2. Cohort 3 included 95 mCRPC patients with the same HRR gene alterations as Cohort 1. Patients received treatment with the same dosing regimen as Cohort 1 with the fixed-dose combination tablet formulation of niraparib and abiraterone acetate.

Demographic and baseline *BRCA*m patient characteristics in MAGNITUDE, Cohort 1 are summarized in Table 7 below. *BRCA*m patient demographics and baseline disease characteristics were generally balanced between the treatment arms, however, more patients with higher ECOG and BPI-SF score were in the niraparib plus AAP arm.

Table 7: Key Baseline Disease Characteristics in *BRCA*m patients, MAGNITUDE Cohort 1

	Placebo + AAP	**Niraparib + AAP**	**Total**
Analysis set: randomized	**112**	**113**	**225**
Time from initial diagnosis to randomization (years)			
Mean (SD)	3.68 (3.506)	3.09 (2.796)	3.39 (3.176)
Median	2.31	2.00	2.26
Range	(0.5; 16.1)	(0.5; 18.3)	(0.5; 18.3)
Time from mCRPC to first dose (years)			
Mean (SD)	0.46 (0.513)	0.34 (0.292)	0.40 (0.420)
Median	0.28	0.27	0.27
Range	(0.0; 2.9)	(0.0; 2.3)	(0.0; 2.9)
Age (years)			
Median	68.0	67.0	68.0
Range	(43; 88)	(45; 100)	(43; 100)
< 65	37 (33.0%)	39 (34.5%)	76 (33.8%)
≥ 65-74	52 (46.4%)	44 (38.95)	96 (42.7%)
≥ 75	23 (20.5%)	30 (26.5%)	53 (23.6%)
Gene Frequency			
*BRCA*1	4 (3.6%)	12 (10.6%)	16 (7.1%)
*BRCA*2	89 (79.5%)	86 (76.1%)	175 (77.8%)
Race			
Asian	20 (17.9%)	18 (15.9%)	38 (16.9%)
Black or African American	0	3 (2.7%)	3 (1.3%)
White	84 (75.0%)	78 (69.0%)	162 (72.0%)
Unknown	8 (7.1%)	14 (12.4%)	22 (9.8%)
Ethnicity			
Hispanic or Latino	13 (11.6%)	13 (11.5%)	26 (11.6%)
Not Hispanic or Latino	91 (81.3%)	83 (73.5%)	174 (77.3%)
Not reported	8 (7.1%)	17 (15.0%)	25 (11.1%)
Metastasis stage at initial diagnosis			
M0	56 (50.0%)	38 (33.6%)	94 (41.8%)
M1	50 (44.6%)	70 (61.9%)	120 (53.3%)
Unknown	6 (5.4%)	5 (4.4%)	11 (4.9%)
Gleason Score at initial diagnosis			
<7	8 (7.1%)	8 (7.1%)	16 (7.1%)
7	27 (24.1%)	16 (14.3%)	43 (19.2%)
3+4	7 (6.3%)	6 (5.4%)	13 (5.8%)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	**112**	**113**	**225**
4+3	19 (17.0%)	10 (8.9%)	29 (12.9%)
unknown	1 (0.9%)	0	1 (0.4%)
>=8	72 (64.3%)	83 (74.1%)	155 (69.2%)
Unknown	5 (4.5%)	5 (4.5%)	10 (4.5%)
PSA at initial diagnosis (µg/l)			
N	101	104	205
Mean (SD)	252.83(693.7)	219.83 (553.9)	236.09 (625.3)
Median	42.00	43.23	42.96
Range	(0.1;5000.0)	(0.1;3687.0)	(0.1;5000.0)
ECOG Performance Status			
0	80 (71.4%)	69 (61.1%)	149 (66.2%)
1	32 (28.6%)	44 (38.9%)	76 (33.8%)
Extent of Disease at study entry[a]			
Bone	93 (83.0%)	99 (87.6%)	192 (85.3%)
Bone only	46 (41.1%)	38 (33.6%)	84 (37.3%)
Visceral	22 (19.6%)	26 (23.0%)	48 (21.3%)
Soft tissue	7 (6.3%)	5 (4.4%)	12 (5.3%)
Nodal[b]	50 (44.6%)	62 (54.9%)	112 (49.8%)
Pelvic	34 (30.4%)	42 (37.2%)	76 (33.8%)
Non-pelvic	34 (30.4%)	40 (35.4%)	74 (32.9%)
Prostate[c]	2 (1.8%)	1 (0.9%)	3 (1.3%)
Number of bone lesions at study entry			
<=10 lesions[d]	67 (59.8%)	68 (60.2%)	135 (60.0%)
> 10 lesions	45 (40.2%)	45 (39.8%)	90 (40.0%)
LDH at study entry (Enzyme U/l)			
N	111	111	222
Mean (SD)	241.09(190.5)	337.90(473.8)	289.50 (363.5)
Median	197.00	204.00	201.50
Range	(98.0;1530.0)	(98.0;2959.0)	(98.0;2959.0)
BPI-SF pain score (item 3)			
0	57 (50.9%)	57 (50.4%)	114 (50.7%)
1 to 3	40 (35.7%)	51 (45.1%)	91 (40.4%)
> 3	15 (13.4%)	5 (4.4%)	20 (8.9%)
Mean (SD)	1.35 (1.976)	1.09 (1.573)	1.22 (1.786)
Median	0.00	0.00	0.00
Range	(0.0; 9.0)	(0.0; 10.0)	(0.0; 10.0)

Key: AAP=abiraterone acetate plus prednisone

[a]Subjects having multiple lesions within each category are counted only once in the category but may be represented on more than one category

[b]Includes lymph nodes not specified as pelvic or non-pelvic.

[c]prostate local recurrence/progression

[d]includes subjects with no bone lesion

The median duration of treatment in Cohort 1 was 13.8 months (12 months in placebo +AAP) and Cohort 3 was 5.4 months respectively at the time of CCO (08 October 2021) . Overall, 95.3% and 93.7% of patients received at least 3 cycles of treatment in Cohort 1 and Cohort 3.

Efficacy Endpoints:
The primary endpoint was radiographic progression free survival (rPFS) as determined by blinded independent central radiology (BICR) review per prostate cancer working group 3 (PCWG3) (for bone lesions) and Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1 (for soft tissue lesions). In patients with alterations in *BRCA*1 or *BRCA*2 genes (*BRCAm* subgroup), rPFS was formally statistically evaluated. Secondary statistically-planned efficacy outcome measures included time to cytotoxic chemotherapy (TCC), time to symptomatic progression (TSP), and overall survival (OS).

Study Results:

Treatment of *BRCA*-mutated mCRPC (MAGNITUDE)
In the *BRCAm* subgroup, a statistically significant and clinically meaningful improvement in rPFS was observed in the niraparib + AAP group, with a 47% reduction in the risk of radiographic progression or death compared with the placebo + AAP group (HR = 0.533; 95% CI: [0.361, 0.789], two-sided p = 0.0014) at interim analysis 1 (Clinical cut-off on 08 October 2021).

The rPFS efficacy was similar between the plasma circulating tumour DNA and tumour tissue DNA testing methods for the *BRCA*m subgroup.

Interim analyses for the secondary endpoints TCC (24% maturity), TSP (30% maturity) and OS (25% maturity) did not meet the pre-specified boundary for statistical significance (CCO on 08 October 2021). At the time of interim analysis 1, efficacy in Cohort 3 is immature. Efficacy results of the *BRCAm* subgroup of Cohort 1 are summarized in Table 8 and Figure 1.

Table 8: Efficacy Results from BRCAm mCRPC population in MAGNITUDE Cohort 1

Endpoints	Niraparib+AAP (N=113)	Placebo + AAP (N=112)
Radiographic Progression-free Survival by BICR		
Event of disease progression or death (%)	45 (39.8%)	64 (57.1%)
Median, months (95% CI)	16.56 (13.86, NE)	10.87 (8.31, 13.80)
Hazard Ratio (95% CI)	0.533 (0.361, 0.789)	
p-value	0.0014	
Time to initiation of Cytotoxic chemotherapy		
Event (%)	22 (19.5%)	33 (29.5%)
Median, months (95% CI)	NE (22.60, NE)	25.99 (20.73, NE)
Hazard Ratio (95% CI)	0.578 (0.332, 1.006)	
p-value[b]	0.0495	
Time to Symptomatic progression [c]		
Event (%)	29 (25.7%)	38 (33.9%)
Median, months (95% CI)	NE (20.53, NE)	19.84 (17.54, NE)
Hazard Ratio (95% CI)	0.683 (0.420, 1.111)	
p-value[b]	0.1224	

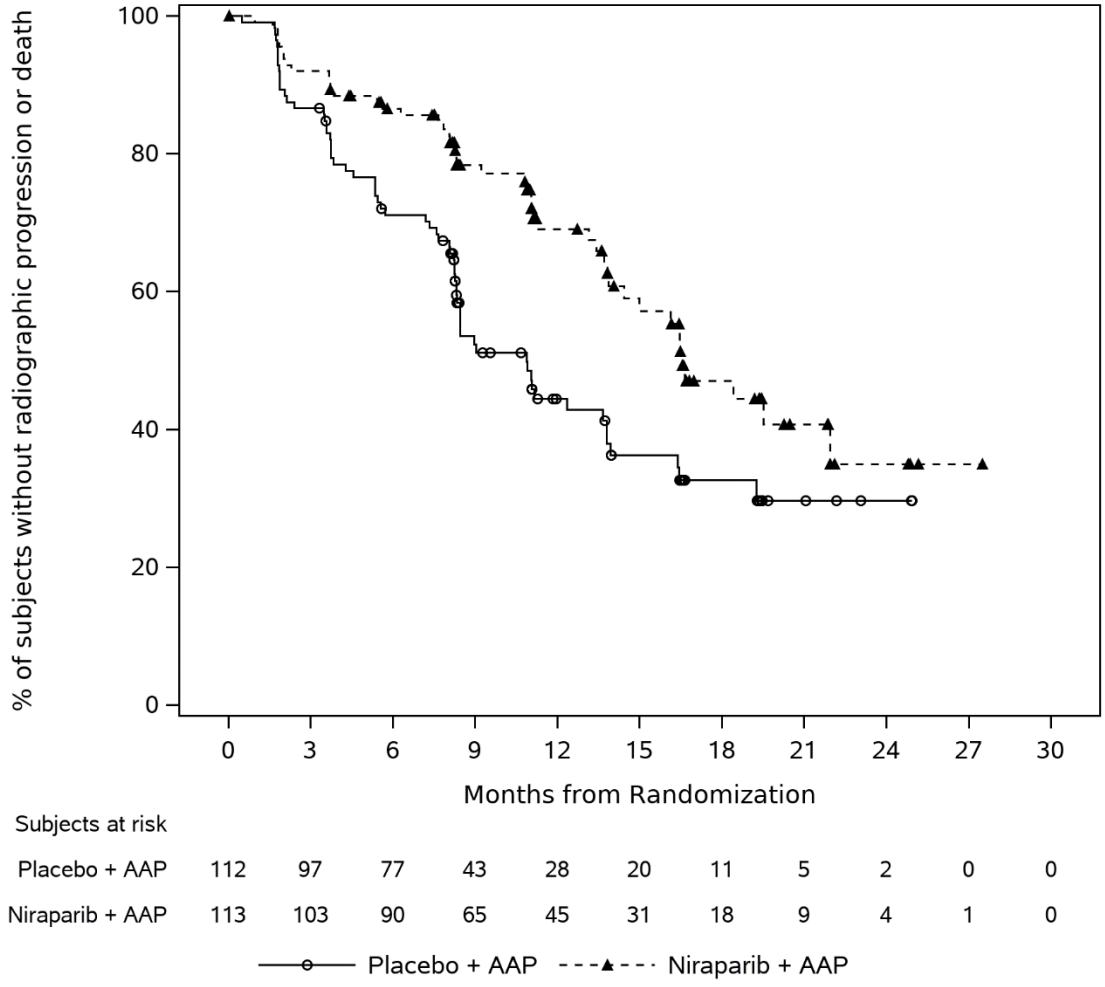
[a] CCO 08 October 2021
Note hazard ratio is estimated based on the stratified Cox's Proportional Hazards Model; p-value is from a stratified log-rank test.

[b] nominal p-value

[c] Time to Symptomatic progression was defined as the time from the date of randomization to the date of the first of any of the following:

- EBRT for skeletal symptoms.
- Tumor-related orthopedic surgical intervention.
- Other cancer-related procedures (e.g., nephrostomy insertion, bladder catheter insertion, EBRT, or surgery for tumor symptoms other than skeletal).
- Cancer-related morbid events (e.g., fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events).
- Initiation of a new systemic anti-cancer therapy because of cancer pain

Figure 1: Kaplan-Meier Plot of Radiographic Progression-free Survival by Central Review in *BRCA*m mCRPC patients in MAGNITUDE Cohort 1



Key: AAP = abiraterone acetate plus prednisone.

In exploratory subgroup analyses, treatment benefit in subjects with visceral metastases was uncertain due to the limited sample size. In Cohort 1, *BRCA* patients with visceral metastases (n=48), the rPFS HR= 1.02 [95% CI 0.50,2.06; the OS HR=2.3 [95% CI: 1.06, 5.1]. In the *BRCA* subgroup with visceral metastases, the median OS was 14 months in the niraparib+AAP arm

compared to 25 months in the placebo+AAP arm at interim analysis (IA) 2 (CCO on 17 Jun 2022). Subgroup analyses are summarized in Table 9.

Table 9: Exploratory subgroup analyses by visceral metastases status

		rPFS PA-IA1		OS IA2	
Subgroup (N) (%)	**Treatment group**	**N(events)**	**HR(95% CI)**	**N(events)**	**HR(95% CI)**
All *BRCA* (N=225)	Placebo+AAP	112(64)	0.533 (0.361,0.789)	112 (49)	0.881 (0.582,1.335)
	Niraparib+AAP	113(45)		113 (43)	
BRCA non-Visceral (N=177) (78.7%)	Placebo+AAP	90(51)	0.386 (0.238,0.626)	90(40)	0.534 (0.320,0.893)
	Niraparib+AAP	87(25)		87(23)	
BRCA Visceral (N=48) (21.3%)	Placebo+AAP	22(13)	1.020 (0.504,2.061)	22(9)	2.334 (1.059,5.143)
	Niraparib+AAP	26(20)		26(20)	

No benefit for treatment with niraparib+ AAP was observed in Cohort 2 patients without HRR gene alterations. The pre-planned futility analysis for Cohort 2 was performed on 13 August 2020, assessing data from 233 subjects with 113 composite progression events observed. With a HR=1.087 for the composite progression endpoint, futility was declared for this cohort.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Nonclinical studies with AKEEGA™ have not been performed. The nonclinical toxicology data are based on findings in studies with niraparib and abiraterone acetate individually. Aside from reproductive organ changes seen in all animal toxicology studies, nonclinical data reveal no special hazard for humans with AKEEGA™ based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

In vitro, niraparib bound to the dopamine transporter (DAT), norepinephrine transporter (NET) and serotonin transporter (SERT) and inhibited uptake of norepinephrine and dopamine in cells with IC50 values that were lower than the C_{min} at steady-state in patients receiving niraparib 300 mg once daily. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Niraparib has the potential to cause effects in patients related to inhibition of these transporters (e.g., cardiovascular or CNS).

In safety pharmacology studies, intravenous administration of niraparib to vagotomized dogs over 30 minutes at 1, 3 and 10 mg/kg resulted in an increased range of arterial pressures of 13-

20, 18-27 and 19-25% and increased range of heart rates of 2-11, 4-17 and 12-21% above pre-dose levels, respectively. The unbound plasma concentrations of niraparib in dogs at these dose levels were approximately 0.7, 2 and 8 times the unbound C_{max} at steady-state in patients receiving niraparib 300 mg once daily. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. In repeat-dose oral toxicity studies, niraparib was administered daily for up to 3 months' duration in rats and dogs. The major primary target organ for toxicity in rats and dogs was the bone marrow, with associated changes in peripheral hematology parameters. Additionally, decreased spermatogenesis was seen in both species. These findings occurred at exposure levels below those seen clinically and were reversible within 4 weeks of cessation of dosing.

In repeated dose toxicity studies in rats and monkeys with abiraterone acetate, circulating testosterone levels were significantly reduced at concentration levels of approximately one half the human clinical exposure. As a result, morphological and/or histopathological changes in the reproductive organs such as aspermia/hypospermia, atrophy/weight reductions in the male genital tract organs and testes, adrenal gland hypertrophy, Leydig cell hyperplasia, pituitary gland hyperplasia and mammary gland hyperplasia were observed. The changes in the reproductive organs and androgen sensitive organs are consistent with the pharmacology of abiraterone. All treatment related changes were partially or fully reversed after a four-week recovery period.

After chronic treatment from 13-weeks onward, bile duct/oval cell hyperplasia, associated with increased serum alkaline phosphatase and/or total bilirubin levels, was seen in rat and monkey livers. After a four-week recovery period, serum parameters reversed, whereas bile duct/oval cell hyperplasia persisted.

A dose dependent increase in cataracts was observed after 26-weeks of treatment in rats which were irreversible after a four-week recovery period.

Carcinogenicity:

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

Genotoxicity: Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an *in vitro* mammalian chromosomal aberration assay and in an *in vivo* rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans. Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests, including an *in vitro* bacterial reverse mutation assay (the Ames test), an *in vitro* mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay.

Reproductive and Developmental Toxicology:

Reproductive and developmental toxicity studies have not been conducted with niraparib. While no direct fertility studies were conducted with niraparib in animals, repeat dose toxicity studies in rats and dogs showed a reduction in spermatogenesis, small testes, and germ cell depletion in the testes and epididymides and these changes were largely reversible within four-weeks of cessation of dosing.

In fertility studies in rats with abiraterone acetate, reduced organ weights of reproductive system, sperm count, sperm motility, altered sperm morphology and reduced fertility were observed in male rats dosed for 4 weeks at ≥ 30 mg/kg/day. Mating of untreated female rats with males that received 30 mg/kg/day abiraterone acetate resulted in a reduced number of corpora lutea, implantations and live embryos and an increased incidence of pre-implantation loss. Female rats dosed for 2 weeks until day 7 of pregnancy at ≥ 30 mg/kg/day had an increased incidence of irregular or extended estrous cycles and preimplantation loss. These effects in male and female rats were completely reversible in 4 to 16 weeks after abiraterone acetate was stopped. The dose of 30 mg/kg/day in rats is approximately 0.3 times the recommended 1000 mg/day dose of abiraterone acetate based on body surface area.

In developmental toxicity study in rats, abiraterone acetate did not have teratogenic potential, however, abiraterone acetate caused developmental toxicity when administered at doses ≥10 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects), urogenital effects (bilateral ureter dilation), decreased fetal ano-genital distance, decreased fetal body weight. The doses tested in rats caused maternal toxicity at systemic exposures lower than the human exposure.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrAKEEGA™

Niraparib and abiraterone acetate tablets

Read this carefully before you start taking AKEEGA™ and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about AKEEGA™.

Serious Warnings and Precautions

- AKEEGA™ may cause **hypertension** (high blood pressure), **hypokalemia** (low blood potassium) and **peripheral edema** (swelling of the legs or hands caused by fluid retention). These will need to be treated before starting AKEEGA™. Your healthcare professional will do tests to check these problems monthly.
- Tell your healthcare professional if you have a history of heart failure, heart attack, or other heart problems. This will help avoid side effects and ensure proper use of AKEEGA™.
- If you have moderate to serious liver problems, you should not take AKEEGA™.
- Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) is a problem with the bone marrow. You may have low red, white, or platelet cell counts. This is serious and can lead to death.

What is AKEEGA™ used for?

For the following indication AKEEGA™ has been approved with conditions (NOC/c). This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to make sure the drug works the way it should. For more information, talk to your healthcare professional.

- AKEEGA™ is used with another medicine called prednisone or prednisolone. It is used to treat adult patients with prostate cancer that has spread to other parts of the body and no longer responds to medical or surgical treatment that lowers testosterone (known as metastatic castration resistant prostate cancer). These adults must also:
    - not currently be recommended to receive chemotherapy by their healthcare professional;
    - have mild or no symptoms; and
    - have alterations in *BRCA* genes

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How does AKEEGA™ work?

AKEEGA™ is a dual action medicine that contains two active substances: niraparib and abiraterone acetate.

Niraparib is a type of anti-cancer medicine called a PARP inhibitor. PARP inhibitors block an enzyme called poly [adenosine diphosphate-ribose] polymerase (PARP). PARP helps cells repair damaged DNA so blocking it means that the DNA of cancer cells cannot be repaired. This results in tumour cell death, helping to control the cancer.

Abiraterone acetate stops your body from making testosterone. This can slow the growth of prostate cancer as testosterone promotes cancer cell growth.

What are the ingredients in AKEEGA™?

Medicinal ingredients: niraparib (as niraparib tosylate), abiraterone acetate

Non-medicinal ingredients:

Colloidal anhydrous silica, crospovidone, glycerol monocaprylocaprate, hypromellose, iron oxide (E172), iron oxide red (E172), iron oxide yellow (E172), lactose monohydrate, magnesium stearate, polyvinyl alcohol, silicified microcrystalline cellulose, sodium lauryl sulfate, talc, titanium dioxide (E171)

AKEEGA™ comes in the following dosage forms:

tablets in the following strengths:

- **100 mg niraparib** (as niraparib tosylate) and **500 mg abiraterone acetate:** orange oval tablets, debossed with "N100 A" on one side and plain on the other side.
- **50 mg niraparib** (as niraparib tosylate)and **500 mg abiraterone acetate:** yellowish orange to yellowish brown oval tablets, debossed with "N 50 A" on one side and plain on the other side.

Both these strengths are available in bottles containing 60 tablets each.

Do not use AKEEGA™ if:

- you are allergic to niraparib or abiraterone acetate or any of the other ingredients of this medicine (see **What are the ingredients in AKEEGA™?**).
- you are a woman. AKEEGA™ is for use in male patients only.
- you have moderate or severe liver disease. Your healthcare professional will decide whether AKEEGA™ can be used if you have mild liver problems.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AKEEGA™. Talk about any health conditions or problems you may have, including if you:

- have low blood-cell count on testing. AKEEGA™ lowers your blood-cell counts, such as your red blood-cell count (anemia), white blood-cell count (neutropenia), or blood-platelet count (thrombocytopenia).

- have or have had high blood pressure or other heart or blood vessel problems. For example, heart failure, irregular or rapid heart rate, shortness of breath.
- have low blood potassium. Low blood potassium may increase the risk of heart rhythm problems.
- have gained weight rapidly, or have swelling in the feet, ankles, or legs.
- have liver problems.
- have low levels of sugar in the blood.
- have an intolerance to lactose. This is because AKEEGA™ contains lactose.
- are 75 years of age or older.

Other warnings you should know about:

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

High blood pressure (hypertension)

- AKEEGA™ may cause high blood pressure.
- To reduce the chance of developing high blood pressure, heart problems or low blood potassium, your healthcare professional will prescribe either prednisone or prednisolone. You need to take one of these drugs daily while you are taking AKEEGA™.
- You may also be advised by your healthcare professional to monitor your blood pressure at home. Your healthcare professional will give you instructions on when to contact them in case of a rise in blood pressure.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES is a rare neurological side effect. Cases of PRES has been reported with the niraparib component of AKEEGA™. Talk to your healthcare professional **right away** if you develop the following symptoms: headaches, vision changes, confusion, or seizure.

Low blood sugar (hypoglycemia)

- AKEEGA™ may affect your blood sugar levels if you have diabetes. Your blood sugar may drop if you take AKEEGA™ plus prednisone/prednisolone with some medicines for diabetes such as pioglitazone or repaglinide.
- Tell your healthcare professional if you take a medicine for diabetes and notice a drop in your blood sugar while monitoring your blood sugar.

Male patients

- During treatment with AKEEGA™, use a condom along with another effective birth control method each time you have sex with a woman who is pregnant, may be pregnant or could get pregnant. Continue using condom and another effective birth control method for 3 months after your last dose.
- If your sexual partner becomes pregnant or think they may be pregnant during your treatment with AKEEGA™, talk to your healthcare professional right away.
- Treatment with AKEEGA™ may affect your ability to have children. Talk to your healthcare professional if you have concerns about this.

Females

- AKEEGA™ is not for use in women.
- AKEEGA™ may harm an unborn baby.
- Women who are pregnant or may be pregnant should not handle AKEEGA™ without protective gloves.

Sensitivity to sunlight (photosensitivity)

- Photosensitivity was reported in patients treated with niraparib, a component of AKEEGA™.
- You should avoid sun exposure during treatment with AKEEGA™. When in the sunlight, wear a sunscreen with a high protection factor of at least SPF 15 and protective clothing.

Check-ups and testing

You will have regular visits with your healthcare professional, before, during and after treatment with AKEEGA™. They will:

- Do blood tests to check your blood cell count, liver enzyme levels, blood potassium levels.
- Check your blood pressure.
- Monitor for side effects of your treatment with AKEEGA™ and prednisone or prednisolone.

Driving and using machinery

AKEEGA™ may cause weakness, fatigue and dizziness. Before you drive or do tasks that require special attention, wait until you know how you respond to AKEEGA™.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements, or alternative medicines.

The following may interact with AKEEGA™:

- medicines typically used to treat epilepsy (seizures) such as phenytoin, carbamazepine, phenobarbital
- medicines to treat bacterial infections such as rifampicin, rifabutin
- an herbal treatment for depression called St. John's wort
- medicines to treat psoriasis, rheumatoid arthritis such as such as ciclosporin, tacrolimus, methotrexate
- medicines for pain such as alfentanil, ergotamine, codeine, oxycodone, and tramadol
- medicines for schizophrenia (mental disorder) such as pimozide, quetiapine, haloperidol, risperidol, or depression such as desipramine, venlafaxine,
- medicines for treating malaria such as halofantrine, clozapine,
- medicines used to treat asthma such as theophylline
- medicines used to treat parkinsons disease (progressive movement disorder) such as ropinirole,
- medicines used to treat high blood pressure such as metoprolol, propranolol, or abnormal heart rhythm such as propafenone, flecainide, or for high cholesterol such as rosuvastatin, simvastatin, atorvastatin, and methotrexate
- medicines used to treat diabetes, such as pioglitazone, repaglinide and metformin
- medicines used in cancer treatment such as irinotecan, radiotherapy

You should not start or stop any medicine before you talk with the healthcare professional that prescribed AKEEGA™.

How to take AKEEGA™:

- Take AKEEGA™ exactly as your healthcare provider tells you.
- Take your prescribed dose of AKEEGA™ once a day.
- **Take AKEEGA™ on an empty stomach.** Do NOT eat food at least two hours before taking AKEEGA™ and at least one hour after taking AKEEGA™. Taking AKEEGA™ with food causes more of this medicine to be absorbed by the body than is needed and this may cause side effects.
- Swallow AKEEGA™ tablets whole with water. Do NOT break, crush, or chew the tablets.
- Do NOT stop taking your prescribed dose of AKEEGA™ without talking to your healthcare professional first.
- AKEEGA™ is taken with a medicine called prednisone or prednisolone. Take the prednisone or prednisolone exactly as your healthcare professional tells you. They will tell you how much of this medicine to take and how to take it.
- You must also start or continue a gonadotropin-releasing hormone (GnRH) analog therapy during your treatment with AKEEGA™ unless you had surgical castration. This is a surgery to remove your testicles to lower the amount of testosterone in your body.

Usual dose:

Recommended adult dose: 200 mg niraparib and 1000 mg abiraterone acetate. To make this dose, take two 100 mg / 500 mg tablets.

Your healthcare professional may change your dose, temporarily stop or completely stop treatment with AKEEGA™. This may happen if you have certain side effects while taking AKEEGA™.

Overdose:

If you think you, or a person you are caring for, have taken too much AKEEGA™, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose of AKEEGA™, prednisone or prednisolone, take your normal dose as soon as possible on the same day. Return to your normal daily dose and normal daily schedule on the following day. DO NOT take extra tablets to make up the missed dose.

What are possible side effects from using AKEEGA™?

These are not all the possible side effects you may have when taking AKEEGA™. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- Decreased appetite
- Difficulty sleeping
- Feeling dizzy
- Constipation
- Shortness of breath

- Nausea and vomiting
- Joint pain
- Feeling weak and very tired
- Increased sensitivity to the sun

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON			
Anemia (low red blood cells): Being short of breath, feeling very tired, having pale skin, loss of energy or extreme weakness, fast heartbeat.		✓	
Hypertension (high blood pressure): shortness of breath, fatigue, dizziness or fainting, chest pain or pressure, swelling in your ankles and legs, bluish colour to your lips and skin, racing pulse or heart palpitations	✓		
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself -- these may be signs of a low blood platelet count.		✓	
Neutropenia or Leukopenia (low white blood cells): Fever or infection, chills, aches and pain and flu-like symptoms. Some infections can be serious and may lead to death.		✓	
Hypokalemia (low level of potassium in the blood): Muscle weakness, muscle twitches or a pounding heartbeat, cramping, constipation, fatigue, tingling or numbness.			✓
COMMON			
Palpitations (Fast, irregular heartbeats)		✓	
Urinary tract infection (infection in urinary system including kidneys, ureters, bladder, and urethra): Burning or pain during urination, frequent urination, blood in urine, pain in the pelvis, strong smelling urine, cloudy urine.		✓	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thromboembolism (blood clot in a vein or artery)**:** pain or tenderness or swelling in your arm or leg, skin that is red or warm, coldness, tingling or numbness, pale skin, muscle pain or spasms, weakness		✓	
UNCOMMON			
Arrhythmias, including QT prolongation and Torsades de Pointes (irregular heart-beat disorders): associated with feeling faint, lightheaded, chest pain, a racing heartbeat, a slow heartbeat, shortness of breath, sweating, or a fluttering in your chest.		✓	
VERY RARE			
Hypoglycemia (low blood sugar): Thirst, frequent urination, hunger, nausea and dizziness, fast heartbeat, tingling trembling, nervousness, sweating, low energy (low blood sugar)		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

- Store AKEEGA™ tablets at room temperature at 15–30°C in original container.
- Keep out of reach and sight of children.
- Do not use after the expiry date which is stated on the label. The expiry date refers to the last day of the month.
  Do not throw away any drugs via wastewater or household waste. Ask your pharmacist how to throw away drugs you no longer use.

If you want more information about AKEEGA™:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website : www.janssen.com/canada, or contact the manufacturer, Janssen Inc., at: 1-800-567-3331 or 1-800-387-8781.

This leaflet was prepared by

Janssen Inc., Toronto, Ontario M3C 1L9

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