1. NAME OF THE MEDICINAL PRODUCT

Akeega 50 /500
Akeega 100 /500

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Akeega 50/500
Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 50 mg of niraparib and 500 mg of abiraterone acetate equivalent to 446 mg of abiraterone.

Akeega 100/500
Each film-coated tablet contains niraparib tosylate monohydrate equivalent to 100 mg of niraparib and 500 mg of abiraterone acetate equivalent to 446 mg of abiraterone.

Excipients with known effect
Each film-coated tablet contains 241 mg of lactose (see section 4.4)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Akeega 50 /500
Yellowish orange to yellowish brown, oval, film-coated tablets debossed with “N 50 A” on one side, and plain on the other side.

Akeega 100 /500
Orange, oval, film-coated tablets debossed with “N 100 A” on one side, and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

4.2 Posology and method of administration

Treatment with Akeega plus prednisone or prednisolone should be initiated and supervised by specialist physicians experienced in the medical treatment of prostate cancer.

Before initiation of Akeega therapy, positive BRCA status must be established using a validated test method (see section 5.1).

Posology
The recommended starting dose of Akeega is 200 mg/1000 mg (two 100 mg niraparib/500 mg abiraterone acetate tablets), as a single daily dose at approximately the same time every day (see “Method of administration” below). The 50 mg/500 mg tablet is available for dose reduction.

Medical castration with a gonadotropin-releasing hormone (GnRH) analogue should be continued during treatment in patients not surgically castrated.

Dosage of prednisone or prednisolone
Akeega is used with 10 mg prednisone or prednisolone daily.

Duration of treatment
Patients should be treated until disease progression or unacceptable toxicity.

Missed dose
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.

Dose adjustments for adverse reactions
Non-haematological adverse reactions
For patients who develop Grade ≥ 3 non-haematological adverse reactions, treatment should be interrupted and appropriate medical management should be instituted (see section 4.4). Treatment with Akeega should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline.

Haematological adverse reactions
For patients who develop a ≥ Grade 3 or intolerable haematological toxicity, dosing with Akeega should be interrupted rather than discontinued and supportive management considered. Akeega should be permanently discontinued if haematological 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 restarting dose.
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 or starting the **lower strength** dose (two 50 mg/500 mg tablets). 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 **lower strength Akeega**. When starting the **lower strength** dose (two 50 mg/500 mg tablets), 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. Treatment may resume at a lower strength of Akeega 50 /500 (2 tablets). For the most common adverse reactions, see section 4.8.

For Grade ≥ 3 anaemia, 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 anaemia persists based on clinical judgment. The dose adjustment recommendations for anaemia are listed in Table 2.

Table 2: Dose adjustment recommendations for anaemia

Grade 1	No change, consider weekly monitoring.
Grade 2	At least weekly monitoring for 28 days, if baseline anaemia 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 strength tablets (50 mg/500 mg)**] should be considered if anaemia 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 **lower strength 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).

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 (see section 4.4).

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/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.

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 Í ULN, and total bilirubin greater than 2 Í ULN, in the absence of biliary obstruction or other causes responsible for the concurrent elevation (see section 4.4).

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 haematologic parameter (see section 4.4).

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. 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 section 5.2), 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 section 4.4).

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.

In patients with pre-existing hypokalaemia or those that develop hypokalaemia whilst being treated with Akeega, consider maintaining the patient's potassium level at ≥ 4.0 mM.

Special populations
Elderly
No dose adjustment is necessary for elderly patients (see section 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with pre-existing mild hepatic impairment (Child-Pugh Class A). There are no data on the clinical safety and efficacy of multiple doses of Akeega when administered to patients with moderate or severe hepatic impairment (Child-Pugh Class B or C). No dose adjustment can be predicted. The use of Akeega should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.4 and 5.2). Akeega is contraindicated in patients with severe hepatic impairment (see sections 4.3, 4.4 and 5.2).

Renal impairment
No dose adjustment is necessary for patients with mild to moderate renal impairment, although close monitoring of safety events should be conducted with moderate renal impairment due to the potential for increased niraparib exposure. There are no data on the use of Akeega in patients with severe renal impairment or end stage renal disease undergoing haemodialysis, Akeega may only be used in patients with severe renal impairment if the benefit outweighs the potential risk, and the patient should be carefully monitored for renal function and adverse events (see sections 4.4 and 5.2).

Paediatric population
There is no relevant use of Akeega in the paediatric population.

Method of administration
Akeega is for oral use.
The tablets must be taken as a single dose, once daily. Akeega should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal (see section 5.2). For optimal absorption, Akeega tablets must be swallowed whole with water, they must not be broken, crushed, or chewed.

Precaution to be taken before manipulating or administering the product
Women who are or may become pregnant should wear gloves when handling the tablets (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see section 4.6).

Severe hepatic impairment [Child-Pugh Class C (see sections 4.2, 4.4 and 5.2)].

Akeega plus prednisone or prednisolone is contraindicated in combination with Ra-223 treatment.

4.4 Special warnings and precautions for use

Haematological adverse reactions
Haematological adverse reactions (thrombocytopenia, anaemia and neutropenia) have been reported in patients treated with Akeega (see section 4.2).

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 haematological parameter while on treatment (see section 4.2).

Based on individual laboratory values, weekly monitoring for the second month may be warranted.

If a patient develops severe persistent haematological 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 section 4.8).

When starting the lower strength dose (two tablets) after dose interruption due to haematological adverse reactions, liver function should be monitored every two weeks for six weeks due to risk of increased abiraterone exposure (see section 5.2), before resuming regular monitoring (see section 4.2).

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, monitored monthly afterwards for the first year and every other month thereafter during treatment with Akeega.

Hypokalaemia, fluid retention, & cardiovascular adverse reactions due to mineralocorticoid excess
Akeega may cause hypokalaemia and fluid retention (see section 4.8) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see section 5.1). 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 hypokalaemia (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 hypokalaemia in association with Akeega treatment. Hypokalaemia 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 ischaemic heart disease), cardiac failure should be treated and cardiac

function optimised. Fluid retention (weight gain, peripheral oedema), 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, dyslipidaemia, and diabetes) should be optimised 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. Mineralocorticoid excess may cause hypertension, hypokalaemia, and fluid retention. Previous androgen deprivation therapy (ADT) exposure as well as advanced age are additional risks for cardiovascular morbidity and mortality. 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 optimised and appropriate management of symptoms instituted. If there is a clinically significant decrease in cardiac function, discontinuation of Akeega should be considered.

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)
In MAGNITUDE, cases of PE were reported in patients treated with Akeega with a higher frequency compared to control. Patients with a prior history of PE or venous thrombosis may be more at risk of a further occurrence. Patients should be monitored 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)
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, there were no PRES cases reported.

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

Hepatotoxicity and hepatic impairment
Hepatotoxicity had been recognised as an 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 studies, 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 Í ULN or direct bilirubin > 1 Í ULN and AST or ALT > 3 Í ULN).

Marked increases in liver enzymes leading to treatment interruption or discontinuation occurred in clinical studies, although these were uncommon (see section 4.8). 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. 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 section 5.2), before resuming regular monitoring. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases should be measured immediately. Development of elevated aminotransferases in patients treated with Akeega should be promptly managed with treatment interruption. If at any time the ALT or AST rises above 5 times the 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 (see section 4.2).

Treatment should be permanently discontinued in patients with elevations of ALT or AST > 20 Í ULN. Treatment should be permanently discontinued in patients who develop a concurrent elevation of ALT > 3 Í ULN and a total bilirubin > 2 Í ULN in the absence of biliary obstruction or other causes responsible for the concurrent elevation.

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 studies; thus, there are no data to support the use of Akeega in this population.

Moderate hepatic impairment (Child-Pugh Class B or any AST and TB > 1.5 x - 3 x ULN) has been shown to increase the systemic exposure to abiraterone and niraparib (see section 5.2). There are no data on the clinical safety and efficacy of multiple doses of Akeega when administered to patients with moderate or severe hepatic impairment. The use of Akeega should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk (see sections 4.2 and 5.2). Akeega should not be used in patients with severe hepatic impairment (see sections 4.2, 4.3 and 5.2).

Hypoglycaemia
Cases of hypoglycaemia 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 (metabolised by CYP2C8) (see section 4.5). Blood sugar should, therefore, be monitored in patients with diabetes.

Myelodysplastic syndrome/acute myeloid leukaemia (MDS/AML)
MDS/AML, including cases with fatal outcome, have been reported in ovarian cancer studies among patients who received 300 mg of niraparib (a component of Akeega).

In the MAGNITUDE study, 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 haematological toxicities that has not resolved with treatment interruption or dose reduction, the patient should be referred to a haematologist for further evaluation. If MDS and/or AML is confirmed, treatment with Akeega should be permanently discontinued, and the patient should be treated appropriately.

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. 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 plus prednisone or prednisolone in combination with Ra-223 treatment is contraindicated (see section 4.3) due to an increased risk of fractures and a trend for increased mortality among asymptomatic or mildly symptomatic prostate cancer patients as observed in clinical studies with abiraterone acetate, a component of Akeega.

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.

Hyperglycaemia
The use of glucocorticoids could increase hyperglycaemia, therefore blood sugar should be measured frequently in patients with diabetes.

Skeletal muscle effects
Cases of myopathy and rhabdomyolysis have not been seen in patients treated with Akeega. In abiraterone acetate (a component of Akeega) monotherapy studies, most cases developed within the first six months of treatment and recovered after abiraterone acetate withdrawal. Caution is recommended in patients concomitantly treated with medicinal products known to be associated with myopathy/rhabdomyolysis.

Interactions with other medicinal products
Strong inducers of CYP3A4 during treatment are to be avoided unless there is no therapeutic alternative, due to risk of decreased exposure of abiraterone (see section 4.5).

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

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
No clinical study 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.

Effects of other medicinal products on niraparib or abiraterone acetate
CYP3A4 inducers and inhibitors
Abiraterone is a CYP3A4 substrate. In a clinical study in healthy subjects pretreated with the strong CYP3A4 inducer rifampicin, 600 mg daily for six days, followed by a single dose of abiraterone acetate 1 000 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 should be avoided unless there is no therapeutic alternative (see section 4.4).

In a separate clinical study in healthy subjects, co-administration of ketoconazole, a strong inhibitor of CYP3A4, had no clinically meaningful effect on the pharmacokinetics of abiraterone.

Effects of niraparib or abiraterone acetate on other medicinal products
CYP2D6 substrates
Abiraterone is an inhibitor of CYP2D6. In a clinical study to determine the effects of abiraterone acetate plus prednisone (AAP) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9-fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol.

CYP2C8 substrates
Abiraterone is an inhibitor of CYP2C8. In a clinical study in healthy subjects, the AUC of pioglitazone, a CYP2C8 substrate, was increased by 46% and the AUCs for M-III and M-IV, the active metabolites of pioglitazone, each decreased by 10% when pioglitazone was given together with a single dose of 1 000 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 because of the abiraterone acetate component. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide (see section 4.4).

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 live or live-attenuated vaccines, immunosuppressant agents or with other cytotoxic medicinal products.

Use with products known to prolong QT interval
Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering Akeega with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes, such as class IA (e.g., quinidine, disopyramide) or class III (e.g., amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.

Use with spironolactone
Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with Akeega is not recommended (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females
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.
- If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method.

Studies in animals have shown reproductive toxicity (see section 5.3).

Pregnancy
Akeega is not for use in women (see section 4.3).

There are no data from the use of Akeega in pregnant women. Akeega has the potential to cause foetal 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 section 5.3).

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 section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
The overall safety profile of Akeega is based on data from a Phase 3, randomised, double-blind, placebo-controlled study, MAGNITUDE cohort 1 (N=212). The most common adverse reactions of all grades occurring in >10% in the niraparib plus AAP arm were anaemia (52.4%), hypertension (34.0%), constipation (34.0%), fatigue (31.1%), nausea (25.0%), thrombocytopenia (24.1%), dyspnoea (18.9%), arthralgia (18.4%), back pain (17.9%), asthenia (17.0%), neutropenia (16.0%), decreased appetite (15.6%), hypokalaemia (15.6%), vomiting (15.1%), dizziness (13.2%), abdominal pain (12.7%), hyperglycaemia (12.7%), blood alkaline phosphatase increased (11.8%), weight decreased (11.8%), insomnia (11.3%), leukopenia (10.8%), lymphopenia (10.8%), blood creatinine increased (10.4%), and urinary tract infection (10.4%). The most frequently observed Grade 3-4 adverse reactions were anaemia (30.7%), hypertension (16.5%), thrombocytopenia (8.5%), neutropenia (6.6%), blood alkaline phosphatase increased (5.7%), and hypokalaemia (5.7%).

Tabulated list of adverse reactions
Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: Adverse reactions identified in clinical studies

System Organ Class	Frequency	Adverse reaction
Infections and infestations	very common	urinary tract infection
	common	pneumoniae, bronchitis, nasopharyngitis
	uncommon	urosepsis, conjunctivitis
Blood and lymphatic system disorders	very common	anaemia, thrombocytopenia, neutropenia, leukopenia, lymphopenia
	not known	pancytopenia[7]
Immune system disorders	not known	hypersensitivity (including anaphylaxis)[7]
Endocrine disorders	not known	adrenal insufficiency[9]
Metabolism and nutrition disorders	very common	decreased appetite, hypokalaemia, hyperglycaemia
	common	hypertriglyceridaemia
Psychiatric disorders	very common	insomnia
	common	depression, anxiety
	uncommon	confusional state
	not known	cognitive impairment[8]
Nervous system disorders	very common	dizziness
	common	headache, cognitive disorder
	uncommon	dysgeusia

	not known	posterior reversible encephalopathy syndrome (PRES)[7]
Cardiac disorders	common	tachycardia, palpitations, atrial fibrillation, cardiac failure[1], myocardial infarction, angina pectoris[2]
	uncommon	QT prolongation
Vascular disorders	very common	hypertension
	not known	hypertensive crisis[7]
Respiratory, thoracic and mediastinal disorders	very common	dyspnoea
	common	cough, pulmonary embolism, pneumonitis
	uncommon	epistaxis
	not known	allergic alveolitis[9]
Gastrointestinal disorders	very common	constipation, nausea, vomiting, abdominal pain[3]
	common	dyspepsia, diarrhoea, abdominal distention, stomatitis, dry mouth
	uncommon	mucosal inflammation
Hepatobiliary disorders	common	hepatic failure4
Skin and subcutaneous tissue disorders	common	rash5
	uncommon	photosensitivity
Musculoskeletal and connective tissue disorders	very common	back pain, arthralgia
	common	myalgia
	not known	myopathy[9], rhabdomyolysis[9]
Renal and urinary disorders	common	haematuria
General disorders and administration site conditions	very common	fatigue, asthenia
	common	oedema peripheral
Investigations	very common	blood alkaline phosphatase increased, weight decreased, blood creatinine increased
	common	AST increased, ALT increased
	uncommon	gamma-glutamyl transferase increased
Injury, poisoning and procedural complications	common	fractures[6]

1 Includes cardiac failure congestive, cor pulmonale, left ventricular dysfunction
2 Includes coronary artery disease, acute coronary syndrome
3 Includes abdominal pain upper, abdominal pain lower
4 Includes hepatic cytolysis, hepatotoxicity, hepatic failure
5 Includes rash, erythema, dermatitis, rash maculo-papular, rash pruritic
6 Includes osteoporosis and osteoporosis-related fractures
7 Not observed with Akeega. Reported in post-marketing experience with niraparib monotherapy
8 Not observed with Akeega. Reported with niraparib monotherapy
9 Not observed with Akeega. Reported in post-marketing experience with abiraterone monotherapy

Description of selected adverse reactions

Haematological toxicities

Haematological toxicities (anaemia, 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 with the incidence decreasing over time.

In the MAGNITUDE study and other Akeega studies, the following haematological parameters were inclusion criteria: absolute neutrophil count (ANC) ⩾ 1 500 cells/ µ L; platelets ⩾ 100 000 cells/ µ L and haemoglobin ⩾ 9 g/dL. Haematological adverse reactions were managed with laboratory monitoring and dose modifications (see sections 4.2 and 4.4).

Anaemia
Anaemia was the most frequent adverse reaction (52.4%) and most commonly observed Grade 3-4 event (30.7%) in the MAGNITUDE study. Anaemia 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 anaemia-related red blood cell transfusion. Anaemia caused discontinuation in a relatively 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 section 4.2). Discontinuation occurred in 0.5% of patients. In the MAGNITUDE study, 1.9% of patients experienced a nonlife-threatening 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% 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 on treatment (see section 4.4).

Cardiac events
In the MAGNITUDE study, the incidence of TEAEs of cardiac disorder (all grades) was similar in both arms, except for the arrhythmia category, where AEs were observed in 13.2% of patients in the niraparib plus AAP arm and 7.6% of patients in the placebo plus AAP arm (see section 4.4). Higher frequency of arrhythmias was largely due to low grade events of palpitations, tachycardias and atrial arrhythmias.

The median time to onset of the events of arrhythmias was 81 days in the niraparib plus AAP arm and 262 days in the placebo plus AAP arm. Events of arrhythmia were resolved in 64.3% of patients in the niraparib plus AAP arm and 62.5% of subjects in the placebo plus AAP arm.

The incidence of cardiac failure, cardiac failure acute, cardiac failure chronic, cardiac failure congestive was 2.8% in the niraparib plus AAP arm vs 1.9% in placebo plus AAP arm. The median time to onset of the AESI of cardiac failure was 312 days in the niraparib plus AAP arm and 83 days in the placebo plus AAP arm. Events of cardiac failure were resolved in 16.7% of patients in the niraparib plus AAP arm and 25% of patients in the placebo plus AAP arm.

The grouped term of ischaemic heart disease (included preferred terms of angina pectoris, acute myocardial infarction, acute coronary syndrome, unstable angina, and arteriosclerosis coronary artery) occurred in 5.2% of the niraparib plus AAP arm vs 4.7% in the placebo plus AAP arm. The median time to onset of the AESI of ischaemic heart disease was 684 days in the niraparib plus AAP arm and 296 days in the placebo plus AAP arm. Events of ischaemic heart disease were resolved in 81.8% of patients in the niraparib plus AAP arm and 80% of patients in the placebo plus AAP arm.

Hepatotoxicity
The overall incidence of hepatotoxicity in the MAGNITUDE study was similar for the niraparib plus AAP (14.2%) and placebo plus AAP (12.8%) arms (see sections 4.2 and 4.4). The majority of these events were low grade aminotransferase elevations. Grade 3 events occurred in 1.4% of patients in the niraparib plus AAP arm 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, 0.9% of patients discontinued treatment due to hepatotoxicity.

Paediatric population
No studies have been conducted in paediatric patients with Akeega.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

4.9 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 should treat patients symptomatically, including monitoring for arrhythmias, hypokalaemia and signs and symptoms of fluid retention. Liver function also should be assessed.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of action
Akeega is a combination of niraparib, an inhibitor of poly(ADP-ribose) polymerase (PARP), and abiraterone acetate (a prodrug of abiraterone), a CYP17 inhibitor targeting two oncogenic dependencies in patients with mCRPC and HRR gene mutations.

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 tumour tissues. CYP17 catalyses 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 section 4.4).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with luteinising hormone releasing hormone

(LHRH) analogues or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

Pharmacodynamic effects

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.

Clinical efficacy and safety

First-line treatment of mCRPC patients with BRCA 1/2 mutations

The efficacy of Akeega was established in a randomised placebo-controlled multicentre Phase 3 clinical study of patients with mCRPC, MAGNITUDE (Study 64091742PCR3001).

MAGNITUDE was a Phase 3, randomised, double-blind, placebo-controlled, multicentre 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. Efficacy data are based on Cohort 1 that consisted of 423 patients with mCRPC and select HRR gene mutations, who were randomised (1:1) to receive either niraparib plus AAP (N=212) or placebo plus AAP (N=211) orally daily. Treatment was continued until disease progression, unacceptable toxicity, or death.

Patients with mCRPC who had not received prior systemic therapy in the mCRPC setting except for a short duration of prior AAP (up to 4 months) and ongoing ADT, were eligible. Plasma, blood, and/or tumour tissue samples for all patients were tested by validated next generation sequencing tests to determine germline and/or somatic HRR gene mutation status. There were 225 subjects with a BRCA1/2 mutation enrolled in the study (113 received Akeega). There were an additional 198 patients with a non-BRCA1/2 mutation (ATM, CHEK2, CDK12, PALB2, FANCA, BRIP1, HDAC2) enrolled in the study (99 received Akeega).

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.

In the All HRR Population, the primary efficacy results with a median follow-up of 18.6 months showed statistically significant improvement in BICR-assessed rPFS with a HR =0.729 (95% CI: 0.556, 0.956; p=0.0217).

Table 4 summarises the demographics and baseline characteristics of BRCA patients enrolled in Cohort 1 of the MAGNITUDE study. The median PSA at diagnosis was 41.07 ug/L (range 01-12080). 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 4: Summary of demographics and baseline characteristics in the MAGNITUDE study Cohort 1 (BRCA)

	Akeega+P[1] N=113 n (%)	**Placebo+AAP[1] 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 randomisation (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)

[1] P=prednisone or prednisolone

A statistically significant improvement in BICR-assessed rPFS was observed in the primary analysis for BRCA subjects treated with niraparib plus AAP, compared with BRCA subjects treated with placebo plus AAP. Key efficacy results in the BRCA population are presented in Table 5. The Kaplan-Meier curves for BICR assessed rPFS in the BRCA population are shown in Figure 1.

Table 5: Efficacy results from the BRCA population of the MAGNITUDE study

Endpoints	**Akeega+P[1] (N=113)**	**Placebo+AAP[1] (N=112)**
Radiographic Progression-free Survival[2]		
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	
Overall Survival[3]		
Hazard Ratio (95% CI)	0.788 (0.554, 1.120)	

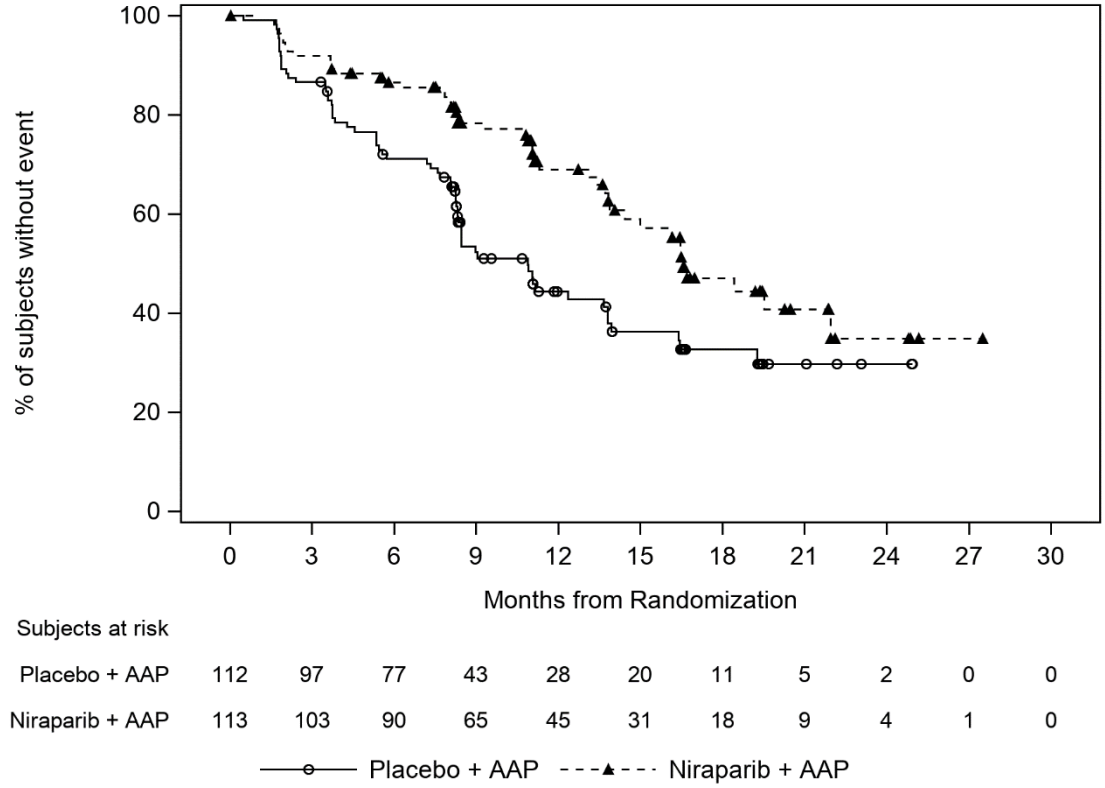
[1] P=prednisone or prednisolone

[2] Primary analysis/Interim analysis (data cut-off: 08OCT2021), with 18.6 months median follow-up

3 Final Analysis (data cut-off: 15May2023), with 35.9 months median follow-up

NE = Not estimable

Figure 1: **Kaplan-Meier Plot of BICR assessed radiologic progression-free survival in the BRCA population (MAGNITUDE, primary analysis)**



5.2 Pharmacokinetic properties

Co-administration of niraparib and abiraterone has no impact on the exposures of the individual moieties. The AUC and C_{max} are comparable for niraparib and abiraterone when administered as Akeega regular strength (100 mg/500 mg) film-coated tablet 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 section 4.2). 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%. Niraparib is a substrate of P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP). However, due to its high permeability and bioavailability, the risk of clinically relevant interactions with medicinal products that inhibit these transporters is unlikely.

Abiraterone acetate

Abiraterone acetate is rapidly converted *in vivo* to abiraterone (see section 5.1).

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 1 117 L and 25 774 L, respectively, indicative of extensive extravascular distribution.

Niraparib

Niraparib was moderately protein-bound in human plasma (83.0%), mainly with serum albumin.

Abiraterone acetate

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%.

Biotransformation

Niraparib

Niraparib is metabolised 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. The potential to inhibit CYP3A4 at the intestinal level has not been established at relevant niraparib concentrations. Niraparib weakly induces CYP1A2 at high concentrations *in vitro*.

Abiraterone acetate

Following oral administration of ^{14}C-abiraterone acetate as capsules, abiraterone acetate is hydrolysed by CEs to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. Abiraterone is a substrate of CYP3A4 and sulfotransferase 2A1 (SULT2A1). 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 represents approximately 43% of total radioactivity. Abiraterone is an inhibitor of the hepatic drug metabolising enzymes CYP2D6 and CYP2C8 (see section 4.5).

Elimination

Akeega

The mean $t_{½}$ 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 pharmacokinetic 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 faeces over 21 days. Radioactive recovery in the urine accounted for 47.5% (range 33.4% to 60.2%) and in the faeces for 38.8% (range 28.3% to 47.0%) of the dose. In pooled samples collected over six days, 40.0% of the dose was recovered in the urine primarily as metabolites and 31.6% of the dose was recovered in the faeces primarily as unchanged niraparib. The metabolite M1 is a substrate of Multidrug And Toxin Extrusion (MATE) 1 and 2.

Abiraterone acetate

Following oral administration of ^{14}C-abiraterone acetate 1 000 mg, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

Effects of niraparib or abiraterone on transporters
Niraparib inhibits P-gp weakly with an IC50=161 μM. Niraparib is an inhibitor of BCRP, Organic Cation Transporter 1 (OCT1), MATE-1 and 2 with IC50 values of 5.8 μM, 34.4 μM, 0.18 μM and ≤ 0.14 μM, respectively. The major metabolites of abiraterone, abiraterone sulphate and N-oxide abiraterone sulphate, were shown to inhibit the hepatic uptake transporter Organic Anion Transport Polypeptide 1B1 (OATP1B1) and as a consequence, the plasma exposures of medicinal products eliminated by OATP1B1 may increase. There are no clinical data available to confirm transporter OATP1B1 based interaction.

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 was 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 1 000 mg dose increased by approximately 1.11-fold and 3.6-fold in subjects with mild and moderate pre-existing hepatic impairment, respectively.

In another study, 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 of abiraterone increased by approximately 7-fold and the fraction of free drug increased by 1.8-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 and severe hepatic impairment (see section 4.2).

Renal impairment
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 (creatinine clearance 60-90 mL/min, n=337) and moderate (creatinine clearance 30-60 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 was compared in patients with end-stage renal disease on a stable haemodialysis 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. There is no clinical experience using Akeega in patients with severe renal impairment (see section 4.2).

Weight, age and race
Based on the population pharmacokinetic analysis of data from clinical studies where prostate cancer patients received niraparib or abiraterone acetate alone or in combination:

- Body weight did not have a clinically meaningful influence on the exposure of niraparib (body weight range: 43.3-165 kg) and abiraterone (body weight range: 56.0-135 kg).
- Age had no significant impact on the pharmacokinetics of niraparib (age range 45-90 years) and abiraterone (age range 19-85 years).
- There is insufficient data to conclude on the impact of race on the pharmacokinetics of niraparib and abiraterone.

Paediatric population
No studies have been conducted to investigate the pharmacokinetics of Akeega in paediatric patients.

5.3 Preclinical safety data

Akeega
Non-clinical studies with Akeega have not been performed. The nonclinical toxicology data are based on findings in studies with niraparib and abiraterone acetate individually.

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 behavioural 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.

Decreased spermatogenesis was observed in both rats and dogs at exposure levels below therapeutic exposure levels and were largely reversible within four weeks of cessation of dosing.

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.

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

Carcinogenicity studies have not been conducted with niraparib.

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.

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

In a developmental toxicity study in the rat, abiraterone acetate affected pregnancy including reduced foetal 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.

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.

Environmental risk assessment (ERA)
The active substance, abiraterone, shows an environmental risk for the aquatic environment, especially to fish (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Akeega 50 /500
Excipients
Silicified microcrystalline cellulose, Lactose monohydrateCrospovidone, Sodium lauryl sulphate, Hypromellose (2910 15 mPa.s), Magnesium stearateColloidal anhydrous silica

Akeega 50 /500 *Film-coating - Opadry AMB II 88A620004 Yellow*
Polyvinyl alcohol, partially hydrolyzed, Talc, Titanium dioxide, Iron oxide yellow,
Glycerol monocaprylocaprate Type 1, Sodium lauryl sulphate, Iron oxide red, Iron oxide black

Akeega 100 /500 film-coated tablets
Excipients
Silicified microcrystalline cellulose, Lactose monohydrateCrospovidone, Sodium lauryl sulphate, Hypromellose (2910 15 mPa.s), Magnesium stearate, Colloidal anhydrous silica

Akeega 100 /500
Film-coating - Opadry AMB II 88A170010 Beige
Polyvinyl alcohol, partially hydrolyzed, Talc, Titanium dioxide, Iron oxide yellow
Glycerol monocaprylocaprate Type 1, Sodium lauryl sulphate, Iron oxide red

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C
Store in the original package.

6.5 Nature and contents of container

Each 28-day carton contains 56 film-coated tablets in two cardboard wallet packs each containing 28 film-coated tablets in a PVdC/PE/PVC blister with an aluminium push-through foil.

6.6 Special precautions for disposal and other handling

Based on its mechanism of action, this medicinal product may harm a developing foetus. Therefore, women who are or may become pregnant should handle Akeega with protection, e.g., gloves (see section 4.6).

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. This medicinal product may pose a risk to the aquatic environment (see section 5.3).

7. MANUFACTURER and REGISTRATION HOLDER

Manufacturer: Patheon France S.A.S, 40 Boulevard de Champaret, Bourgoin Jallieu, 38300, France

Registration Holder: J-C Health Care Ltd., Kibbutz Shefayim, 6099000, Israel

8. MARKETING AUTHORISATION NUMBER(S)

AKEEGA 50/500 175-82-37788-99
AKEEGA 100/500 175-83-37789-99

Revised in Sep2024