



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2024-N-1056]

Clovis Oncology, Inc., AstraZeneca Pharmaceuticals LP, and GlaxoSmithKline LLC;

Withdrawal of Approval of the Indications for Advanced Ovarian Cancer for Poly (ADP-ribose) Polymerase Inhibitors RUBRACA (Rucaparib) Tablets, LYNPARZA (Olaparib) Tablets, and ZEJULA (Niraparib) Capsules

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA or Agency) is announcing that it is withdrawing approval of the indications for the treatment of adult patients with advanced ovarian cancer for poly (ADP-ribose) polymerase (PARP) inhibitors under three new drug applications (NDAs) from multiple applicants. The applicants Clovis Oncology, Inc. (Clovis), AstraZeneca Pharmaceuticals LP (AZ), and GlaxoSmithKline, LLC (GSK) have each voluntarily requested that the Agency withdraw approval of the indications for the treatment of adult patients with advanced ovarian cancer for their respective PARP inhibitors and waived their opportunities for hearings. Applicant and indication details are further discussed in SUPPLEMENTARY INFORMATION.

DATES: Approval is withdrawn as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

FOR FURTHER INFORMATION CONTACT: Kimberly Lehrfeld, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6226, Silver Spring, MD 20993-0002, 301-796-3137, Kimberly.Lehrfeld@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: The PARP inhibitors and their respective applicants, NDA numbers, and indications being withdrawn are included in the following table.

Application No.	Drug	Applicant	Indication Being Withdrawn
NDA 209115	Rubraca (rucaparib) Tablets, equivalent to (EQ) 200 milligrams (mg) base, EQ 250 mg base, and EQ 300 mg base	Clovis Oncology, Inc., 5500 Flatiron Pkwy., Boulder, CO 80301	for the treatment of adult patients with a deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.
NDA 208558	Lynparza (olaparib) Tablets, 100 mg and 150 mg	AstraZeneca Pharmaceuticals LP, 1800 Concord Pike, Wilmington, DE 19803	for the treatment of adult patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.
NDA 208447	Zejula (niraparib) Capsules, EQ 100 mg base	GlaxoSmithKline, LLC, 2929 Walnut St., Suite 1700, Philadelphia, PA 19104	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: <ul style="list-style-type: none"> • a deleterious or suspected deleterious BRCA mutation, or • genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic device for ZEJULA.

I. RUBRACA (rucaparib) Tablets

A. Application Background

On December 19, 2016, FDA approved NDA 209115 for RUBRACA (rucaparib)

Tablets, EQ 200 mg base, EQ 250 mg base, and EQ 300 mg base, for the treatment of adult

patients with advanced ovarian cancer (see table for full indication¹). On May 4, 2022, FDA met with Clovis to discuss the final results from the clinical trial entitled “ARIEL4 (Assessment of Rucaparib in Ovarian CancEr Trial): A Phase 3 Multicenter, Randomized Study of Rucaparib Versus Chemotherapy in Patients With Relapsed, BRCA Mutant, High Grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer.”² The results indicated that patients in the intent-to-treat population who were taking rucaparib potentially had a shorter overall survival (OS) than patients not on rucaparib. At that meeting FDA conveyed that these results constituted a serious risk for patients receiving treatment with rucaparib. On May 10, 2022, the Agency asked Clovis, in writing, to voluntarily permit FDA to withdraw approval of the indication for the treatment of adult patients with deleterious BRCA mutation-associated epithelial ovarian, fallopian tube or primary peritoneal cancer who have been treated with two or more chemotherapies, pursuant to § 314.150(d) (21 CFR 314.150(d)) and waive its opportunity for a hearing. On June 1, 2022, Clovis submitted a letter requesting withdrawal of approval of this indication for RUBRACA (rucaparib) Tablets pursuant to § 314.150(d) and waiving its opportunity for a hearing.

B. Withdrawal of Approval of Indication for RUBRACA Tablets

Therefore, under § 314.150(d), approval of the indication for the treatment of adult patients with deleterious BRCA mutation-associated epithelial ovarian, fallopian tube or primary peritoneal cancer who have been treated with two or more chemotherapies for RUBRACA (rucaparib) Tablets is withdrawn as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Withdrawal of approval of this indication does not affect any other approved indication for RUBRACA (rucaparib) Tablets.

¹ The initially approved indication was “as monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic)-associated *advanced ovarian cancers* [emphasis added] who have been treated with two or more chemotherapies. Select patients for therapy based on an FDA-approved companion diagnostic for RUBRACA.” On April 6, 2018, the Agency approved a revised indication that, among other things, clarified the indication by listing the following specific advanced ovarian cancers in the indication: epithelial ovarian, fallopian tube, and primary peritoneal cancer.

² The study, under its abbreviated title “ARIEL4: A Study of Rucaparib Versus Chemotherapy BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients,” is available on the National Institutes of Health (NIH) National Library of Medicine’s ClinicalTrials.gov web page at <https://clinicaltrials.gov/ct2/show/NCT02855944>.

II. LYNPARZA (olaparib) Tablets

A. Application Background

On August 17, 2017, FDA approved NDA 208558 for LYNPARZA (olaparib) Tablets, 100 mg and 150 mg, for the treatment of adult patients with advanced ovarian cancer (see table for full indication). On July 14, 2022, FDA met with AZ to discuss the final OS results from the clinical trial entitled “A Phase III, Open Label, Randomised, Controlled, Multi-centre Study to Assess the Efficacy and Safety of Olaparib Monotherapy Versus Physician’s Choice Single Agent Chemotherapy in the Treatment of Platinum Sensitive Relapsed Ovarian Cancer in Patients Carrying Germline BRCA1/2 Mutations” (SOLO3).³ The results indicated that patients who were taking olaparib potentially had a shorter OS than patients not on olaparib, particularly in the subgroup analysis of patients who had received three or more lines of chemotherapy. On July 26, 2022, the Agency asked AZ, in writing, to voluntarily permit FDA to withdraw approval of the indication for the treatment of adult patients with deleterious germline BRCA mutation-associated advanced ovarian cancer who have been treated with three or more chemotherapies, pursuant to § 314.150(d) and waive its opportunity for a hearing for NDA 208558. On August 19, 2022, AZ submitted a letter requesting withdrawal of approval of this indication for LYNPARZA (olaparib) Tablets (NDA 208558) pursuant to § 314.150(d) and waiving its opportunity for a hearing.

B. Withdrawal of Approval of Indication for Lynparza Tablets

Therefore, under § 314.150(d), approval of the indication for the treatment of adult patients with deleterious germline BRCA mutation-associated advanced ovarian cancer who have been treated with three or more chemotherapies for LYNPARZA (olaparib) Tablets is withdrawn as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

³ The study, under its abbreviated title “Olaparib Treatment in Relapsed Germline Breast Cancer Susceptibility Gene (BRCA) Mutated Ovarian Cancer Patients Who Have Progressed at Least 6 Months After Last Platinum Treatment and Have Received at Least 2 Prior Platinum Treatments (SOLO3),” is available on the NIH National Library of Medicine’s ClinicalTrials.gov web page at <https://clinicaltrials.gov/ct2/show/NCT02282020>.

Withdrawal of approval of this indication does not affect any other approved indication for LYNPARZA (olaparib) Tablets.

III. ZEJULA (niraparib) Capsules

A. Application Background

On October 23, 2019, FDA approved NDA 208447 for ZEJULA (niraparib) Capsules, EQ 100 mg base, for the treatment of adult patients with advanced ovarian cancer (see table for full indication). On August 4, 2022, FDA met with GSK to discuss the status of the ZEJULA (niraparib) Capsules indication for the treatment of adult patients with advanced ovarian cancer. FDA requested that GSK voluntarily permit FDA to withdraw approval of this indication because the results from randomized trials of rucaparib and olaparib in similar treatment settings showed OS may be reduced in patients receiving PARP inhibitors. FDA stated that these results from two independent trials were concerning and suggested a class-wide effect for PARP inhibitors. In correspondence dated August 24, 2022, GSK acknowledged that because of the uncontrolled nature of the trial entitled “A Phase 2, Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Niraparib in Patients With Advanced, Relapsed, High-Grade Serous Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Who Have Received Three or Four Previous Chemotherapy Regimens”⁴ on which approval of this indication was based, it would be difficult to demonstrate that niraparib does not impact survival in this treatment setting. Therefore, GSK agreed to voluntarily withdraw the advanced ovarian cancer indication. On September 7, 2022, GSK submitted a letter requesting withdrawal of approval of this indication for ZEJULA (niraparib) Capsules pursuant to § 314.150(d) and waiving its opportunity for a hearing.

B. Withdrawal of Approval of Indication for Zejula Capsules

⁴ The study, under its abbreviated title “A Study of Niraparib in Patients With Ovarian Cancer Who Have Received Three or Four Previous Chemotherapy Regimens (QUADRA),” is available on the NIH National Library of Medicine’s ClinicalTrials.gov web page at <https://clinicaltrials.gov/ct2/show/NCT02354586>.

Therefore, under § 314.150(d), approval of the 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 HRD positive status defined by either a deleterious or suspected deleterious BRCA mutation or genomic instability and who have progressed more than 6 months after response to the last platinum-based chemotherapy for ZEJULA (niraparib) Capsules is withdrawn as of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Withdrawal of approval of this indication does not affect any other approved indication for ZEJULA (niraparib) Capsules.

Dated: March 19, 2024.

Lauren K. Roth,

Associate Commissioner for Policy.

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