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APPLICATION NUMBER:

214876Orig1s000

CLINICAL REVIEW(S)

Clinical Review Memo

Application Type (NDA/BLA)	NDA
Application Number(s)/ Supplement number	214876
Submission Received Date	June 30, 2022
PDUFA Goal Date	April 30, 2023
Review Completion Date	*Electronic stamp date*
Division/Office	DO1/OOD/OND
Clinical Review Team	Mirat Shah, MD
Associate Director for Oncology Labeling	William Pierce, PharmD, MPH, BCPS
Designated Signatory (Division Director)	Laleh Amiri-Kordestani, MD
Product: Established Name (Trade name)	Niraparib, ZEJULA®
Established Pharmacologic Class (EPC)	PARP inhibitor
Applicant	Glaxosmithkline, LLC
Dosing regimen	300 mg daily
Dosage form	100 mg, 200 mg, and 300 mg tablets for oral use
Recommended Regulatory Action	Regular Approval

1. Executive Summary

The Applicant (Glaxosmithkline, LLC) is seeking approval for a new tablet formulation for ZEJULA (niraparib) in this New Drug Application (NDA). The reference product is ZEJULA (niraparib tosylate, 100 mg capsules) which was initially approved on March 27, 2017, under NDA 208447. Niraparib is an oral inhibitor of poly(ADP-ribose) polymerase (PARP) enzymes, including PARP-1 and PARP-2, and is currently approved for the following indications:

- 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 (g*BRCA*mut) recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

In a Type C Written Response Only (WRO) meeting on August 11, 2017, the Applicant proposed submission of a biowaiver to establish bioequivalence between niraparib capsules to niraparib tablets. FDA stated that an *in vivo* bioavailability/bioequivalence (BA/BE) study at the highest niraparib dose (300 mg) would be necessary to support approval for niraparib tablets.

Biowaiver requests for the lower strength niraparib tablets (200 mg and 100 mg) would be acceptable.

The Applicant initially submitted this NDA on June 16, 2020, but requested to withdraw it on January 29, 2021, after learning that FDA would require a food-effect study for approval of the tablet formulation. The NDA was re-submitted on June 30, 2022.

The Applicant included results from the following studies to support this NDA:

- Study 3000-01-004, Stage 1 and 2: a single-dose, two-period, two-treatment, two-way, crossover study in patients with advanced solid tumors. This is a relative BA/BE study.

- Study 3000-01-004, Stage 3: A single-dose, two-period, two-treatment, two-way, crossover study in patients with advanced solid tumors. This is a food effect study which characterized the effect of a high-fat high-calorie meal on the BA of the proposed tablet formulation.

- Additionally, the Applicant submitted a biowaiver request for the lower strengths (100 mg and 200 mg tablets) based on comparative multi-media dissolution testing.

The recommended dosing for niraparib tablets is based on the recommended dosing in the current USPI for niraparib capsules.

Of note, after this NDA was resubmitted on June 30, 2022, the following indication was removed from niraparib labeling under the capsule formulation NDA 208447, Supplement 26 on September 14, 2022.

- treatment of adult patients with advanced ovarian, fallopian tube, or primary peritoneal cancer who have been treated with 3 or more prior chemotherapy regimens and whose cancer is associated with homologous recombination deficiency (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.

In addition, the following indication was restricted to patients with germline *BRCA* mutations only under NDA 208447, Supplement 25 on December 8, 2022.

- For the maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.

When the indication was restricted, FDA issued a PMC for a companion diagnostic device to select patients with germline *BRCA* mutations for treatment with niraparib. The Applicant submitted a PMC final report and an sNDA (NDA 208447, Supplement 27) to add language

regarding the companion diagnostic device to product labeling. The device Applicant submitted a 180-day PMA supplement (P140020/S027) to CDRH for the Myriad BRACAnalysis CDx as a companion diagnostic device. NDA 214876 will be contemporaneously approved with NDA 208447, Supplement 27 and PMA 140020, Supplement 27.

Reviews from other disciplines are summarized here:

Clinical Pharmacology

Per the Clinical Pharmacology team's review, the pharmacokinetic (PK) exposure was comparable between the niraparib tablets and niraparib capsules. Additionally, the food effect study results suggested that a high-fat meal did not have a clinically meaningful effect on the PK of niraparib tablets. Please refer to Dr. Yixuan Dong's review in DARRRTS for details.

Product Quality

Per the Product Quality team's review, the information included in the submission is sufficient to assure the identify, strength, purity, and quality of the proposed drug product. In addition, all associated manufacturing, testing, and packaging facilities are acceptable. Please refer to the Integrated Quality Review authored by Dr. Xing Wang and the review team in DARRTS for more details.

In conclusion, in accordance with 21 Code of Federal Regulations (CFR) 320.21(a), the review teams recommend regular approval of NDA 214876 for niraparib tablets (100 mg, 200 mg, and 300 mg tablets for oral use) for all indications that the niraparib capsule currently has under NDA 208447.

2. Risk Management Plan

(b) (4) In a Type C WRO meeting on October 16, 2019, FDA stated that the Applicant should provide a transition plan for patients currently taking niraparib capsules to switch to niraparib tablets. The FDA also stated that the Sponsor should provide a risk assessment of medication error risk during the transition from capsules to tablets.

The Applicant included a risk management plan in the NDA for the transition between niraparib capsules to niraparib tablets (b) (4). The Division of Medication Error Prevention and Analysis 2 (DMEPA 2) reviewed this plan and found it acceptable from a medication error perspective. The Clinical review team agrees with DMEPA 2's conclusions.

3. Labeling Considerations:

Changes in the niraparib tablet USPI are shown in Table 1. Changes made in product labeling related to NDA 208447, Supplement 27 were also included in the labeling for this NDA.

Table 1: Summary of Labeling Changes

Section of Approved USPI	Labeling Change Implemented
Highlights of Prescribing information	• Throughout section, modified "capsules" to "tablets" • In Dosage Forms and Strengths, listed tablet dosage forms "Tablets: 100 mg, 200 mg, 300 mg" • Removed information for Allergic Reactions: "Allergic Reactions to FD&C Yellow No. 5 (Tartrazine)" as this is not applicable to the tablet formulation • Modified instructions under Dosage and Administration to "Continue treatment until disease progression or unacceptable toxicity" rather than "Continue treatment until disease progression or unacceptable adverse reaction." • Added the following clarifying language (in bold) regarding the companion diagnostic device to the indication for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer: "For the maintenance treatment of adult patients with deleterious or suspected deleterious germline *BRCA*-mutated recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in complete or partial response to platinum-based chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA".

Section 1	• Added the following statement to Section 1.2 Maintenance Treatment of Recurrent Germline *BRCA*-mutated Ovarian Cancer: "Select patients for therapy based on an FDA-approved companion diagnostic for ZEJULA [see Dosage and Administration (2.1)]."
Section 2	• Modified "capsule" to "tablet" throughout section • In section 2.1 Patient Selection, added the following clarifying statement and removed prior information to select patients for maintenance treatment of recurrent germline *BRCA*-mutated ovarian cancer: "Information on FDA-approved tests for the detection of deleterious or suspected deleterious *BRCA* mutations for this indication is available at https://www.fda.gov/companiondiagnostics" (b) (4) (b) (4) • In Section 2.2 Recommended Dosage, removed information regarding the number of capsules for each indication. • In Section 2.3 Dosage Adjustments for Adverse Reactions, removed the sentence "The recommended dose modifications for adverse reactions are listed in Tables 1, 2, and 3." • In Section 2.3 Dosage Adjustments for Adverse Reactions, removed capsule information from Table 1.

Section 3	• Removed information on the capsule dosage forms and strengths. • Added information on the tablet dosage forms and strengths.
Section 5	• Removed Section 5.6 Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) as this does not apply to the tablet formulations.
Section 6	• In Section 6.1 Clinical Trials Experience, added "g*BRCA*mut Cohort" to the heading in Table 8
Section 8	• Revised Section 8.2 Lactation to advise a lactating woman not to breastfeed during treatment and for 1 month after receiving the "last dose" rather than the "final dose".
Section 11	• Removed the description of the capsules. • Added the description of the tablet.
Section 12	• In 12.3 Pharmacokinetics, under Absorption, added a more detailed description of the pharmacokinetic parameters following a high-fat meal.
Section 14	• In Section 14.1 First-Line Maintenance Treatment of Advanced Ovarian Cancer, added a footnote under Table 10 clarifying the abbreviation "BICR". • In Section 14.2 Maintenance Treatment of Recurrent Germline BRCA-mutated Ovarian

	Cancer, specified the accompanying companion diagnostic device that was utilized in the clinical trial, as follows: "Eligible patients were assigned to 1 of 2 cohorts based on the results of germline BRCA testing with Myriad BRACAnalysis CDx".
Section 16	• Removed information on storage and handling of the capsules • Added information on the storage and handling of the tablets. • Added instructions to "Store and dispense in the original bottle."
Section 17	• Changed "capsule" to "tablet" throughout section. • Removed information on Allergic Reactions to FD&C Yellow No. 5 (Tartrazine) • Revised Contraception guidance to state that patients should use effective contraception for "6 months after receiving the last dose" rather than "at least 6 months after receiving the last dose". • Added information stating that Opadry is a trademark owned by or licensed to its respective owner and not owned by or licensed to the GSK group of companies. Also stated that the maker of Opadry is no affiliated with or endorse the GSK group of companies or its products.

Medication Guide	• Changed “capsules” to “tablets” throughout the section. • Removed information on allergic reactions to FD&C Yellow No. 5 (Tartrazine) • Revised pregnancy instructions to change “may” to “should” in the following sentence: “If you are able to become pregnant, your healthcare provider should perform a pregnancy test before you start treatment with ZEJULA.” • Reorganized the most common side effects section to be consistent with the Highlights section. • Changed “healthcare provider” to “doctor” in the instructions to call for medical advice about side effects. • Added an instruction to store the tablets in the original bottle. • Removed the capsule inactive ingredients and added the tablet inactive ingredients • Added information stating that Opadry is a trademark owned by or licensed to its respective owner and not owned by or licensed to the GSK group of companies. Also stated that the maker of Opadry is no affiliated with or endorse the GSK group of companies or its products.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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