Clinical Policy Title:	niraparib
Policy Number:	RxA.573
Drug(s) Applied:	Zejula®
Original Policy Date:	03/06/2020
Last Review Date:	04/13/2023
Line of Business Policy Applies to:	All lines of business

Background

Niraparib (Zejula®) is a poly (ADP-ribose) polymerase (PARP) inhibitor. It is indicated:

- For the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to first line platinum-based chemotherapy.
- For the maintenance treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAmut) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
niraparib (Zejula®)	Advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer	For patients weighing <77 kg (<170 lbs) or with a platelet count < 150,000/µL, 200 mg orally once daily. For patients weighing ≥77 kg (≥170 lbs) and a platelet count ≥150,000/µL, 300 mg orally once daily. For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily.	300 mg/day
niraparib (Zejula®)	Deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer	300 mg orally once daily	300 mg/day

Dosage Forms

- Capsules: 100 mg

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Ovarian Cancer (must meet all):

1. Diagnosis of advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Members request meets one of the following (a or b):
   a. Both i and ii:
      i. Newly diagnosed stage II-IV disease;
      ii. Completed first-line platinum-based chemotherapy regimen and is in a complete or partial response;
   b. Both i and ii (see Appendix D):
      i. Documentation of deleterious or suspected deleterious germline BRCA-mutation;
      ii. Completed platinum-based chemotherapy and is in a complete or partial response;
5. Member has not previously received a PARP inhibitor (e.g., Lynparza®, Rubraca®, Talzenna®);
6. Request meets one of the following (a or b):*
   a. Dose does not exceed 300 mg (3 capsules) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Uterine Cancer (off-label) (must meet all):

1. Diagnosis of advanced, recurrent/metastatic, or inoperable uterine sarcoma;
2. Prescribed by or in consultation with an oncologist;
3. Age ≥ 18 years;
4. Member has tried one systemic regimen (examples of a systemic regimen include one or more of the following products: dacarbazine, docetaxel, doxorubicin, epirubicin, gemcitabine, ifosfamide, vinorelbine);
5. Member has BRCA2 mutation;
6. Member has not previously received a PARP inhibitor (e.g., Lynparza®, Rubraca®, Talzenna®);
7. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).*

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

II. Continued Therapy Approval

A. All Indication in Section I (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance, or member has met initial approval criteria for the covered indication and has received this medication for at least 30 days;
2. Member is responding positively to therapy;
3. If request is for a dose increase, request meets one of the following (a or b):*
   a. New dose does not exceed 300 mg (3 capsules) per day;
   b. Dose is supported by practice guidelines or peer-reviewed literature for the relevant off-label use (prescriber must submit supporting evidence).

*Prescribed regimen must be FDA-approved or recommended by NCCN.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
FDA: Food and Drug Administration
PARP: Poly (ADP-ribose) polymerase
HRD: homologous recombination deficiency
PRES: Posterior Reversible Encephalopathy Syndrome
MDS: Myelodysplastic Syndrome
AML: Acute Myeloid Leukemia

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Ovarian Cancer		
pemetrexed (Alimta®)	Various	Varies
melphalan (Alkeran®)	Various	Varies
bevacizumab (Avastin®)	Various	Varies
carboplatin (Paraplatin®)	Various	Varies
cisplatin	Various	Varies
cyclophosphamide	Various	Varies
docetaxel	Various	Varies
doxorubicin (Doxil®, Adriamycin®)	Various	Varies
etoposide	Various	Varies
gemcitabine	Various	Varies
ifosfamide (Ifex®)	Various	Varies
irinotecan (Camptosar®)	Various	Varies

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Ovarian Cancer		
oxaliplatin	Various	Varies
topotecan (Hycamtin®)	Various	Varies
Altretamine (Hexalen®)		

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - None reported.

- Boxed Warning(s):
  - None reported.

APPENDIX D: General Information

- Zejula® has high bioavailability (around 73%) and extensive tissue distribution, as well as a long half-life (36 hours).
- Platinum-based chemotherapies have served as the standard of care for ovarian cancer treatment for decades. It induces cross-linking between purine bases in DNA, lesions that require homologous recombination (HR) to repair. In ovarian cancer patients who harbor a homologous recombination deficiency, compromised repair of DNA lesions is thought to contribute to their response to platinum-based chemotherapies.
- Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): MDS/AML occurred in patients exposed to Zejula®, and some cases were fatal. Monitor patients for hematological toxicity and discontinue if MDS/AML is confirmed.
- Bone Marrow Suppression: Test complete blood counts weekly for the first month, monthly for the next 11 months, and periodically thereafter for clinically significant changes.
- Hypertension and Cardiovascular Effects: Monitor blood pressure and heart rate at least weekly for the first 2 months, then monthly for the first year and periodically thereafter during treatment with Zejula®. Manage with antihypertensive medications and adjustment of the dose of Zejula®, if necessary.
- Posterior Reversible Encephalopathy Syndrome (PRES): PRES has occurred in patients treated with Zejula®. Discontinue Zejula® if PRES is confirmed.
- Embryo-Fetal Toxicity: Zejula® can cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception.
- Allergic Reactions to FD&C Yellow No. 5 (Tartrazine): Contains FD&C Yellow No. 5 (tartrazine) as a color additive, which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.
- There are insufficient data regarding the use of consecutive PARP inhibitors. Most PARP inhibitor pivotal trials excluded prior PARP inhibitor use, the NCCN does not make any explicit recommendations (other than for ovarian cancer, where they state data is limited), and there are no randomized controlled trials evaluating such use.

Restricted Second or Later Line Setting Indication to Germline BRCA Mutated Population

- GlaxoSmithKline, manufacturer of Zejula®, restricted the indication of Zejula® for the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy received in the second or later line setting to the germline BRCA-mutated patient population only in the United States.
- The decision was made at the request of the FDA following the final OS analysis of the NOVA (NCT01847274) study. The observed OS results from NOVA study are shown:
  - Germline BRCA-mutated cohort (N = 203): median OS was 43.6 months for patients with Zejula® compared to 41.6 months for patients on placebo (HR = 0.93 [95% CI 0.63, 1.36]).
  - Non-germline BRCA-mutated cohort (N = 350): median OS was 31.3 months for patients treated with Zejula® compared to 41.6 months for patients on placebo (HR = 1.10 [95% CI 0.83, 1.46]).
  - Non-germline BRCA-mutated, HRD positive subgroup: median OS was 37.3 months for patients treated with Zejula® compared to 41.4 months for patients on placebo (HR = 1.32 [95% CI 0.84, 2.06]).
- The current OS results indicate possible OS detriment to patients in the overall non- germline BRCA-mutated cohort and to patients in the non-germline BRCA-mutated/HRD positive subgroup who received Zejula® maintenance in this setting compared to placebo.
- Physicians who are currently treating patients with Zejula® for patients with non-germline BRCA-mutated platinum sensitive recurrent ovarian cancer in the second or later line maintenance setting are asked to discuss this information with those patients for an individual benefit-risk assessment so that they can make an informed decision regarding their ongoing care.

References

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Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/2020	03/06/2020
Policy was reviewed: 1. Clinical policy title was updated as “niraparib”. 2. Background updated to include more indications 3. Line of business policy applies to all lines of business. 4. Initial approval criteria I.A.1 was updated to add new diagnosis criteria. 5. Dosing information updated. 6. Continued therapy approval criteria II.A.1 was rephrased to “Member is currently receiving medication that has been authorized by RxAdvance..” 7. Appendices A, B & D updated. 8. References were reviewed and updated.	11/05/2020	12/07/2020
Policy was reviewed: 1. Dosing information is updated to include “For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily.” In dosing regimen. 2. Statement about provider sample ‘‘The provision of provider samples does not guarantee coverage…” was added to Clinical Policy. 3. Appendix A was updated to include abbreviations for “PRES”, “MDS”, “AML”. 4. Statement about drug listing format in Appendix B is updated to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand, Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 5. Appendix D was updated to include Warning and precautions. 6. References were reviewed and updated.	10/08/2021	12/07/2021
PA policy was reviewed: 1. Initial Approval Criteria I.A.4: Updated to remove Completed ≥ 2 platinum-based chemotherapy regimens and is in a complete or partial response. 2. Initial and Continued Therapy Criteria I.A.5 and II.B.3: Updated to add disclaimer Prescribed regimen must be FDA-approved or	07/28/2022	10/19/2022

recommended by NCCN. 3. Appendix B: Updated to include altretamine (Hexalen®) as treatment alternative. 4. References were reviewed and updated.		
Policy was reviewed: 1. Background: Updated to remove indication "For the treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with three or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (HRD) positive status defined by either: • deleterious or suspected deleterious BRCA mutation, or • genomic instability and who have progressed more than six months after response to the last platinum-based chemotherapy." 2. Background: Updated to include details regarding indication recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer "deleterious or suspected deleterious germline BRCA-mutated (gBRCAmut)". 3. Dosing Information, Indication: Updated to include new indication Deleterious or suspected deleterious germline BRCA-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. 4. Initial Approval Criteria, I.A.1: Updated diagnostic criteria to Diagnosis of advanced or recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. 5. Initial Approval Criteria, I.A.1.c: Updated diagnostic criteria to remove "Disease is associated with HRD positive status defined by one of the following (a or b): a. Documentation of deleterious or suspected deleterious germline BRCA mutation; b. Documentation of genomic instability and disease has progressed > 6 months after response to the last platinum-based chemotherapy; c. Failure of ≥ 3 prior chemotherapy regimens (see Appendix B), unless contraindicated or clinically significant adverse effects are experienced;	03/24/2023	04/13/2023

6. Initial Approval Criteria, I.A.4: Updated to include new criteria Members request meets one of the following (a or b): a. Both i and ii: i. Newly diagnosed stage II-IV disease; ii. Completed first-line platinum-based chemotherapy regimen and is in a complete or partial response; b. Both i and ii (see Appendix F): i. Documentation of deleterious or suspected deleterious germline BRCA-mutation; ii. Completed platinum-based chemotherapy and is in a complete or partial response 7. Initial Approval Criteria, I.A.5: Updated to include new prior therapy criteria Member has not previously received a PARP inhibitor (e.g., Lynparza®, Rubraca®, Talzenna®). 8. Initial Approval Criteria, I.B: Updated to include approval criteria for indication, Uterine Cancer. 9. Initial Approval Duration for all indications: Updated from 6 months to 12 months. 10. Appendix D, General Information: Updated to include new information regarding: a. Restricted Second or Later Line Setting Indication to Germline BRCA Mutated Population. b. Insufficient data regarding use of PARP inhibitors. 11. References were reviewed and updated.		