Niraparib and Abiraterone acetate (Akeega®) and prednisoLONE Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Niraparib in combination with abiraterone acetate (Akeega®) and predniSONE/prednisoLONE for the treatment of adults with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.	C61	00848	CDS 01/11/2023

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Niraparib/abiraterone (Akeega®) is administered as a single oral daily dose until disease progression or unacceptable toxicity.

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

Drug	Dose	Route	Cycle
Niraparib/abiraterone (Akeega®)	200mg/1000mg once daily [1]	PO[2,3]	Continuous
predniSONE or prednisoLONE	10mg daily	PO with food	Continuous

[1] Niraparib/abiraterone (Akeega®) tablets are available in two presentations:

- Akeega® 50 mg/500 mg film-coated tablets
- Akeega® 100 mg/500 mg film-coated tablets

The starting dose of 200mg/ 1000mg would comprise of two tablets of the 100mg/ 500mg strength. Niraparib/abiraterone (Akeega®) tablets should be taken as a single daily dose at approximately the same time every day.

[2]Niraparib/abiraterone (Akeega®) tablets should be taken on an empty stomach, at least 1 hour before or 2 hours after a meal. For optimal absorption, the tablets must be swallowed whole with water, they must not be broken, crushed, or chewed.

[3]Women who are or may become pregnant should wear gloves when handling the tablets.

If a dose of either niraparib/abiraterone (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.

ELIGIBILITY:

- Indication as above

- BRCA 1/2 mutation (germline and/or somatic) as demonstrated by an accurate and validated test method
- Metastatic prostate cancer in the setting of castrate levels of testosterone ≤50 ng/dL on a GnRHa or bilateral orchiectomy
- ECOG status 0-2
- Adequate haematological function

CAUTION:

Use with caution in:

- Patients with a history of cardiovascular disease

EXCLUSIONS:

- Hypersensitivity to niraparib, abiraterone, predniSONE or prednisoLONE or any of the excipients
- Prior treatment with a PARP inhibitor
- Symptomatic brain metastases
- History or current diagnosis of myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)
- Severe hepatic impairment
- Clinically significant heart disease (LVEF < 50% at baseline)
- Uncontrolled hypertension (systolic blood pressure >160mmHg or diastolic > 95mmHg)
- Abiraterone with predniSONE or prednisoLONE is contraindicated in combination with Ra-223
- Active or symptomatic viral hepatitis
- History of adrenal dysfunction

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Confirmation of BRCA 1/2 mutation (germline and/or somatic) using a validated test method
- Blood pressure
- Glucose
- Echocardiogram and ECG (and consider Echocardiogram) if clinically indicated or history of cardiac problems

Regular tests:

- FBC weekly for the first month, then every two weeks for the next two months, then monthly thereafter for the first year, then every 2nd month for remainder of treatment.
- Serum aminotransferases and total bilirubin every two weeks for the first three months, followed by monthly thereafter for the first year and then every 2nd month for the duration of treatment.
  - If starting lower strength dose of niraparib/abiraterone (Akeega®) after dose interruption, liver tests every two weeks for six weeks, before resuming regular monitoring.
- Renal profile
- Blood pressure weekly for the first two months, followed by monthly for the first year and then every other month for the duration of treatment.
- Glucose as clinically indicated
- ECG as clinically indicated
- Cardiovascular assessment as clinically indicated

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

Table 1: Recommended dose reductions for niraparib/abiraterone (Akeega®) for adverse reactions

Dose level	Dose recommendation for haematological toxicity	Dose recommendation for hepatotoxicity
First dose reduction	2 x 50mg/500mg niraparib/abiraterone (Akeega®) tablets	1 x 100mg/500mg niraparib/abiraterone (Akeega®) tablets
Second dose reduction	Consider discontinuation	Discontinue

Haematological:

Table 2: Dose modification of niraparib/abiraterone (Akeega®) for neutropenia and thrombocytopenia

Grade	Dose
≤1	• No dose adjustment, consider weekly monitoring
2	• At least weekly monitoring and consider withholding niraparib/abiraterone (Akeega®) until recovery to Grade 1 or baseline[1] • Resume niraparib/abiraterone (Akeega®) with recommendation of weekly monitoring for 28 days after restarting dose
≥3	**1st occurrence:** • Withhold niraparib/abiraterone (Akeega®) and monitor at least weekly until recovery to Grade 1 or baseline[1] • Then resume niraparib/abiraterone (Akeega®) or, if warranted, reduce by one dose level (Refer to Table 1 for recommended dose reductions for haematological toxicity)

	• Weekly monitoring of blood counts is recommended for 28 days after restarting full dose or starting reduced dose[2] **2nd occurrence:** • Withhold niraparib/abiraterone (Akeega®) and monitor at least weekly until recovery to Grade 1 • Resume treatment, reducing by one dose level (Refer to Table 1 for recommended dose reductions for haematological toxicity) • Weekly monitoring is recommended for 28 days after resuming treatment with reduced dose[2] • If patient was already on reduced dose, consider treatment discontinuation **3rd occurrence:** • Permanently discontinue treatment
[1] During niraparib/abiraterone (Akeega®) treatment interruption, abiraterone acetate and predniSONE/prednisoLONE may be considered to maintain daily dose of abiraterone acetate.	
[2] 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, before resuming regular monitoring.	

Table 3: Dose modification of niraparib/abiraterone (Akeega®) for anaemia

Grade	Dose
≤1	• No change, consider weekly monitoring
2	• At least weekly monitoring for 28 days, if baseline anaemia was Grade ≤ 1
≥3	**1st occurrence:** • Withhold niraparib/abiraterone (Akeega®) [1] and provide supportive management with monitoring at least weekly until recovered to Grade ≤ 2 If anaemia persists, based on clinical judgement, consider reducing by one dose level[2] (Refer to Table 1 for recommended dose reductions for haematological toxicity) **2nd occurrence:** • Withhold niraparib/abiraterone (Akeega®), provide supportive management and monitor at least weekly until recovered to Grade ≤ 2 • Resume treatment, reducing by one dose level (Refer to Table 1 for recommended dose reductions for haematological toxicity) • Weekly monitoring is recommended for 28 days after resuming treatment with reduced dose[2] • If patient was already on reduced dose, consider treatment discontinuation **3rd occurrence:** • Consider discontinuing treatment based on clinical judgment
[1] During niraparib/abiraterone (Akeega®) treatment interruption, abiraterone acetate and predniSONE/prednisoLONE may be considered to maintain daily dose of abiraterone acetate.	
[2] 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, before resuming regular monitoring.	

Renal and Hepatic Impairment:

Table 4: Dose modification of niraparib/abiraterone (Akeega®) in renal and hepatic impairment

Renal Impairment		Hepatic Impairment	
Mild	No dose adjustment necessary.	**Mild (Child-Pugh Class A)**	No dose adjustment is necessary for patients with pre-existing mild hepatic impairment.
Moderate	No dose adjustment necessary although close monitoring of safety events should be conducted in patients with moderate renal impairment due to the potential for increased niraparib exposure.	**Moderate (Child-Pugh Class B)**	There are no data on the clinical safety and efficacy when administered to patients with moderate hepatic impairment. No dose adjustment can be predicted. Use of niraparib/abiraterone (Akeega®) should be cautiously assessed in patients, in whom the benefit clearly should outweigh the possible risk.
Severe renal impairment or end stage renal disease undergoing haemodialysis	There are no data. Niraparib/abiraterone (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.	**Severe (Child-Pugh Class C)**	There are no data on the clinical safety and efficacy when administered to patients with moderate hepatic impairment. Contraindicated in patients with severe hepatic impairment.

Management of adverse events:

Table 5: Dose Modification of niraparib/abiraterone (Akeega®) for Adverse Events

Adverse reactions	Recommended dose modification
Non-haematological adverse reactions Grade ≥ 3	• Treatment should be interrupted and appropriate medical management should be instituted • Treatment with niraparib/abiraterone (Akeega®) should not be reinitiated until symptoms of the toxicity have resolved to Grade 1 or baseline
Hepatotoxicity: • **Grade ≥ 3 (ALT or AST > 5 x ULN)**	• Treatment with niraparib/abiraterone (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 reduction of one dose level[1] (Refer to Table 1 for recommended dose reductions for **hepatotoxicity**) • If hepatotoxicity recurs at the reduced dose level, treatment with niraparib/abiraterone (Akeega®) should be discontinued
• **Severe hepatotoxicity (ALT or AST 20 x ULN)**	• Permanently discontinue treatment
• **Concurrent elevation of ALT > 3 x ULN and total bilirubin > 2 x ULN (in the absence of biliary obstruction or other causes)**	• Permanently discontinue treatment
[1]For patients being re-treated, serum transaminases should be monitored at a minimum of every two weeks for three months and monthly thereafter.	

Hypokalemia Management:
Patients with pre-existing hypokalaemia or those that develop hypokalaemia while treated with abiraterone, consider maintaining the patient's potassium level at ≥4.0mM.

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: Moderate to high **(Refer to local policy).**

PREMEDICATIONS: Not usually required

OTHER SUPPORTIVE CARE:

- During treatment and for four months after the last dose of niraparib/abiraterone acetate:
  - 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
- Niraparib/abiraterone acetate has moderate influence on the ability to drive or use machines. Patients who take niraparib/abiraterone acetate may experience asthenia, fatigue, dizziness or difficulties concentrating. Patients should use caution when driving or using machines
- Prophylactic anti-emetics should be considered for the first 2 weeks of treatment as clinically indicated **(Refer to local policy)**
- Patients who stop abiraterone may require a gradual withdrawal of the prednisoLONE

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Haematological adverse reactions**: Haematological adverse reactions have been reported in patients treated with niraparib/abiraterone (Akeega®). If a patient develops severe persistent haematological toxicity including pancytopenia that does not resolve within 28 days following interruption, niraparib/abiraterone (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 niraparib/abiraterone (Akeega®).
- **Hypertension**: Niraparib/abiraterone (Akeega®) may cause hypertension and pre-existing hypertension should be adequately controlled before starting Niraparib/abiraterone (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 niraparib/abiraterone (Akeega®).
- **Hypokalaemia, fluid retention, & cardiovascular adverse reactions due to mineralocorticoid excess**: Niraparib/abiraterone (Akeega®) may cause hypokalaemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. 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, or fluid retention
- QT prolongation has been observed in patients experiencing hypokalaemia in association with niraparib/abiraterone (Akeega®) treatment
- Hypokalaemia and fluid retention should be corrected and controlled
- Before treating patients with a significant risk for congestive heart failure, cardiac failure should be treated and cardiac function optimised. Fluid retention and other signs and symptoms of congestive heart failure should be monitored every two weeks for three months, then monthly thereafter and abnormalities corrected
- Niraparib/abiraterone (Akeega®) should be used with caution in patients with a history of cardiovascular disease. Management of cardiac risk factors should be optimised in patients receiving niraparib/abiraterone (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. 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 niraparib/abiraterone (Akeega®) should be considered

- **Infections**: Patients should be monitored for signs and symptoms of infection. Severe infections may occur in absence of neutropenia and/or leukopenia.
- **Pulmonary embolism (PE)**: 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. There have been reports of PRES in patients receiving 300 mg niraparib (a component of niraparib/abiraterone (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 niraparib/abiraterone (Akeega®) should be permanently discontinued and appropriate medical management should be instituted.
- **Hepatotoxicity and hepatic impairment**: Hepatotoxicity has been recognised as an important identified risk for abiraterone acetate, a component of niraparib/abiraterone (Akeega®). The mechanism for hepatotoxicity of abiraterone acetate is not fully understood. Development of elevated aminotransferases in patients treated with niraparib/abiraterone (Akeega®) should be promptly managed with treatment interruption (Refer to Table 5). The use of niraparib/abiraterone (Akeega®) should be cautiously assessed in patients with moderate hepatic impairment, in whom the benefit clearly should outweigh the possible risk. Niraparib/abiraterone (Akeega®) should not be used in patients with severe hepatic impairment.
- **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). 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 300mg of niraparib. No cases of MDS/AML have been observed in patients treated with 200mg of niraparib and 1000mg 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 niraparib/abiraterone (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 niraparib/abiraterone (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 niraparib/abiraterone (Akeega®) plus predniSONE or prednisoLONE in combination with Ra-223 treatment is contraindicated 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 niraparib/abiraterone (Akeega®). It is recommended that subsequent treatment with Ra-223 not be initiated for at least five days after the last administration of niraparib/abiraterone (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 niraparib/abiraterone (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.

DRUG INTERACTIONS:

- No clinical study evaluating drug interactions has been performed using niraparib/abiraterone (Akeega®). Interactions that have been identified in studies with individual components of niraparib/abiraterone (Akeega®)) determine the interactions that may occur with Akeega®.
- Abiraterone is a CYP3A4 substrate. Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St. John's wort [Hypericum perforatum]) during treatment with niraparib/abiraterone (Akeega®) should be avoided unless there is no therapeutic alternative.
- Abiraterone is an inhibitor of CYP2D6. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered.
- Abiraterone is an inhibitor of CYP2C8. Patients should be monitored for signs of toxicity related to a CYP2C8 substrate with a narrow therapeutic index if used concomitantly with niraparib/abiraterone

(Akeega®) because of the abiraterone acetate component. Examples of medicinal products metabolised by CYP2C8 include pioglitazone and repaglinide.

- Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering niraparib/abiraterone (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.
- The use of niraparib/abiraterone (Akeega®) with vaccines or immunosuppressant agents has not been studied. Caution should be taken if niraparib/abiraterone (Akeega®) is used in combination with live or live-attenuated vaccines, immunosuppressant agents or with other cytotoxic medicinal products.
- Spironolactone binds to the androgen receptor and may increase prostate specific antigen (PSA) levels. Use with niraparib/abiraterone (Akeega®) is not recommended.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Chi KN et al. MAGNITUDE Principal Investigators. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. J Clin Oncol. 2023 Jun 20; 41(18):3339-3351.
2. Chi KN et al. Niraparib plus abiraterone acetate with prednisone in patients with metastatic castration-resistant prostate cancer and homologous recombination repair gene alterations: second interim analysis of the randomized phase III MAGNITUDE trial. Ann Oncol. 2023 Jul 1:S0923-7534(23)00757-3.
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Niraparib and abiraterone acetate (Akeega®) SmPC EMA. Last updated 02/06/2023. Accessed September 2023. Available at: https://www.ema.europa.eu/en/documents/product-information/akeega-epar-product-information_en.pdf

Version	Date	Amendment	Approved By
1	01/11/2023		Dr Richard Bambury

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.