Iowa Medicaid
IOWA HHS

PDL DRUG REVIEW

Proprietary Name: Akeega®
Common Name: niraparib tosylate / abiraterone acetate
PDL Category: Antineoplastics

Comparable Products	Preferred Drug List Status
Lynparza	Non-Recommended with Conditions
Rubraca	Non-Recommended with Conditions

Pharmacology/Usage: Akeega® is a combination tablet that contains niraparib tosylate (a poly (ADP-ribose) polymerase (PARP) inhibitor) and abiraterone acetate (an inhibitor of CYP17).

Niraparib is an inhibitor of PARP enzymes, including PARP-1 and PARP-2, that 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. Niraparib decreased tumor growth in mouse xenograft models of human cancer cell lines with deficiencies in *BRCA1/2* and in human patient-derived xenograft tumor models with homologous recombination deficiency (HRD) that had either mutated or wild-type *BRCA1/2*.

Abiraterone acetate is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor, that inhibits CYP17. This enzyme is expressed in testicular, adrenal, and prostatic tumor tissues and is required for androgen biosynthesis. CYP17 catalyzes two sequential reactions, including the conversion of pregnenolone and progesterone to their 17α-hydroxy derivatives by 17α-hydroxylase activity, as well as the subsequent formation of dehydroepiandrosterone (DHEA) and androstenedione, respectively. DHEA and androstenedione are androgens and are precursors of testosterone. Inhibition of CYP17 by abiraterone can also result in increased mineralocorticoid production by the adrenals.

Androgen sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with gonadotropin-releasing hormone (GnRH) agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumor. Abiraterone decreased serum testosterone and other androgens in patients in the placebo-controlled trials. It is not necessary to monitor the effect of abiraterone on serum testosterone levels. Changes in serum prostate specific antigen (PSA) levels may be observed but have not been shown to correlate with clinical benefit in individual patients.

In mouse xenograft models of prostate cancer, the combination of niraparib and abiraterone acetate increased anti-tumor activity when compared to either drug alone.

Indication: With prednisone, for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for Akeega®.

There is no pregnancy category for this medication; however, the risk summary indicates that the safety and efficacy of use have not been established in females. Based on findings from animal studies and mechanism of action, Akeega® can cause fetal harm and potential loss of pregnancy. There are no human data on use in pregnant women. Based

on findings in animal reproduction studies and its mechanism of action, advise males with female partners of reproductive potential to use effective contraception during treatment and for 4 months after the last dose of Akeega®. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Film-Coated Tablets containing niraparib/abiraterone: 50mg/500mg, 100mg/500mg.

Swallow tablets whole with water. Do not break, crush, or chew tablets.

Recommended Dosage: Select patients for the treatment of mCRPC with Akeega® based on the presence of a *BRCA* gene alteration. Information on FDA-approved tests is available at http://www.fda.gov/CompanionDiagnostics.

The recommended dosage is Akeega® is 200mg/1,000mg PO QD in combination with prednisone 10mg daily until disease progression or unacceptable toxicity. Take on an empty stomach. Do not eat food two hours before and one hour after taking Akeega®. If a patient misses a dose, instruct the patient to take the dose as soon as possible on the same day and resume their next dose at the normal schedule the following day.

Patients receiving Akeega® should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Refer to the prescribing information for the recommended dosage modifications for adverse reactions, such as myelosuppression, hepatotoxicity, or other non-hematological adverse reactions that persist despite medical management. Treatment with Akeega® should not be reinitiated until the toxicity has resolved to Grade 1 or baseline. If the toxicity is attributed to one component of Akeega®, the other component of Akeega® may be continued as a single agent at the current dose until the adverse reaction resolves and Akeega® can be resumed.

Dose modification is not needed for patients with mild hepatic impairment. Avoid Akeega® use in patients with moderate or severe hepatic impairment. No dosage modification is recommended for patients with mild to moderate renal impairment. Monitor patients with severe renal impairment for increased adverse reactions and modify dosage as recommended for adverse reactions.

Drug Interactions: Abiraterone is a substrate of CYP3A4. Strong CYP3A4 inducers may decrease abiraterone concentrations, which may reduce the effectiveness of abiraterone. Avoid co-administration with strong CYP3A4 inducers.

Abiraterone is a CYP2D6 moderate inhibitor. Akeega® increases the concentration of CYP2D6 substrates, which may increase the risk of adverse reactions related to these substrates. Avoid co-administration unless otherwise recommended in the prescribing information for CYP2D6 substrates for which minimal changes in concentration may lead to serious toxicities. If alternative treatments cannot be used, consider a dose reduction of the concomitant CYP2D6 substrate drug.

Abiraterone is a CYP2C8 inhibitor. Akeega® increases the concentration of CYP2C8 substrates, which may increase the risk of adverse reactions related to these substrates. Monitor patients for signs of toxicity related to a CYP2C8 substrate for which a minimal change in plasma concentration may lead to serious or life-threatening adverse reactions.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (Akeega® with prednisone) minus reported % incidence for placebo with abiraterone and prednisone for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included musculoskeletal pain (2%), fatigue (13%), constipation (14%), hypertension (6%), nausea (12%), edema (8%), dyspnea (7%), decreased appetite (7%), vomiting (8%), dizziness (4%), COVID-19 (4%), abdominal pain (0%), hemorrhage (4%), headache (3%), urinary tract infection (3%), cough (6%), insomnia (8%), weight decreased (6%), arrhythmia (6%), fall (0%), and pyrexia (4%).

Listed % incidence for adverse drug reactions= reported % incidence for drug (Akeega® with prednisone) minus reported % incidence for placebo with abiraterone and prednisone for Select Laboratory Abnormalities for all grades. Please note that an incidence of 0% means the incidence was the same as or less than placebo. The most frequently reported adverse events included hemoglobin decreased (14%), lymphocyte decreased (23%), WBC decreased (30%), platelets decreased (15%), neutrophils decreased (16%), ALP increased (5%), creatinine increased (17%), potassium increased (4%), potassium decreased (0%), AST increased (0%), ALT increased (1%), and bilirubin increased (2%).

Akeega® may cause myelodysplastic syndrome/acute myeloid leukemia (MDS/AML). MDS/AML, including cases with fatal outcome, has been observed in patients treated with niraparib. All treated with niraparib who developed secondary MDS/cancer-therapy-related AML had received previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy. For suspected MDS/AML or prolonged hematological toxicities, refer the patient to a hematologist for further evaluation. Discontinue Akeega® if MDS/AML is confirmed.

Akeega® may cause myelosuppression (anemia, thrombocytopenia, or neutropenia). Monitor complete blood counts weekly during the first month of Akeega® treatment, every 2 weeks for the next 2 months, monthly for the remainder of the first year, and then every other month, and as clinically indicated. Do not start Akeega® until patients have adequately recovered from hematologic toxicity caused by previous therapy. If hematologic toxicities do not resolve within 28 days following interruption, discontinue Akeega® and refer the patient to a hematologist for further investigations.

Akeega® may cause hypokalemia and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. In post-marketing experience, QT prolongation and Torsade de Pointes have been observed in patients who develop hypokalemia while taking abiraterone. Hypertension and hypertensive crisis have also been reported in patients treated with niraparib. Monitor patients for hypertension, hypokalemia, and fluid retention at least weekly for the first two months, then once a month. Closely monitor patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia, or fluid retention, such as those with heart failure, recent MI, cardiovascular disease, or ventricular arrhythmia. Control hypertension and correct hypokalemia before and during Akeega® treatment. Discontinue Akeega® in patients who develop hypertensive crisis or other severe cardiovascular adverse reactions.

Akeega® may cause hepatotoxicity. Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with Akeega®, every 2 weeks for the first 3 months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient's baseline should prompt more frequent monitoring and may require dosage modifications.

Akeega® may cause adrenal insufficiency. Monitor patients for symptoms and signs of adrenocortical insufficiency, especially if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with abiraterone. If clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased doses of corticosteroids may be indicated before, during, and after stressful situations.

Akeega® may cause hypoglycemia in patients being treated with other medications for diabetes. Severe hypoglycemia has been reported when abiraterone was administered to patients receiving medications containing thiazolidinediones (including pioglitazone) or repaglinide. Monitor blood glucose in patients with diabetes during and after discontinuation of treatment with Akeega®. Assess if antidiabetic drug dosage needs to be adjusted to minimize the risk of hypoglycemia.

Akeega® with prednisone is not recommended for use in combination with Ra-223 dichloride outside of clinical trials. It is recommended that subsequent treatment with Ra-223 not be initiated for at least 5 days after the last administration of Akeega®, in combination with prednisone.

Akeega® may cause Posterior Reversible Encephalopathy Syndrome (PRES). PRES has been observed in patients treated with niraparib as a single agent at higher than the recommended dose of niraparib included in Akeega®. Monitor all patients treated with Akeega® for signs and symptoms of PRES. If PRES is suspected, promptly discontinue Akeega® and administer appropriate treatment. The safety of restarting Akeega® in patients previously experiencing PRES is not known.

Contraindications: There are no contraindications listed with this product.

Manufacturer: Janssen Biotech, Inc.

Analysis: The efficacy of Akeega® was assessed in Cohort 1 of MAGNITUDE, a randomized, double-blind, placebo-controlled, multicohort, multicenter study in which patients with homologous recombination repair (HRR) gene-mutated (HRRm) mCRPC (N=423) were randomized to receive niraparib 200mg and abiraterone 1000mg (N=212) or placebo and abiraterone (N=211) until unacceptable toxicity or progression. All patients received prednisone 10mg daily and a GnRH analog or had prior bilateral orchiectomy. Patients with mCRPC who had not received prior systemic therapy in the mCRPC setting except for a short duration of prior abiraterone plus prednisone and ongoing ADT, were eligible. Of the 423 patients enrolled, 225 (53%) had *BRCA* gene mutations (*BRCA*m).

Of the 225 patients with *BRCA*m, the median age was 68 years (range 43 to 100), while 66% were 65 years and older. In addition, 72% were white, 66% had baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 34% had ECOG performance status of 1. Thirty-seven percent had bone-only metastases and 21% had visceral metastases.

The primary efficacy outcome measure was radiographic progression free survival (rPFS) determined by blinded independent central radiology (BICR) review evaluated per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (soft tissue lesions) and Prostate Cancer Working Group-3 (PCWG-3) criteria (bone lesions). Overall survival (OS) was an additional efficacy outcome measure. Results suggested that a statistically significant improvement in rPFS for niraparib plus abiraterone compared to placebo plus abiraterone was observed in *BRCA*m patients, and the Cohort 1 intention to treat (ITT) population.

In an exploratory analysis in the subgroup of 198 patients (47%) with non-*BRCA*m, the rPFS hazard ratio was 0.99 and the OS hazard ratio was 1.13, indicating that the improvement in the ITT population was mainly attributed to the results seen in the subgroup of patients with *BRCA*m. Efficacy results are presented in the table below, which was adapted from the prescribing information.

Patients in Cohort 1 with *BRCA* mutations	Akeega® (N=113)	Placebo (N=112)
Radiographic Progression-free Survival (rPFS)		
Event of disease progression or death	45 (40%)	64 (57%)
Median, months	16.6	10.9
Hazard Ratio, p-value	0.53; p=0.0014	
NNT *calculated by CHC*	6	

At the protocol pre-specified final OS analysis in Cohort 1, 60 deaths (53%) and 70 deaths (63%) were observed in the Akeega® arm and placebo arm, respectively, for patients with *BRCA*m. In an exploratory OS analysis in the subgroup of patients with *BRCA*m, the median in the Akeega® arm was 30.4 months and 28.6 months in the placebo arm, with an OS hazard ratio of 0.79.

Place in Therapy: Akeega® is a combination of niraparib and abiraterone that, used with prednisone, is indicated for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic

castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved test for Akeega®.

The efficacy of treatment were assessed in Cohort 1 of MAGNITUDE, a randomized, double-blind, placebo-controlled, multicohort, multicenter study that included patients with homologous recombination repair (HRR) gene-mutated (HRRm) mCRPC who were randomized to receive niraparib 200mg and abiraterone 1000mg or placebo and abiraterone until unacceptable toxicity or progression. In addition, all patients received prednisone 10mg daily and a GnRH analog or had prior bilateral orchiectomy. The major efficacy outcome was radiographic progression free survival (rPFS), and results suggested that a statistically significant improvement in rPFS for niraparib plus abiraterone compared to placebo plus abiraterone was observed in *BRCA*m patients, and the Cohort 1 intention to treat (ITT) population. In an exploratory analysis in the subgroup of 198 patients with non-*BRCA* mutations, the rPFS hazard ratio was 0.99 and the overall survival hazard ratio was 1.13, indicating that improvement in the ITT population was mainly due to the results seen in the subgroup of patients with *BRCA*m. Akeega® is the first and only dual action oral tablet with this indication.

It is recommended that Akeega® should be non-recommended in order to confirm the appropriate diagnosis and clinical parameters for use.

PDL Placement: ☐ **Recommended**
☒ **Non-Recommended with Conditions**

References

[1] Akeega [package insert]. Horsham, PA: Janssen Biotech Inc; 2023.