niraparib (Zejula®), niraparib-abiraterone (Akeega®)
EOCCO POLICY

Policy Type: PA/SP Pharmacy Coverage Policy: EOCCO139

Description
Niraparib (Zejula) is an orally administered poly (ADP-ribose) polymerase (PARP) inhibitor indicated for maintenance therapy, of ovarian, fallopian tube, or primary peritoneal cancer.
Niraparib-abiraterone acetate (Akeega) is a combination therapy containing abiraterone, an androgen biosynthesis inhibitor, indicated for prostate cancer.

Length of Authorization
- Initial: Six months
- Renewal: 12 months

Quantity limits

Product Name	Indication	Dosage Form	Quantity Limit
niraparib (Zejula)	Maintenance for: recurrent or advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	100 mg capsules*	30 capsules/30 days
		100 mg tablet	30 tablets/30 days
		200 mg tablet	30 tablets/30 days
		300 mg tablet	30 tablets/30 days
niraparib-abiraterone acetate (Akeega)	Metastatic prostate cancer, Castration-resistant, deleterious or suspected deleterious BRCA-mutated	50 mg/500 mg	60 tablets/30 days
		100 mg/500 mg	60 tablets/30 days

* Capsule formulation is being withdrawn from the market by end of year 2023

Initial Evaluation

I. **Niraparib (Zejula), niraparib-abiraterone acetate (Akeega)** may be considered medically necessary when the following criteria below are met:
   A. Member is 18 years of age or older; **AND**
   B. Medication is prescribed by, or in consultation with, an oncologist; **AND**
   C. Medication will not be used in combination with any other oncolytic medication; **AND**
   D. Member has not progressed on prior PARP inhibitor therapy (e.g. olaparib [Lynparza], rucaparib [Rubraca], talazoparib [Talzenna]) therapy; **AND**
   E. The request is for niraparib (Zejula); **AND**
      1. A diagnosis of one of the following:
         i. **Advanced (stage III or IV) ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
            a. Member has completed at least **one** prior platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **AND**

b. The member has **not** received bevacizumab (Avastin) in prior treatment; **AND**
c. Niraparib (Zejula) will **not** be used in combination with bevacizumab (Avastin); **OR**

ii. **Recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer**; **AND**
a. Member has experienced disease progression on or after at least two or more prior platinum-based chemotherapy regimens (e.g., cisplatin, carboplatin, oxaliplatin); **AND**
b. Member had complete or partial response to prior platinum-based chemotherapy (i.e., platinum-sensitive) (e.g. cisplatin, oxaliplatin, carboplatin); **AND**
c. Provider attests that member's epithelial ovarian, fallopian tube, or primary peritoneal cancer has not progressed since the most recent platinum-based chemotherapy regimen (e.g. cisplatin, oxaliplatin, carboplatin); **OR**

F. The request is for niraparib-abiraterone (Akeega); **AND**
1. A diagnosis of **metastatic, castration-resistant prostate cancer** (**mCRPC**); **AND**
2. Documentation of deleterious (pathogenic) or suspected deleterious (likely pathogenic) BRCA-mutation; **AND**
3. Evidence of disease progression despite therapy with a gonadotropin-releasing hormone analog (GnRH) or bilateral orchiectomy; **AND**
i. The member has not had disease progression on a second-generation antiandrogen agent (e.g. abiraterone, enzalutamide (Xtandi), apalutamide (Erleada), darolutamide (Nubeqa)); **AND**
4. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone; **AND**
5. Documentation of clinical rationale why combination therapy, abiraterone and olaparib (Lynparza), would not be an effective regimen (use of generic abiraterone 250 mg tablets required)

II. Niraparib (Zejula) and niraparib-abiraterone acetate (Akeega) are considered investigational when used for all other conditions, including but not limited to:
A. Used in combination with other chemotherapy or targeted therapy regimen.
B. Breast Cancer
C. Lung Cancer
D. Advance Solid Tumors
E. Melanoma

F. Pancreatic cancer
G. Gastroesophageal cancer
H. Treatment of advanced ovarian cancer after 3 of more lines of therapy
I. High risk localized or locally advanced prostate cancer
J. Metastatic castration resistant prostate cancer with SPOP gene mutation

Renewal Evaluation

I. Member has received a previous prior authorization approval for this agent through this health plan or has been established on therapy from a previous health plan; **AND**
II. Member is not continuing therapy based off being established on therapy through samples, manufacturer coupons, or otherwise. If they have, initial policy criteria must be met for the member to qualify for renewal evaluation through this health plan; **AND**
III. Clinical documentation of response to treatment (e.g., stabilization of disease, decrease in tumor size or tumor spread, lack of disease progression); **AND**
- **Ovarian, fallopian tube, or primary peritoneal cancer; AND**
  i. Medication will not be used in combination with any other oncolytic medication; **OR**
- **Metastatic, castration-resistant, prostate cancer; AND**
  i. Niraparib-abiraterone (Akeega) will not be used in combination with other anti-cancer agents (outside of gonadotropin-releasing hormone agonist [e.g., leuprolide] or endocrine therapy [e.g., anastrozole, tamoxifen, fulvestrant] or bevacizumab or abiraterone); **AND**
  ii. Niraparib-abiraterone acetate (Akeega) will be used in combination with prednisone or prednisolone

Supporting Evidence

Ovarian, fallopian tube, or primary peritoneal cancer

I. The safety and efficacy of niraparib (Zejula) in the setting of maintenance therapy for recurrent ovarian cancer was studied in a double-blind, placebo-controlled trial in adult patients with platinum-sensitive recurrent epithelial, ovarian fallopian tube, or primary peritoneal cancer. The patients were randomized 2:1 niraparib (Zejula) 300 mg orally daily or matched placebo within eight weeks of the last platinum-based chemotherapy regimen. The trial demonstrated a statistically significant improvement in progression free survival (PFS) for patients randomized to niraparib (Zejula) as compared with placebo in the gBRCAmut cohort and the non-gBRCAmut cohort.
   A. gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 21 and 5.5 in the placebo arm with a HR of 0.26 and 95% CI (0.17, 0.41).

B. Non-gBRCAmut Cohort: PFS in the niraparib (Zejula) arm was 9.3 and 3.9 in the placebo arm with a HR of 0.45 and 95% CI (0.34, 0.61).

II. Therapy in the maintenance setting was initiated within eight weeks after completion of the last dose of platinum-based chemotherapy. Therefore, the inclusion of this as criteria (see above) is that treatment is started within a reasonable timeframe consistent with a maintenance treatment plan (i.e. as close to eight weeks as possible) while still recognizing that scheduling or other factors may impact the ability of a patient to start exactly within these first eight weeks.

III. Efficacy and safety of niraparib (Zejula) in the first-line maintenance treatment was assessed in a phase three, double-blind, randomized (PRIMA) clinical trial in patients with newly diagnosed advanced (stage III or IV) ovarian cancer. Seven hundred and thirty-three patients, who were in complete or partial response to first-line platinum-based chemotherapy, were randomized 2:1 to niraparib (Zejula) or matched placebo. Patients with and without homologous recombination deficiency (HRD, e.g. gBRCA*m*) were included. At the end of treatment period, niraparib (Zejula) treatment arm showed a statistically significant improvement in median progression free survival (PFS) as compared to placebo arm.

A. Homologous recombination deficiency (HRD; e.g. gBRCA*m*) cohort: median PFS was 21.9 months in niraparib (Zejula) arm and 10.4 months in placebo arm (hazard ratio 0.43; 95% CI, 0.31 to 0.59; P<0.001)

B. Overall population (without HRD; gBRCA*m*) cohort: median PFS was 13.8 months in niraparib (Zejula) arm and 8.2 months in placebo arm (HR 0.62; 95% CI, 0.5 to 0.76; *p*<0.001).

None of the treated patients had a history of taking bevacizumab (Avastin). Therefore, efficacy and safety of niraparib (Zejula) after first-line therapy with bevacizumab (Avastin), or in combination with, bevacizumab (Avastin) is not supported.

IV. During PRIMA trial, serious adverse events occurred in 98.8% (N=478) patients in the treatment arm with 70.5% being grade ≥ 3. These numbers were 91.8% (N=224) and 46%, respectively in the placebo arm. Serious adverse events led to 79.5% dose interruption rates, 70.9% dose reduction rates, and 12% treatment discontinuation in the treatment group vs. 18%, 8.2%, and 2.5%, respectively, in the placebo group.

V. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy to support the use of a subsequent PARP inhibitor following progression of disease on another PARP inhibitor.

Prostate cancer

I. Niraparib-abiraterone acetate (Akeega) is FDA approved for the treatment of metastatic castration resistant prostate cancer (mCRPC) with *BRCA1/2* mutation.

II. The safety and efficacy of Niraparib/abiraterone acetate (Akeega) is demonstrated in the MAGNITUDE trial, which is a randomized, double blind, placebo-controlled, phase 3 trial. A total of 423 adult patients were randomized 1:1 to either receive abiraterone/prednisone in combination with niraparib or placebo. The primary outcome was radiographic progression free

survival (rPFS) assessed by blinded independent central review per RECIST 1.1 (soft tissue disease) and Prostate Cancer Clinical Trials Working Group 3 (bone disease). Treatment with niraparib-abiraterone resulted in a 45% lower risk of radiographic progression or death compared to the placebo/abiraterone arm (HR 0.55 95% CI 0.39-0.78, P = 0.0007). An overall survival benefit was also seen in the *BRCA* subgroup in a prespecified IPCW analysis (HR 0.54, 95% CI 0.33-0.90, P=0.0181). The most common adverse effects in the treatment group were anemia (50%), hypertension (33%), and constipation (33%). Treatment-emergent adverse events leading to dose interruption, dose reduction, or discontinuation of niraparib occurred in 49.7%, 20.3%, and 15.1% of patients in the active arm respectively. Niraparib/abiraterone for *BRCA mutation* is listed as a Category 1 recommendation per NCCN guidelines.

III. One of the key inclusion criteria in MAGNITUDE was bilateral orchiectomy or ongoing androgen deprivation therapy (ADT) with a GnRH agonist/antagonist. ADT was required to be continued throughout the study for patients who had not undergone bilateral orchiectomy. The safety and efficacy of Akeega in patients with prior treatment and progression on a second-generation AR inhibitor (i.e., enzalutamide, apalutamide and darolutamide) has not been established as these patients were excluded from the trial.

IV. The PROPel trial investigating olaparib (Lynparza) versus placebo in combination with abiraterone targeted a similar patient population as MAGNITUDE, men with metastatic castration resistant prostate cancer with HRR related mutations. The treatment group demonstrated a reduced risk of disease progression or death by 34% versus abiraterone alone (HR 0.66; 95% CI 0.54-0.81; p<0.0001). As of November 2023, head-to-head trials have not been conducted to suggest superiority of one regimen over the other. Abiraterone is currently available as a generic formulation.

Investigational or Not Medically Necessary Uses

I. There is a lack of strong scientific evidence from randomized controlled trials supporting safety and efficacy for the use of niraparib (Zejula) in the following settings listed below:
   A. Used in combination with other chemotherapy or targeted therapy regimen.
   B. Breast Cancer
   C. Prostate Cancer
   D. Lung Cancer
   E. Advance Solid Tumors
   F. Melanoma
   G. Pancreatic cancer
   H. Gastroesophageal cancer
   I. Treatment of advanced ovarian cancer after 3 of more lines of therapy
      i. Niraparib (Zejula) was studied in the QUADRA trial, evaluating niraparib (Zejula) for the treatment of advanced ovarian cancer after three or more

chemotherapies. This was a single arm trial with investigator assessment of objective response rate (ORR) as the efficacy outcome measure. Given the setting of the QUADRA trial (single arm, uncontrolled nature), no comparative overall survival information can be obtained from the study, and it is difficult to assess any potential effect of niraparib (Zejula) on time to event endpoints.

ii. In September 2022, the manufacturer of niraparib (Zejula) voluntarily withdrew the indication for treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens. This withdrawal was based on a totality of information from PARP inhibitors in the late line treatment setting in ovarian cancer. A potential detrimental effect on overall survival was observed with two different PARP inhibitors in two independent randomized, active-controlled clinical trials conducted in a BRCA mutant 3L+ advanced ovarian cancer population.

References

1. Zejula [Prescribing Information]. Research Triangle Park, NC: GlaxoSmithKline LLC. September 2022.
2. AKEEGA [Prescribing Information]. Horsham, PA: Janssen Biotech, Inc. August 2023.
3. González-Martín A, Pothuri B, Vergote I, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381(25):2391-2402
4. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines). Ovarian Cancer Including: Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer & Less Common Histopathologies. Version 1.2020 [Updated March 11, 2020 Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian_blocks.pdf
5. ASCO guidelines for gynecological cancer: PARP inhibitors in the management of ovarian cancer, J. Clin. Oncol.; 2020, e-pub 8/2020; DOI: 10.1200/JCO.20.01924
6. Chi KN, Rathkopf D, Smith MR, et al. Niraparib and Abiraterone Acetate for Metastatic Castration-Resistant Prostate Cancer. *J Clin Oncol*. 2023;41(18):3339-3351. doi:10.1200/JCO.22.01649
7. Chi KN, Sandhu S, Smith MR, 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;34(9):772-782. doi:10.1016/j.annonc.2023.06.009
8. National Comprehensive Cancer Network. Prostate Cancer (Version 4.2023) NCCN. September 7, 2023. Accessed October 31, 2023. prostate.pdf (nccn.org)

Related Policies

Policies listed below may be related to the current policy. Related policies are identified based on similar indications, similar mechanisms of action, and/or if a drug in this policy is also referenced in the related policy.

Policy Name	Disease state
Olaparib (Lynparza) Policy	Breast cancer, metastatic, HER2-negative, germline BRCA-mutated (gBRCAm)
	Prostate cancer, metastatic castration-resistant (mCRPC)
Talazoparib (Talzenna) Policy	Breast cancer, locally advanced or metastatic, BRCA-mutated

	Prostate cancer, metastatic castration-resistant, homologous recombination repair (HRR) gene-mutated
Second Generation Anti-Androgen Agents	Prostate cancer

Policy Implementation/Update:

Action and Summary of Changes	Date
Updated Zejula policy to include Akeega based on expanded indication in metastatic castration resistant prostate cancer (mCRPC). Updated QL table, general formatting, verbiage to align with current policies, and supporting evidence.	12/2023
Add 100, 200, and 300 mg tablets to the QL table with a 30/30 QL; reducing the QL from 90/30 due to the manufacturer's website promoting conversion to the once daily tablet (regardless of dose), rather than taking 1 to 3 capsules daily.	08/2023
Removal of ovarian cancer indication in the late line (3+) treatment setting following voluntarily withdrawal of the indication by the manufacturer.	09/2022
Addition of new indication and supporting evidence for first-line maintenance therapy in women with advanced ovarian cancer; Updated policy format to categorize recommendation for niraparib (Zejula) based treatment OR maintenance therapy; added split fill management	09/2020
Criteria transition into policy with the following updates made: addition of supporting evidence and investigation section, broke out the different indications (treatment versus maintenance therapy) due to the newly approved indication for late-line treatment in women with recurrent ovarian cancer, included mutation status for the treatment of recurrent ovarian cancer, included criterion around prior PARP inhibitor use, increase initial approval duration from three months to six months to be consistent with other payers, included age criterion per label, and removed the 8 weeks criterion around most recent platinum-based therapy in the setting of maintenance therapy in recurrent ovarian cancer; in place of the 8 weeks criterion, provider attestation and documentation is required instead.	11/2019
Criteria created	08/2017