PRODUCT NAME

AKEEGA® (niraparib/abiraterone acetate) film-coated tablets

DOSAGE FORMS AND STRENGTHS

AKEEGA® (100 mg niraparib/500 mg abiraterone acetate) film-coated tablets

Orange, oval, film-coated tablets (22 mm x 11 mm), debossed with "N 100 A" on one side, and plain on the other side.

AKEEGA® (50 mg niraparib/500 mg abiraterone acetate) film-coated tablets

Yellowish orange to yellowish brown, oval, film-coated tablets (22 mm x 11 mm), debossed with "N 50 A" on one side, and plain on the other side.

For excipients, see *Pharmaceutical Information - List of Excipients*.

CLINICAL INFORMATION

Indication

AKEEGA®, the combination of niraparib and abiraterone acetate with prednisone or prednisolone, is indicated as treatment for adults with metastatic castration-resistant prostate cancer (mCRPC) and BReast CAncer (BRCA) gene mutations (germline and/or somatic), in whom chemotherapy is not clinically indicated.

Dosage and Administration

AKEEGA® is a dual action combination of niraparib, a PARP inhibitor, and abiraterone acetate, a CYP17 inhibitor.

When considering the use of AKEEGA®, positive BRCA status must be established using a validated test method (see *Pharmacodynamic effects - Clinical studies*).

Dosage

The recommended dosage of AKEEGA® is 200 mg niraparib/1000 mg abiraterone acetate (two 100 mg/500 mg tablets), as a single daily dose at approximately the same time every day. 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 *Pharmacokinetic Properties – Absorption)*.

Dosage of prednisone or prednisolone

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

Missed dose(s)

If a dose of either AKEEGA®, prednisone or prednisolone is missed, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra tablets must not be taken to make up for the missed dose.

Treatment withdrawal

Treatment should be continued until disease progression or unacceptable toxicity.

Dose modification

Non-hematologic adverse reactions
For patients who develop Grade ≥ 3 non-hematologic adverse reactions, treatment should be interrupted and appropriate medical management should be instituted (see *Warnings and Precautions*). Treatment with AKEEGA® should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline. 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.

Hematologic adverse reactions
For patients who develop a ≥ Grade 3 or intolerable hematological toxicity, dosing with AKEEGA® should be interrupted rather than discontinued, and supportive management considered. Permanently discontinue AKEEGA® if hematological toxicity has not returned to acceptable levels within 28 days of the dose interruption period. The dose adjustment recommendations for thrombocytopenia and neutropenia are listed in Table 1.

Table 1: Dose Adjustment Recommendations for Thrombocytopenia and Neutropenia

Grade 1	No change, consider weekly monitoring
Grade 2	At least weekly monitoring and consider withholding AKEEGA® until recovery to Grade 1 or baseline.[1] Resume AKEEGA® with recommendation of weekly monitoring for 28 days after restart.
Grade ≥ 3	Withhold AKEEGA® (and monitor at least weekly) until platelets and neutrophils recover to Grade 1 or baseline.[1] Then resume AKEEGA® or, if warranted, use two **lower strength** tablets (50 mg/500 mg). Weekly monitoring of blood counts is recommended for 28 days after restarting dose. When starting the lower strength dose, please refer to "*Recommended monitoring*" below for further information regarding liver function.
Second occurrence ≥ Grade 3	Withhold AKEEGA® and monitor at least weekly until platelets and/or neutrophils recover to Grade 1. Further treatment should restart with **two lower strength** tablets (50 mg/500 mg). Weekly monitoring is recommended for 28 days after resuming treatment with AKEEGA®. When starting the lower strength dose, please refer to "*Recommended monitoring*" below for further information regarding liver function. If patient was already on **lower strength** AKEEGA® tablet (50 mg/500 mg), consider treatment discontinuation.
Third occurrence ≥ Grade 3	Permanently discontinue treatment.

[1] During AKEEGA® treatment interruption, abiraterone acetate and prednisone or prednisolone may be considered by the physician and given to maintain daily dose of abiraterone acetate (see abiraterone acetate prescribing information).

Further dosing with AKEEGA® may be resumed only when toxicity due to thrombocytopenia and neutropenia is improved to Grade 1 or resolved to baseline. If warranted, treatment may resume at a lower strength of AKEEGA® 50 mg/500 mg (2 tablets). For the most common adverse reactions, see *Adverse Reactions*.

For Grade ≥ 3 anemia, AKEEGA® should be interrupted and supportive management provided until recovered to Grade ≤2. Dose reduction (two 50 mg/500 mg tablets) should be considered if anemia persists based on clinical judgment. The dose adjustment recommendations for anemia are listed in Table 2.

Table 2: 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 provide supportive management with monitoring at least weekly until recovered to Grade ≤ 2. Dose reduction [**two lower**

Table 2: Dose adjustment recommendations for anemia

	strength tablets (50 mg/500 mg)] should be considered if anemia persists based on clinical judgment. When starting the lower strength dose, please refer to "*Recommended monitoring*" below for further information regarding liver function.
Second occurrence ≥ Grade 3	Withhold AKEEGA®, provide supportive management and monitor at least weekly until recovered to Grade ≤ 2. Further treatment should restart with **two lower strength tablets (50 mg/500 mg).** Weekly monitoring is recommended for 28 days after resuming treatment with **AKEEGA®**. When starting the lower strength dose, please refer to "*Recommended monitoring*" below for further information regarding liver function. If patient was already on **lower strength AKEEGA® tablet (50 mg/500 mg),** consider treatment discontinuation.
Third occurrence ≥ Grade 3	Consider discontinuing treatment with AKEEGA® based on clinical judgment.

[1] During AKEEGA® treatment interruption, abiraterone acetate and prednisone or prednisolone may be considered by the physician and given to maintain daily dose of abiraterone acetate (see abiraterone acetate prescribing information).

Recommended monitoring

Complete blood counts should be obtained prior to starting treatment, weekly for the first month, every two weeks for the next two months, followed by monthly monitoring for the first year and then every other month for the remainder of treatment to monitor for clinically significant changes in any hematologic parameter (see *Warnings and Precautions*).

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 (see *Warnings and Precautions*). When starting the lower strength dose (two tablets) after dose interruption, liver function should be monitored every two weeks for six weeks due to risk of increased abiraterone exposure (see *Pharmacokinetic Properties*), before resuming regular monitoring.

Serum potassium should be monitored monthly for the first year and then every other month for the duration of treatment (see *Warnings and Precautions*). In patients with pre-existing hypokalemia or those that develop hypokalemia whilst being treated with AKEEGA®, consider maintaining the patient's potassium level at ≥ 4.0 mM.

Blood pressure monitoring should occur weekly for the first two months, monthly for the first year and then every other month for the duration of treatment. Fluid retention (weight gain, peripheral edema) and other signs and symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter, and abnormalities corrected (see *Warnings and Precautions*).

Special populations

Pediatrics (17 years of age and younger)

The safety and effectiveness of AKEEGA® in children have not been evaluated.

There is no relevant use of AKEEGA® in pediatric patients aged 17 years and younger.

Elderly (65 years of age and older)

No dose adjustment is necessary for elderly patients (see *Pharmacodynamic Properties – Clinical studies* and *Pharmacokinetic Properties – Special populations*).

Hepatic impairment

AKEEGA® must not be used in patients with moderate to severe hepatic impairment (see *Pharmacokinetic Properties – Special populations*).

Hepatotoxicity

For patients who develop ≥ Grade 3 hepatotoxicity (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases above 5 times the upper limit of normal [ULN]) or total bilirubin increases above 3 times the ULN, treatment with AKEEGA® should be interrupted and liver function closely monitored (see *Warnings and Precautions*).

If patients develop severe hepatotoxicity (ALT or AST 20 times the ULN) while on AKEEGA®, treatment should be permanently discontinued.

Permanently discontinue AKEEGA® for patients who develop a concurrent elevation of ALT greater than 3 times ULN and total bilirubin greater than 2 times ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation (see *Warnings and Precautions*).

Renal impairment

No dosage adjustment is necessary for patients with mild to moderate renal impairment. AKEEGA® should be used with caution in patients with severe renal impairment (see *Pharmacokinetic Properties – Special populations*).

Administration

The tablets must be taken as a single dose, once daily 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®. AKEEGA® tablets must be swallowed whole with water. Do not break, crush, or chew tablets.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in *Pharmaceutical Information*.

Women who are or may become pregnant (see *Pregnancy, Breast-feeding and Fertility - Pregnancy*).

Moderate or severe hepatic impairment (see *Dosage and Administration*, *Warnings and Precautions* and *Pharmacokinetic Properties – Special populations*).

Warnings and Precautions

Hematologic adverse reactions

Hematologic adverse reactions (thrombocytopenia, anemia and neutropenia) have been reported in patients treated with niraparib (see *Dosage and Administration*).

Testing complete blood counts weekly for the first month, every two weeks 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 to monitor for clinically significant changes in any hematologic parameter while on treatment (see *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® (see *Adverse Reactions*).

Myelodysplastic syndrome/acute myeloid leukemia (MDS/AML)

MDS/AML, including cases with fatal outcome, have been reported in ovarian cancer trials among patients who received 300 mg of niraparib (a component of AKEEGA®).

In MAGNITUDE, no cases of MDS/AML have been observed in patients treated with 200 mg of niraparib and 1000 mg of abiraterone acetate plus prednisone or prednisolone.

For suspected MDS/AML or prolonged hematological toxicities 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, and the patient should be treated appropriately.

Hypertension

AKEEGA® may cause hypertension and 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®.

AKEEGA® should be permanently discontinued in patients who develop treatment-related hypertensive crisis.

Hypokalemia, fluid retention, and cardiovascular adverse reactions due to mineralocorticoid excess

AKEEGA® may cause hypokalemia and fluid retention (see *Adverse Reactions*) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see *Pharmacodynamic Properties*). 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 (e.g., those on cardiac glycosides), or fluid retention (e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia), and those with severe renal impairment. QT prolongation has been observed in patients experiencing hypokalemia in association with AKEEGA® treatment. Hypokalemia and fluid retention should be corrected and controlled.

Before treating 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. Fluid retention (weight gain, peripheral edema) and other signs and symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter, and abnormalities corrected. AKEEGA® should be used with caution in patients with a history of cardiovascular disease.

Management of cardiac risk factors (including hypertension, dyslipidemia, and diabetes) should be optimized in patients receiving AKEEGA® and these patients should be monitored for signs and symptoms of cardiac disease.

Abiraterone acetate, a component of AKEEGA®, increases mineralocorticoid levels and carries a risk for cardiovascular events. Previous ADT exposure, as well as advanced age, are additional risks for cardiovascular morbidity and mortality. Mineralocorticoid excess may cause hypertension, hypokalemia, and fluid retention. The MAGNITUDE study excluded 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%. Patients with a history of cardiac failure should be clinically optimized and appropriate management of symptoms instituted. If there is a clinically significant decrease in cardiac function, consider discontinuation of AKEEGA®.

Hepatotoxicity and hepatic impairment

Marked increases in liver enzymes leading to treatment interruption or discontinuation occurred in clinical studies, although these were uncommon (see *Adverse Reactions*). 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 for the first year and then every other month for the duration of treatment. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum aminotransferases should be measured immediately. If at any time

the ALT or AST rises above 5 times the ULN or total bilirubin rises above 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 times the ULN and total bilirubin greater than 2 times the ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

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 AKEEGA® tablet (equivalent to 100 mg niraparib/500 mg abiraterone acetate) (see *Dosage and Administration*). For patients being re-treated, serum aminotransferases 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 (one tablet), treatment with AKEEGA® should be discontinued.

When starting the lower strength dose (two tablets) after dose interruption, liver function should be monitored every two weeks for six weeks due to risk of increased abiraterone exposure (see *Pharmacokinetic Properties*), before resuming regular monitoring.

If patients develop severe hepatotoxicity (ALT or AST 20 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.

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] greater than 3 times the ULN or Child-Pugh Class B or C). AKEEGA® must not be used in patients with moderate to severe hepatic impairment (see *Dosage and Administration*, *Contraindications* and *Pharmacokinetic Properties*).

Infections

In MAGNITUDE, severe infections including COVID-19 infections with fatal outcome occurred more frequently in patients treated with AKEEGA®. Patients should be monitored for signs and symptoms of infection. Severe infections may occur in absence of neutropenia and/or leukopenia.

Pulmonary embolism (PE)

Metastatic malignant disease is a known risk factor for PE. In MAGNITUDE, PE was reported with a higher frequency in patients treated with AKEEGA® compared to control. Patients with a prior history of PE or venous thrombosis may be more at risk of a further occurrence. Monitor patients for clinical signs and symptoms of PE. If clinical features of PE occur, patients should be evaluated promptly, followed by appropriate treatment.

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 300 mg niraparib (a component of AKEEGA®) as a monotherapy in the ovarian cancer population. In the MAGNITUDE study, among prostate cancer patients treated with 200 mg of niraparib and 1000 mg of abiraterone acetate plus prednisone or prednisolone, there were no PRES cases reported.

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

Hypoglycemia

Cases of hypoglycemia have been reported when abiraterone acetate (a component of AKEEGA®) plus prednisone or prednisolone was administered to patients with pre-existing diabetes receiving pioglitazone or repaglinide (metabolized by CYP2C8) (see *Interactions*); therefore, blood sugar should be monitored in patients with diabetes.

Corticosteroid withdrawal and coverage of stress situations

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 (see information above).

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.

Bone density

Decreased bone density may occur in men with metastatic advanced prostate cancer (castration resistant prostate cancer). The use of abiraterone acetate (a component of AKEEGA®) in combination with a glucocorticoid could increase this effect.

Increased fractures and mortality in combination with Radium Ra-223 Dichloride

Treatment with AKEEGA® in combination with Ra-223 is not recommended. An increased risk of fracture and a trend for increased mortality was observed in patients with asymptomatic or mildly symptomatic prostate cancer treated with abiraterone acetate plus prednisone or prednisolone in combination with Ra-223.

It is recommended that subsequent treatment with Ra-223 not be initiated for at least five days after the last administration of AKEEGA®, in combination with prednisone or prednisolone.

Use with chemotherapy

The safety and efficacy of concomitant use of AKEEGA® with cytotoxic chemotherapy has not been established (see *Pharmacological Properties – Clinical studies*).

Intolerance to excipients

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.

Interactions

Effect of food

Food effect studies with AKEEGA® have not been performed; however, such studies have been conducted with the individual active substances (niraparib and abiraterone acetate). Although food does not impact exposures of niraparib, administration of food significantly increases the absorption of abiraterone acetate. AKEEGA® must be taken at least two hours after eating and food must not be eaten for at least one hour after taking AKEEGA® (see *Dosage and Administration* and *Pharmacokinetic Properties –Absorption*).

Pharmacokinetic interactions

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

No formal drug interaction studies have been performed with niraparib.

In Vitro Studies
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 AKEEGA® is combined with active substances, the metabolism of which is CYP3A4-dependent and, notably, those having a narrow therapeutic range (e.g., ciclosporin, tacrolimus, alfentanil, ergotamine, pimozide, quetiapine, and halofantrine), because of the niraparib component.

Induction of CYPs: Neither niraparib nor M1 is a CYP3A4 inducer *in vitro*. Niraparib weakly induces CYP1A2 *in vitro*. Therefore, caution is recommended when AKEEGA® is combined with active substances, the metabolism of which is CYP1A2-dependent and, notably, those having a narrow therapeutic range (e.g., clozapine, theophylline, and ropinirole), because of the niraparib component.

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 IC50 = 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). Caution is recommended when AKEEGA® is combined with substrates of BCRP (irinotecan, rosuvastatin, simvastatin, atorvastatin, and methotrexate), because of the niraparib component.

Niraparib is an inhibitor of MATE-1 and -2 with IC50 of 0.18 μM and ≤ 0.14 μM, respectively. *In vitro*, niraparib weakly inhibits the organic cation transporter 1 (OCT1) with an IC50 = 34.4 μM. Caution is recommended when AKEEGA® is combined with active substances that undergo an uptake transport by OCT1 such as metformin, because of the niraparib component.

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 MRP2, but 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

In Vitro Studies

In vitro studies indicated that CYP3A4 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. *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.

Clinical Studies: Effects of Other Drugs on Abiraterone

Strong CYP3A4 Inducers: In a clinical pharmacokinetic interaction study of healthy subjects pretreated with a strong CYP3A4 inducer (rifampin, 600 mg daily for 6 days) followed by a single dose of abiraterone acetate 1000 mg, the mean plasma AUC∞ of abiraterone was decreased by 55%. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin,

rifabutin, rifapentine, phenobarbital, St. John's wort [*Hypericum perforatum*]) during treatment with AKEEGA® are to be avoided unless there is no therapeutic alternative.

Strong CYP3A4 Inhibitors: Co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Clinical Studies: Effects of Abiraterone on Other Drugs
CYP2D6 Substrates: The C_{max} and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively when dextromethorphan 30 mg was given with abiraterone acetate 1000 mg daily (plus prednisone 5 mg twice daily). The AUC for dextrorphan, the active metabolite of dextromethorphan, increased approximately 1.3-fold. Caution is advised when administering AKEEGA® with medicinal products activated by or metabolized by CYP2D6 (e.g., metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol), particularly with medicinal products that have a narrow therapeutic index because of the abiraterone acetate component. Dose reduction of medicinal products with a narrow therapeutic index that are metabolized by CYP2D6 should be considered.

CYP2C8 Substrates: The AUC of pioglitazone (CYP2C8 substrate) was increased by 46% when pioglitazone was given to healthy subjects 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 (e.g., pioglitazone and repaglinide), if used concomitantly with AKEEGA® because of the abiraterone acetate component.

Pharmacodynamic interactions

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.

Pregnancy, Breast-feeding and Fertility

Contraception

It is not known whether components of AKEEGA® or their metabolites are present in semen. During treatment and for four months after the last dose of AKEEGA®:

- A condom is required if the patient is engaged in sexual activity with a pregnant woman
- A condom is required along with another effective contraceptive method if the patient is engaged in sexual activity with a woman of childbearing potential.

Studies in animals have shown reproductive toxicity (see *Non-clinical Information – Reproductive Toxicology*).

Pregnancy

AKEEGA® is not for use in women.

There are no data from 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 *Non-clinical Information – Reproductive Toxicology*).

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant, should handle AKEEGA® tablets with protection, e.g., gloves.

Breast-feeding

AKEEGA® is not for use in 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 No*n-clinical Information – Reproductive Toxicology*).

Effects on Ability to Drive and Use Machines

Patients who take AKEEGA® may experience asthenia, fatigue, dizziness or difficulties concentrating. AKEEGA® may influence the ability to drive or use machines. Patients should use caution when driving or using machines.

Adverse Reactions

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of AKEEGA® based on the comprehensive assessment of the available adverse event information. A causal relationship with AKEEGA® cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials

of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The overall safety profile of AKEEGA® is based on data from a Phase 3, randomized, double-blind, placebo-controlled study, MAGNITUDE cohort 1 (BRCA positive subjects; N=113).

The most common adverse reactions of all grades, occurring in >10% of the 113 patients in the nirarparib plus AAP arm were anemia (48.7%), constipation (35.4%), hypertension (34.5%), nausea (32.7%), fatigue (27.4%), thrombocytopenia (23.9%), asthenia (20.4%), back pain (19.5%), decreased appetite (15%), vomiting (15.9%), neutropenia (15.9%), arthralgia (17.7%), lymphopenia (12.4%), urinary tract infection (12.4%), insomnia (11.5%), headache (12.4%), dyspnea (13.3%), cough (12.4%), abdominal pain (13.3%), peripheral edema (13.3%), hypokalemia (12.4%), and dizziness (10.6%). The most frequently observed Grade 3-4 adverse reactions were anemia (29.2%), hypertension (15%), thrombocytopenia (9.7%), neutropenia (7.1%), blood alkaline phosphatase increased (6.2%), and lymphopenia (5.3%).

Table 3 shows adverse reactions on the AKEEGA® arm in the MAGNITUDE study that occurred with a ≥ 1% absolute increase in frequency compared to placebo and abiraterone acetate plus prednisone (AAP) or were events of special interest. ARs are also listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1000 to < 1/100), and rare (≥ 1/10000 to < 1/1000). Within each frequency grouping, ARs are presented in order of decreasing frequency.

Table 3: Adverse Reactions in MAGNITUDE – Cohort 1 (BRCA population)

System/Organ Class		**AKEEGA®+ P N=113**			**Placebo+AAP N=112**		
Adverse Reaction	**Frequency Category[a]**	**All Grades %**	**Grade 3 %**	**Grade 4 %**	**All Grades %**	**Grade 3 %**	**Grade 4 %**
Infections and infestations							
Urinary tract infection	very common	12.4	2.7	0	8.9	0.9	0
Nasopharyngitis	common	2.7	0	0	3.6	0	0
Bronchitis	common	2.7	0	0	0	0	0
Conjunctivitis	common	1.8	0	0	0	0	0
Sepsis	uncommon	0.9	0	0.9	0	0	0
Blood and lymphatic system disorders							
Anemia	very common	48.7	26.5	2.7	25.9	8.9	0
Thrombocytopenia	very common	23.9	4.4	5.3	8.9	2.7	0
Neutropenia	very common	15.9	6.2	0.9	7.1	1.8	0.9

Lymphopenia	very common	12.4	4.4	0.9	2.7	1.8	0
Leukopenia	common	9.7	1.8	0	3.6	0.9	0
Metabolism and nutrition disorders							
Decreased appetite	very common	15.0	1.8	0	9.8	0	0
Hypokalemia	very common	12.4	4.4	0.9	9.8	5.4	0
Hypertriglyceridemia	common	2.7	0	0	0.9	0	0
Psychiatric disorders							
Insomnia	very common	11.5	0	0	5.4	0	0
Depression	common	3.5	0	0	1.8	0	0
Anxiety	common	1.8	0	0	3.6	0	0
Confusional state	uncommon	0.9	0	0	0.9	0	0
Nervous system disorders							
Headache	very common	12.4	0.9	0	9.8	0	0
Dizziness	very common	10.6	0	0	8.9	0	0
Cardiac disorders							
Palpitations	common	5.3	0	0	0	0	0
Atrial fibrillation	common	4.4	1.8	0	1.8	0	0
Tachycardia	common	1.8	0	0	0.9	0	0
Cardiac failure[b]	common	1.8	0.9	0.9	0	0	0
Myocardial infarction	uncommon	0.9	0	0.9	0	0	0
Vascular disorders							
Hypertension	very common	34.5	15.0	0	25.9	16.1	0
Respiratory, thoracic and mediastinal disorders							
Dyspnea	very common	13.3	0.9	0	7.1	1.8	0
Cough	very common	12.4	0	0	5.4	0	0
Pulmonary embolism	common	2.7	1.8	0	0.9	0.9	0
Pneumonitis	common	1.8	0	0	0	0	0
Gastrointestinal disorders							
Constipation	very common	35.4	0.9	0	20.5	0	0
Nausea	very common	32.7	0.9	0	20.5	0	0
Vomiting	very common	15.9	0.9	0	8.0	0.9	0
Abdominal pain[c]	very common	13.3	1.8	0	11.6	0.9	0
Dyspepsia	common	5.3	0	0	4.5	0	0
Dry mouth	common	4.4	0	0	1.8	0	0

Abdominal distention	common	3.5	0	0	0.9	0	0
Stomatitis	common	2.7	0	0	1.8	0	0
Hepatobiliary disorders							
Hepatic failure[d]	common	2.7	0.9	0	0	0	0
Skin and subcutaneous tissue disorders							
Rash[e]	common	3.5	0	0	5.4	0	0
Photosensitivity	uncommon	0.9	0	0	0	0	0
Musculoskeletal and connective tissue disorders							
Back pain	very common	19.5	2.7	0	24.1	1.8	0
Arthralgia	very common	17.7	0	0	9.8	2.7	0
Renal and urinary disorders							
Hematuria	common	8.8	2.7	0	8.0	1.8	0
General disorders and administration site conditions							
Fatigue	very common	27.4	4.4	0	21.4	3.6	0
Asthenia	very common	20.4	1.8	0	10.7	0	0
Edema peripheral	very common	13.3	0	0	8.0	0	0
Investigations							
Blood alkaline phosphatase increased	very common	12.4	5.3	0.9	9.8	3.6	0
Weight decreased	Very common	12.4	0.9	0	4.5	0.9	0
Blood creatinine increased	common	9.7	1.8	0	4.5	0	0.9
AST increased	common	6.2	1.8	0	10.7	1.8	0
ALT increased	common	6.2	0	0	9.8	3.6	0
Gamma-glutamyl transferase increased	common	1.8	0	0	0.9	0	0
Injury, poisoning and procedural complications							
Fractures[f]	common	6.2	1.8	0	8.9	1.8	0

[a] Adverse reaction frequencies presented are based on the placebo-controlled period of the clinical study
[b] Includes cardiac failure congestive, cor pulmonale, left ventricular dysfunction
[c] Includes abdominal pain upper, abdominal pain lower
[d] Includes hepatic cytolysis, hepatotoxicity, hepatic failure
[e] Includes rash, erythema, dermatitis, rash maculo-papular, rash pruritic
[f] Includes osteoporosis and osteoporosis-related fractures

Hematological toxicities

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

In the MAGNITUDE study and other AKEEGA® studies, the following hematologic parameters were inclusion criteria: absolute neutrophil count (ANC) ≥ 1500 cells/μL; platelets ≥ 100000 cells/μL and hemoglobin ≥ 9 g/dL. Hematological adverse reactions were managed with laboratory monitoring and dose modifications (see *Dosage and Administration* and *Warnings and Precautions*).

Anemia

Anemia was the most frequent adverse reaction (52%) and most commonly observed Grade 3-4 event (30.7%) in the MAGNITUDE study. Anemia occurred early during the course of therapy (median time to onset of 64 days) In the MAGNITUDE study, dose interruptions occurred in 24.1% and dose reductions in 13.7% of patients. Twenty-seven percent of patients received at least one anemia-related red blood cell transfusion. Anemia caused discontinuation in a small number of patients (2.8%).

Thrombocytopenia

In the MAGNITUDE study, 24.1% of treated patients reported thrombocytopenia, while 8.5% of patients experienced Grade 3-4 thrombocytopenia. Median time from first dose to first onset was 71 days. In the MAGNITUDE study, thrombocytopenia was managed with dose modification (interruption 11.3% and reduction in 2.8%) and platelet transfusion (3.8%), where appropriate (see *Dosage and Administration*). Discontinuation occurred in 0.5% of patients. In the MAGNITUDE study, 1.9% of patients experienced a concurrent bleeding event.

Neutropenia

In the MAGNITUDE study, 16.0% 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 65 days. Neutropenia led to treatment interruption in 6.6% of patients and dose reduction in 1.4%. There were no treatment discontinuations due to neutropenia. In the MAGNITUDE study, 0.9% of patients had a concurrent infection.

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 studies. Hypertension was reported in 34.0% of patients, of whom 16.5% had Grade ≥ 3. The median time to onset of hypertension was 60.5 days. Hypertension was managed with adjunctive medicinal products.

Patients should have blood pressure controlled before initiating AKEEGA® and blood pressure should be monitored during treatment (see *Warnings and Precautions*).

Cardiac events

In the MAGNITUDE study, the most frequent major adverse cardiovascular event [MACE (Ischemic Heart Disease, Cardiac Failure)] was ischemic heart disease (5.2%). Cardiac failure was also reported in 2.8% of patients.

Additionally, arryhthmias were reported in 13.2% of patients. These were mainly low grade events of palpitations, tachycardias and atrial arrhythmias.

Hepatotoxicity

Hepatotoxicity had been recognized as important identified risk for abiraterone acetate, a component of AKEEGA®. The mechanism for hepatotoxicity of abiraterone acetate is not fully understood. 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 and all combination clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with baseline hepatitis or significant abnormalities of liver function tests (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 similar in the AKEEGA® (14.2%) and placebo plus AAP (12.8%) arms (see *Dosage and Administration* and *Warnings and Precautions*). The majority of these events were low grade serum aminotransferase elevations. 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 also 1.4%. The median time to onset of hepatotoxicity in the MAGNITUDE study was 43 days. Hepatotoxicity was managed with dose interruptions in 1.9% and dose reduction in 0.9% of patients. In the MAGNITUDE study, treatment was discontinued in 0.9% of patients due to hepatotoxicity.

Serum aminotransferases 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. Abnormal liver function tests developing in patients treated with AKEEGA® should be vigorously managed with treatment interruption. Treatment should resume only after return of liver function tests to the patient's baseline. (see *Dosage and Administration*). Treatment in patients with elevations of ALT or AST > 20 x ULN should be permanently discontinued. Treatment in patients who develop a concurrent elevation of ALT >3 x ULN and a total bilirubin >2 x ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation should be permanently discontinued.

Overdose

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, including monitoring for arrhythmias, hypokalemia and for signs and symptoms of fluid retention. Liver function should also be assessed.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: antineoplastic agents, other antineoplastic agents, ATC code: L01XK52.

Mechanism of action

AKEEGA® is a combination of niraparib, a PARP inhibitor, and abiraterone acetate (a prodrug of abiraterone), a CYP17 inhibitor, targeting two oncogenic dependencies in patients with mCRPC and HRR gene alterations.

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 BRCA2 wild-type VCaP model and the BRCA2 mutant LuCaP 96 model.

Niraparib and other PARP inhibitors have been studied in both patients and preclinical models with deficiencies in HR genes including BRCA1, ATM, BRIP1, PALB2, HDAC2, CHEK2, FANCA, CDK12 and others. Mutations in these genes were demonstrated to sensitize tumors of various histologies to PARP inhibition.

Niraparib

Niraparib is an inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, PARP-1 and PARP-2, which play a role in DNA repair. *In vitro* studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death.

Abiraterone acetate

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

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with LHRH analogues 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 LHRH analogues (or orchiectomy).

Pharmacodynamic effects

As AKEEGA® contains niraparib and abiraterone acetate, the pharmacodynamic effects of each component should be considered.

Niraparib

When tested as an individual active substance in BRCA2-deficient prostate patient-derived xenograft (PDX) models (LuCaP96 and LuCaP174.1), niraparib demonstrated efficacy as measured by both tumor growth inhibition and survival.

Abiraterone acetate

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH analogues alone or by orchiectomy. This results from the selective inhibition of the CYP17 enzyme required for androgen biosynthesis. PSA serves as a biomarker in patients with prostate cancer. In a Phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 38% of patients treated with abiraterone acetate, versus 10% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Use of Spironolactone

Patients in pivotal clinical trials with abiraterone acetate were not allowed to use spironolactone, as spironolactone binds to the androgen receptor and may increase PSA levels.

Clinical studies

The efficacy of AKEEGA® was established in a randomized placebo-controlled multicenter Phase 3 clinical study of patients with mCRPC, MAGNITUDE (Study 64091742PCR3001).

MAGNITUDE was a Phase 3, randomized, double-blind, placebo-controlled, multicenter study that evaluated treatment with the combination of niraparib (200 mg) and abiraterone acetate (1000 mg) plus prednisone (10 mg) daily versus AAP standard of care in 423 patients with mCRPC and select HRR gene alterations. 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) and ongoing ADT, were eligible. Plasma, blood, and/or tumor tissue samples for all patients were tested by validated next generation sequencing tests to determine germline and/or somatic HRR mutation status. A summary of the individual gene alterations by treatment is provided in Table 4.

Table 4: Individual Gene Mutations by Treatment from the MAGNITUDE Study Cohort 1

	AKEEGA®+ P N=212 n (%)	**Placebo+AAP N=211 n (%)**
Single Alteration	183 (86)	180 (85.3)
BRCA2	86 (40.6)	89 (42.2)
BRCA1	12 (5.7)	4 (1.9)
ATM	43 (20.3)	42 (19.9)
CHEK2	18 (8.5)	20 (9.5)
CDK12	5 (2.4)	8 (3.8)
PALB2	8 (3.8)	4 (1.9)
FANCA	5 (2.4)	6 (2.8)
BRIP1	4 (1.9)	4 (1.9)
HDAC2	2 (0.9)	3 (1.4)
Co-Occurring Alterations[1]	29 (13.7)	31 (14.7)

[1] Patients (N=34) with co-occurring alterations with BRCA1 or BRCA2 were assigned to the BRCA strata

Efficacy data is based on the BRCA subgroup of Cohort 1 that consisted of 225 patients who were randomized (1:1) to receive either niraparib plus AAP (N=113) or placebo plus AAP (N=112) orally daily. Treatment was continued until disease progression, unacceptable toxicity, or death.

Table 5 summarizes the demographics and baseline characteristics of BRCA patients enrolled in Cohort 1 of the MAGNITUDE study. The median PSA at initial diagnosis was 41.07 ug/L (range 0.1-12080). All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry. All patients who had not received prior orchiectomy continued background androgen deprivation therapy with a GnRH analogue.

Table 5: Summary of demographics and baseline characteristics in the MAGNITUDE study Cohort 1 (BRCA)

	AKEEGA®+P N=113 n (%)	**Placebo+AAP N=112 n (%)**	**Total N=225 n (%)**
Age (years)			
< 65	39 (34.5)	37 (33.0)	76 (33.8)
≥ 65-74	44 (38.9)	52 (46.4)	96 (42.7)
≥ 75	30 (26.5)	23 (20.5)	53 (23.6)
Median	67.0	68.0	68.0
Range	45-100	43-88	43-100
Race			
Caucasian	78 (69.0)	84 (75.0)	162 (72.0)
Asian	18 (15.9)	20 (17.9)	38 (16.9)
Black	3 (2.7)	0	3 (1.3)
Unknown	14 (12.4)	8 (7.1)	22 (9.8)
Stratification factors			

Past taxane-based chemotherapy exposure	26 (23.0)	29 (25.9)	55 (24.4)
Past AR-targeted therapy exposure	6 (5.3)	5 (4.5)	11 (4.9)
Prior AAP use	30 (26.5)	29 (25.9)	59 (26.2)
Baseline disease characteristics			
Gleason score ≥ 8	83 (74.1)	72 (64.3)	155 (69.2)
Bone involvement	99 (87.6)	93 (83.0)	192 (85.3)
Visceral disease (liver, lung, adrenal gland, other)	26 (23.0)	22 (19.6)	48 (21.3)
Metastasis stage at initial diagnosis (M1)	70 (61.9)	50 (44.6)	120 (53.3)
Median time from initial diagnosis to randomization (years)	2.00	2.31	2.26
Median time from mCRPC to first dose (years)	0.27	0.28	0.27
BPI-SF pain score (last score before first dose) 0 1 to 3 > 3	 57 (50.4) 51 (45.1) 5 (4.4)	 57 (50.9) 40 (35.7) 15 (13.4)	 114 (50.7) 91 (40.4) 20 (8.9)
ECOG Performance Status Score 0 1	 69 (61.1) 44 (38.9)	 80 (71.4) 32 (28.6)	 149 (66.2) 76 (33.8)

The primary endpoint was radiographic progression free survival (rPFS) as determined by blinded independent central radiology (BICR) review based on Response Evaluation Criteria In Solid Tumours (RECIST) 1.1 (soft and tissue lesions) and Prostate Cancer Working Group-3 (PCWG-3) criteria (bone lesions). Time to symptomatic progression (TSP), time to cytotoxic chemotherapy (TCC), and overall survival (OS) were included as secondary efficacy endpoints.

Primary and key secondary efficacy results in the BRCA population of the MAGNITUDE study are summarized in Table 6 and Figures 1, 2, 3 and 4. There was a statistically significant improvement in BICR-assessed rPFS for niraparib plus AAP compared with AAP alone. The primary efficacy results are supported by benefit in key secondary endpoints of TSP and TCC in favor of the combination arm. Furthermore, at the final analysis, there was a trend toward improved OS with niraparib plus AAP. A pre-specified multivariate analysis for OS to adjust for imbalances in baseline prognostic factors showed improvement in OS with treatment with niraparib plus AAP.

Table 6: Efficacy results from the MAGNITUDE study Cohort 1 (BRCA)

Endpoints	AKEEGA®+P (N=113)	Placebo+AAP (N=112)
Radiographic Progression-free Survival[1]		
Event of disease progression or death (%)	45 (39.8%)	64 (57.1%)
Median, months (95% CI)	16.6 (13.9, NE)	10.9 (8.3, 13.8)
Hazard Ratio (95% CI)	0.533 (0.361, 0.789)	
p-value	0.0014	
Time to Symptomatic Progression[2]		
Event (%)	38 (33.6%)	58 (51.8%)
Median, months (95% CI)	NE (36.2, NE)	21.7 (17.6, 35.8)
Hazard Ratio (95% CI)	0.562 (0.371, 0.849)	
Nominal p-value	0.0056	
Time to Cytotoxic Chemotherapy[2]		
Event (%)	35 (31.0%)	51 (45.5%)
Median, months (95% CI)	NE (31.4, NE)	28.2 (20.7, NE)
Hazard Ratio (95% CI)	0.598 (0.387,0.924)	
Nominal p-value	0.0192	
Overall Survival[2]		
Hazard Ratio (95% CI)	0.788 (0.554,1.120)	
Nominal p-value	0.1828	
Overall Survival (multivariate analysis)[2]		
Hazard Ratio (95% CI)	0.663 (0.464,0.947)	
Nominal p-value	0.0237	

[1] Primary analysis

[2] Final analysis

NE = not estimable

Figure 1: Kaplan-Meier Plot of BICR Assessed Radiologic Progression-Free Survival (MAGNITUDE Cohort 1, BRCA, primary analysis)

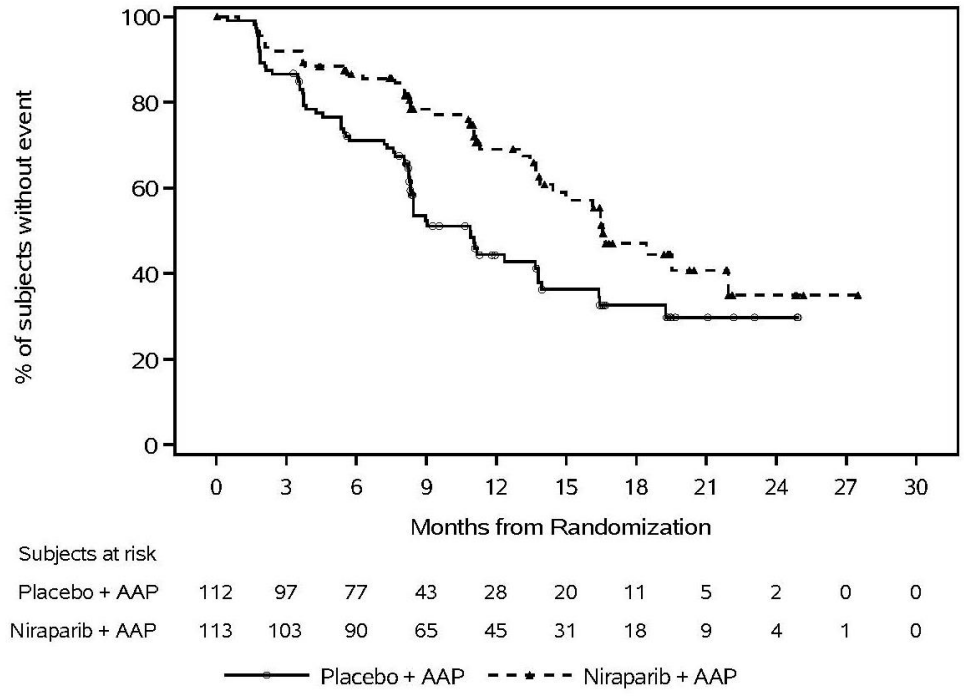


Figure 2: Kaplan-Meier Plot of Time to Symptomatic Progression (MAGNITUDE Cohort 1, BRCA, final analysis)

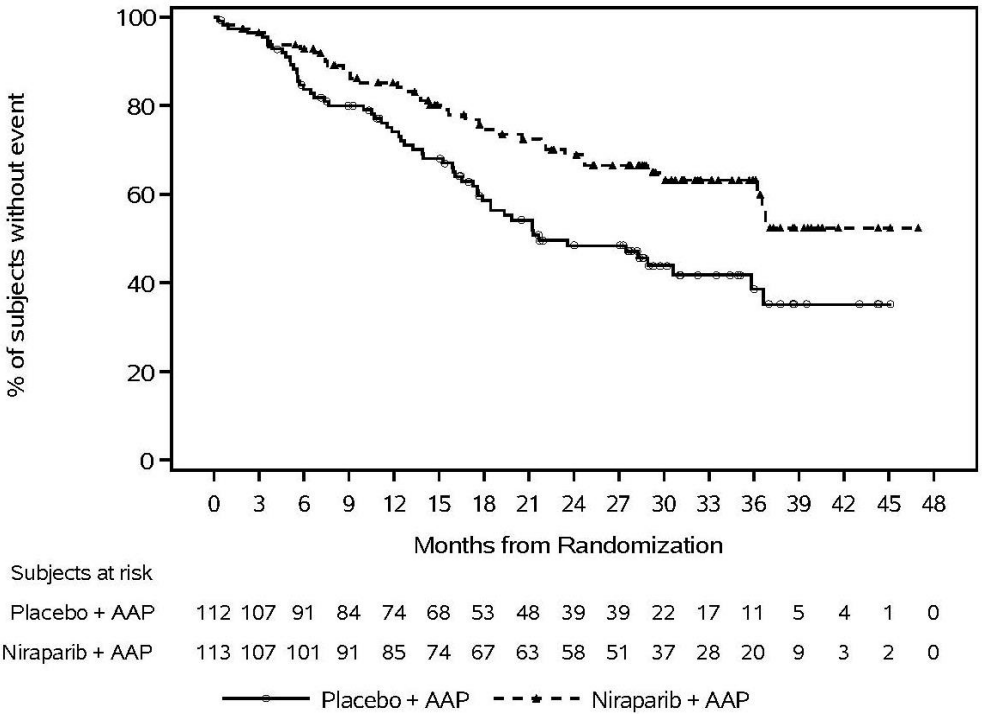


Figure 3: **Kaplan-Meier Plot of Initiation of Cytotoxic Chemotherapy (MAGNITUDE Cohort 1, BRCA, final analysis)**

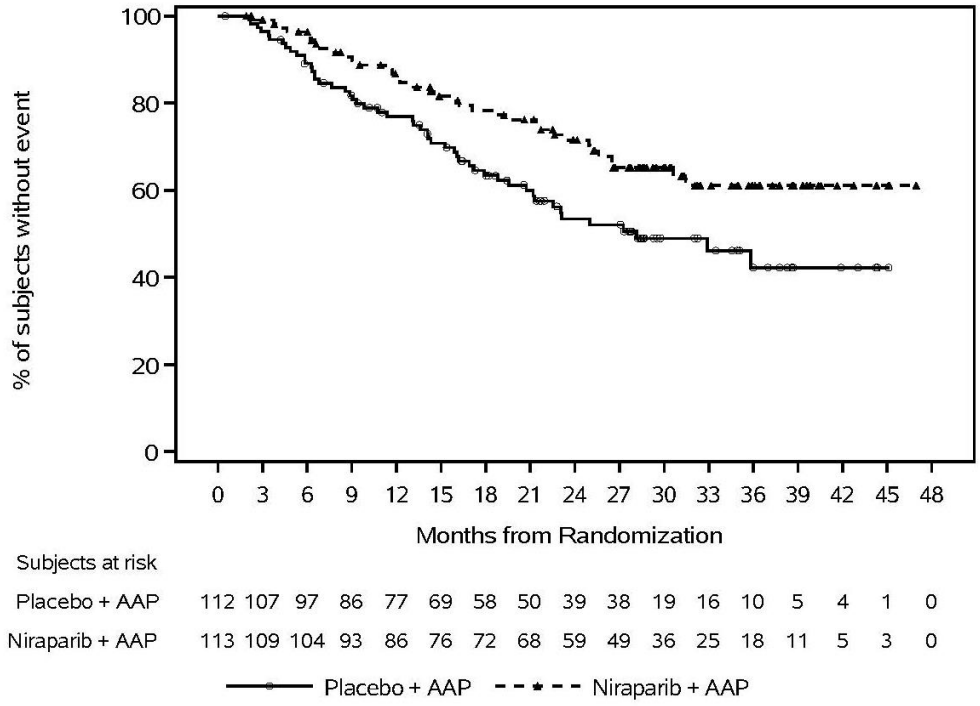
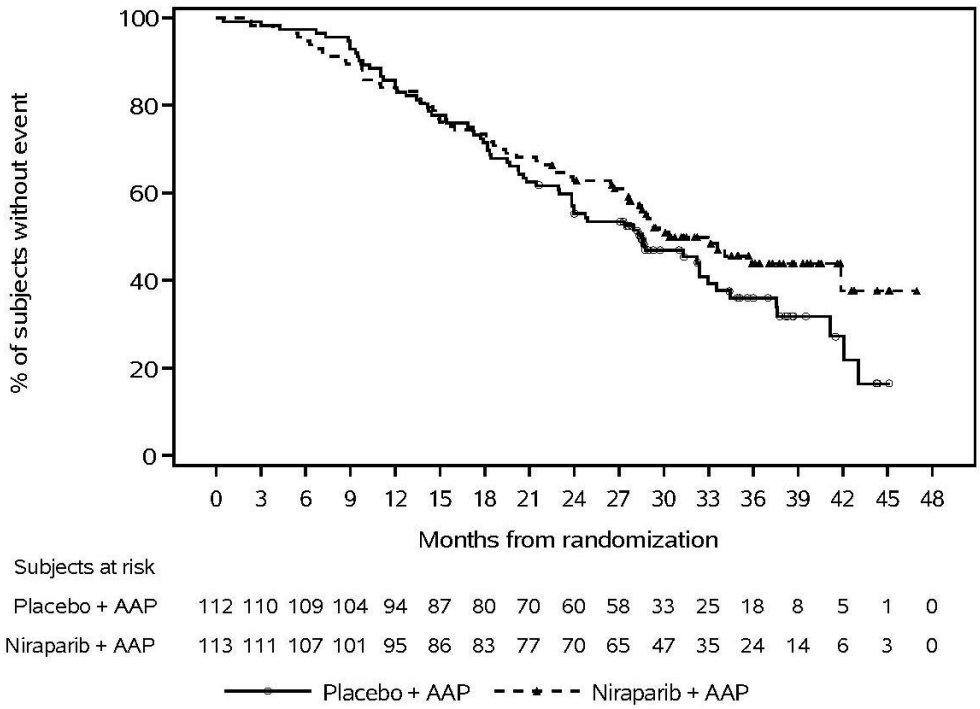


Figure 4: **Kaplan-Meier Plot of Overall Survival (MAGNITUDE Cohort 1, BRCA, final analysis)**



Pharmacokinetic Properties

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 AKEEGA® regular strength tablet (equivalent to 100 mg niraparib/500 mg abiraterone acetate) or as combination of individual components, when compared to respective monotherapy exposures.

Absorption

AKEEGA®

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

In a relative bioavailability study, the maximum (C_{max}) and total (AUC_{0-72h}) exposure of abiraterone in mCRPC patients (n=67) treated with AKEEGA® lower strength film-coated tablets (2 x 50 mg/500 mg) was 33% and 22% higher, respectively, when compared to exposures in patients (n=67) taking individual single agents (100 mg niraparib capsule and 4 x 250 mg abiraterone acetate tablets) (see *Dosage and Administration*). The inter-subject variability (%CV) in exposures were 80.4% and 72.9%, respectively. Niraparib exposure was comparable between AKEEGA® lower strength film-coated tablets and single agents.

Niraparib

The absolute bioavailability of niraparib is approximately 73%, indicating minimal first pass effect.

Abiraterone acetate

Abiraterone acetate is rapidly converted in vivo to abiraterone.

Food effect studies conducted during clinical development of abiraterone suggested that administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold (C_{max}) increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking abiraterone acetate with meals has the potential to result in highly variable exposures. Therefore, abiraterone acetate must not be taken with food.

Distribution

Based on population pharmacokinetic analysis, the apparent volume of distribution of niraparib and abiraterone were 1117 L and 25774 L, respectively, indicative of extensive extravascular distribution.

Niraparib

Niraparib was moderately protein-bound in human plasma (83 %), mainly with serum albumin.

Abiraterone acetate

The plasma protein binding of ^{14}C-abiraterone in human plasma is >99%.

Metabolism

Niraparib

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.

Abiraterone acetate

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, two main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represent approximately 43% of total radioactivity.

Elimination

AKEEGA®

The mean t½ of niraparib and abiraterone when given in combination were approximately 62 hours and 20 hours, respectively, and apparent CL/F of niraparib and abiraterone were 16.7 L/h and 1673 L/h, respectively, based on the population PK analysis in subjects with mCRPC.

Niraparib

Niraparib is eliminated primarily through the hepatobiliary and renal routes. Following an oral administration of a single 300 mg dose of [^{14}C]-niraparib, on average 86.2% (range 71% to 91%) of the dose was recovered in urine and feces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the feces for 38.8% (range 28.3% to 47.0%) of the dose. In pooled samples collected over six days, 40% of the dose was recovered in the urine primarily as metabolites and 31.6% of the dose was recovered in the feces, primarily as unchanged niraparib.

Abiraterone acetate

Following oral administration of ^{14}C-abiraterone acetate 1000 mg, approximately 88% of the radioactive dose is recovered in feces and approximately 5% in urine. The major compounds present in feces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Special populations

Hepatic impairment

Based on the population pharmacokinetic analysis of data from clinical studies where prostate cancer patients received niraparib alone or niraparib/AA 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-Pugh Class A and B, respectively) and in 8 healthy control subjects. Systemic exposure to abiraterone after a single oral 1000 mg dose increased approximately 1.11-fold and 3.6-fold in subjects with mild and moderate pre-existing hepatic impairment, respectively.

In another trial, the pharmacokinetics of abiraterone were examined in subjects with pre-existing severe (n = 8) hepatic impairment (Child-Pugh Class C) and in 8 healthy control subjects with normal hepatic function. The AUC to abiraterone increased by approximately 7-fold and the fraction of free drug increased by 2-fold in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

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

Renal impairment

No renal impairment study was done using AKEEGA®. Based on the population pharmacokinetic analysis of data from clinical studies where prostate cancer patients received niraparib alone or niraparib/AA in combination, patients with mild (CLcr: 60 to 90 mL/min, n=337) and moderate (CLcr: 30 to 60 mL/min, n=114) renal impairment had mildly reduced niraparib clearance compared to individuals with normal renal function (up to 13% higher exposure in mild and 13-40% higher exposure in moderate renal impairment).

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 1000 mg dose did not increase in subjects with end-stage renal disease on dialysis.

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

Weight, age and race/ethnicity

No clinically significant effects on the PK of niraparib and abiraterone were observed based on body weight (43.3-165 kg for niraparib and 46.0-165 kg for abiraterone), age (45-90 years for niraparib and 43-90 years for abiraterone) and race/ethnicity (White, Asian, and Hispanic).

Pediatric population

No studies have been conducted to investigate the pharmacokinetics of AKEEGA® in pediatric patients.

Effects on the QT interval

Niraparib

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

Abiraterone acetate

In a multi-center, open-label, single arm trial, 33 patients with metastatic CRPC received abiraterone acetate orally at a dose of 1000 mg once daily at least one hour before or two hours after a meal in combination with prednisone 5 mg orally twice daily. Assessments up to Cycle 2 Day 2 showed no large (> 20 ms) increases in the QTc interval from baseline. However, small increases in the QTc interval (i.e., < 10 ms) due to abiraterone acetate cannot be excluded.

NON-CLINICAL INFORMATION

Nonclinical studies with AKEEGA® have not been performed. The nonclinical toxicology data are based on findings in studies with niraparib and abiraterone acetate individually.

Carcinogenicity and Mutagenicity

Niraparib

Carcinogenicity studies have not been conducted with niraparib.

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

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. 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. Abiraterone acetate was not carcinogenic in female rats.

Reproductive Toxicology

Niraparib

Reproductive and developmental toxicity studies have not been conducted with niraparib.

Abiraterone acetate

In fertility studies in both male and female rats, abiraterone acetate reduced fertility, which was completely reversible in 4 to 16 weeks after abiraterone acetate was stopped.

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced fetal weight and survival. Effects on the external genitalia were observed though abiraterone acetate was not teratogenic.

In these fertility and developmental toxicity studies performed in the rat, all effects were related to the pharmacological activity of abiraterone.

Animal Toxicology and/or Pharmacology

Niraparib

In vitro, niraparib inhibited the dopamine transporter at concentration levels below human exposure levels. In mice, single doses of niraparib increased intracellular levels of dopamine and metabolites in cortex. Reduced locomotor activity was seen in one of two single dose studies in mice. The clinical relevance of these findings is not known. No effect on behavioral and/or neurological parameters have been observed in repeat-dose toxicity studies in rats and dogs at estimated CNS exposure levels similar to or below expected therapeutic exposure levels.

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 observed in both species. These findings occurred at exposure levels below those seen clinically, and were largely reversible within four weeks of cessation of dosing.

Abiraterone acetate

In animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-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 4-week recovery period, serum parameters reversed, whereas bile duct/oval cell hyperplasia persisted.

Cataracts were seen in rats after 26 weeks of treatment. These changes were still present after a 4-week recovery period. Cataracts were not seen in monkeys after 39 weeks of treatment.

PHARMACEUTICAL INFORMATION

List of Excipients

100 mg/500 mg

Tablet core

Colloidal anhydrous silica

Crospovidone

Hypromellose

Lactose monohydrate

Magnesium stearate

Silicified microcrystalline cellulose

Sodium lauryl sulfate

Film-coating

Iron oxide red (E172)

Iron oxide yellow (E172)

Sodium lauryl sulphate

Glycerol monocaprylocaprate

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

50 mg/500 mg

Tablet core

Colloidal anhydrous silica

Crospovidone

Hypromellose

Lactose monohydrate

Magnesium stearate

Silicified microcrystalline cellulose

Sodium lauryl sulfate

Film-coating

Iron oxide black (E172)

Iron oxide red (E172)

Iron oxide yellow (E172)

Sodium lauryl sulphate

Glycerol monocaprylocaprate

Polyvinyl alcohol

Talc

Titanium dioxide (E171)

Incompatibilities

Not applicable.

Shelf Life

See expiry date on the outer pack.

Storage Conditions

Store at or below 30°C.

Keep out of sight and reach of children.

Nature and Contents of Container

AKEEGA® is available in a PVdC/PE/PVC film blister with an aluminum push through foil sealed inside a cardboard wallet.

- Each 28-day carton contains 56 film-coated tablets in two cardboard wallet packs of 28 film-coated tablets each.

Instructions for Use and Handling and Disposal

Based on its mechanism of action, this medicinal product may harm a developing fetus; therefore, women who are or may become pregnant should handle AKEEGA® tablets with protection, e.g., gloves (see *Pregnancy, Breast-feeding and Fertility – Pregnancy*).

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

BATCH RELEASER

Janssen Cilag S.P.A
Via C. Janssen
(loc. Borgo San Michele)
04100 Latina
Italy

PRODUCT REGISTRANT

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