CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214876Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND RISK MANAGEMENT PLAN
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	January 20, 2023
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 214876
Product Name and Strength:	Zejula (niraparib) tablets, 100 mg, 200 mg, and 300 mg
Applicant/Sponsor Name:	GlaxoSmithKline LLC (GSK)
TTT ID #:	2022-841-1
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 PURPOSE OF MEMORANDUM

GSK submitted revised container labels received on January 17, 2023 for Zejula. The Division of Oncology 1 (DO1) requested that we review the revised container labels for Zejula (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

DO1 also requested we review the risk management plan[b] that outlines the Sponsor's plan to transition from capsules to tablet formulation while both formulations are on the market to determine if the risk management plan is acceptable from a medication error perspective.

2 REVIEW OF THE REVISED CONTAINER LABELS

GSK clarified the that the product should be stored and dispensed in original bottle[c], and revised the statement "Store in original container" to "Store and dispense in the original

[a] Gao, T. Label and Labeling Review for Zejula (NDA 214876). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 Nov 28. TTT ID No.: 2022-841.
[b] Transition Plan and Risk Management. NDA 214876: Niraparib (Zejula) tablets, Revised 1.16.1 Risk Management Plan (Non-REMS). Philadelphia (PA): GlaxoSmithKline LLC (GSK). 2022 July 22. Available from: \\CDSESUB1\EVSPROD\nda214876\0021\m1\us\116-risk-management-plans\1161-non-rems\risk-mgmt.pdf.
[c] Proposed Prescribing Information for Zejula. Philadelphia (PA): GlaxoSmithKline LLC (GSK). 2023 Jan 6. Available from: \\CDSESUB1\EVSPROD\nda214876\0029\m1\us\114-labeling\1141-draft\draft-annotated.pdf.

bottle". The proposed revised container labels are acceptable from a medication error perspective.

3 REVIEW OF THE RISK MANAGEMENT PLAN

Zejula was approved in 2017 and is currently marketed as 100 mg capsules. GSK proposed the tablet formulation in strengths of 100 mg, 200 mg, and 300 mg to decrease patient's pill burden and to minimize risk of wrong dose errors. The proposed Zejula tablets are substitutable with the currently marketed Zejula capsules on a milligram-to-milligram basis.

(b) (4)

GSK outlined the following in their risk assessment and mitigation strategy to minimize the risk of medication errors between Zejula capsules and tablets:

- Differentiation between Zejula capsules and tablets through labeling, product design, and packaging
- A communication plan to inform dispensers, prescribers and patients regarding the tablet transition
- Pharmacovigilance monitoring

3.1 DIFFERENTIATION BETWEEN ZEJULA CAPSULES AND TABLETS THROUGH LABELING, PRODUCT DESIGN, AND PACKAGING

We reviewed the container labels for Zejula tablets and Zejula capsules and determined that they are adequately differentiated through the use of non-overlapping strength colors (gray, blue, and green for Zejula tablets vs. purple for Zejula capsules) and the use of actual image of Zejula tablet or capsule on the principal display panel (PDP).

Zejula tablets container principal display panel	Zejula capsules container principal display panel
(b) (4)	
Container closure: (b) (4) high-density polyethylene (HDPE) white bottle	Container closure: (b) (4) , high-density

	polyethylene (HDPE) white bottle

Furthermore, the Zejula capsule and tablet products are differentiated by formulation size, debossment of strength, and color. See figure below.

These differences provide adequate differentiation between Zejula tablets and Zejula capsules and minimize the risk of dispensing errors.

3.2 COMMUNICATION PLAN AND PHARMACOVIGILANCE MONITORING

We reviewed GSK's communication plan to specialty pharmacies, prescribers and patients and pharmacovigilance monitoring and find GSK's proposal acceptable from a medication error perspective.

Therefore, based on the aforementioned reasons above, we do not anticipate that the proposed Zejula tablets would introduce new risk of medication errors. Therefore, the proposed Zejula tablets are acceptable from am medication error perspective.

4 CONCLUSION

GSK implemented all of our recommendations for the Zejula container labels and we have no additional recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

APPENDIX B. RISK MANAGEMENT PLAN

Zejula Risk Management Plan received on July 22, 2022 July 22, available from \\CDSESUB1\EVSPROD\nda214876\0021\m1\us\116-risk-management-plans\1161-non-rems\risk-mgmt.pdf.

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	November 28, 2022
Requesting Office or Division:	Division of Oncology 1 (DO1)
Application Type and Number:	NDA 214876
Product Name, Dosage Form, and Strength:	Zejula (niraparib) tablets, 100 mg, 200 mg, and 300 mg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GlaxoSmithKline LLC
FDA Received Date:	June 30, 2022
TTT ID #:	2022-841
DMEPA 2 Safety Evaluator:	Tingting Gao, PharmD
DMEPA 2 Team Leader:	Ashleigh Lowery, PharmD, BCCCP

1 REASON FOR REVIEW

Zejula is currently available as a 100 mg capsules (NDA 208447). GlaxoSmithKline submitted NDA 214876 (subject of this review) to propose new film-coated tablets in strengths of 100 mg, 200 mg, and 300 mg.

As part of the approval process for Zejula (niraparib) tablets, the Division of Oncology 1 (DO1) requested that we review the proposed Zejula prescribing information (PI) and container labels for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

GlaxoSmithKline previously submitted NDA 214876 on June 16, 2020. However, the Agency informed GlaxoSmithKline that a food-effect study is required prior to approval of the proposed niraparib tablet formulation, in order to ensure adequate guidance on dosing/administration in labeling.[a] Thus, GlaxoSmithKline withdrew NDA 214876 on January 29, 2021.[b] DMEPA did not review the associated labels and labeling during the previous review cycle.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C – N/A
ISMP Newsletters*	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

[a] Lee, A. NDA 214876-Zejula--Feedback on Dec 22 Submission (Food Effect). Silver Spring (MD): FDA, CDER, OND, DO1 (US); 2021 January 13. NDA 214876.

[b] NDA 214876; Sequence 0019. Niraparib (ZEJULA®) tablets. WITHDRAWAL OF NDA 214876. Philadelphia (PA): GlaxoSmithKline LLC. 2021 Jan 29. Available from: \\CDSESUB1\EVSPROD\nda214876\0019\m1\us\102-cover-letters\cover.pdf

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Zejula PI and container labels and determined that they may be improved for clarity.

4 CONCLUSION & RECOMMENDATIONS

The proposed Zejula PI and container labels may be improved for clarity. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

(b) (4)

4.2 RECOMMENDATIONS FOR GLAXOSMITHKLINE

We recommend the following be implemented prior to approval of this NDA:

A. Container Labels

1. We noted that there is an image of the tablet present on the Principal Display Panel (PDP) for each strength. Ensure the tablet image reflects the actual size, shape, color, and code imprint for the corresponding dosage form.[c]
2. As currently displayed, the sample statement "Sample - Not for Sale" competes for prominence with other important information such as the proprietary name, established name, strength and dosage form. Relocate the sample statement, "Sample - Not for Sale" below the "30 tablets" at the bottom of the principal display panel to decrease the prominence of this statement.
3. (b) (4)

[c] Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Zejula tablets received on June 30, 2022 from GlaxoSmithKline, and Zejula capsules.

Table 2. Relevant Product Information for Zejula tablets and Zejula capsules		
Product Name	Zejula tablets	Zejula capsules[d] (NDA 208447)
Initial Approval Date	N/A	3/27/2017
Active Ingredient	niraparib	niraparib
Indication	• 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. (b) (4)	
Route of Administration	Oral	Oral
Dosage Form	tablets	Capsules
Strength	100 mg, 200 mg, and 300 mg	100 mg

Dose and Frequency	• *First-line maintenance treatment of advanced ovarian cancer:*
	  • For patients weighing <77 kg (<170 lbs) OR with a platelet count <150,000/mcL, the recommended dosage is 200 mg taken orally once daily.
	  • For patients weighing ≥77 kg (≥170 lbs) AND a platelet count ≥150,000/ mcL, the recommended dosage is 300 mg taken orally once daily.
	(b) (4)
	For patients with moderate hepatic impairment, reduce the starting dosage of niraparib to 200 mg once daily.	

How Supplied	Bottle of 30 tablets	Bottle of 90 capsules and bottle of 30 capsules
Storage	Store (b) (4) at 20°C to 25°C (68°F to 77°F)	Store at 20°C to 25°C (68°F to 77°F)
Container Closure	high-density polyethylene (HDPE) bottle (b) (4)	(b) (4), high-density polyethylene white bottle (DMF (b) (4)) with a (b) (4)

[d] Zejula [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2022 Sept 14. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/208447s026lbl.pdf.

		(b) (4)

APPENDIX B. PREVIOUS DMEPA REVIEWS

On October 12, 2022, we searched for previous DMEPA reviews relevant to this current review using the terms, Zejula capsules (NDA 208447). Our search identified 7 previous reviews[e,f,g,h,i,j,k], and we considered our previous recommendations to see if they are applicable for this current review.

[e] Gao, T. Label and Labeling Review for Zejula (NDA 208447/S-022). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 Feb 9. RCM No.: 2021-233.

[f] Gao, T. Label and Labeling Review for Zejula (NDA 208447/S-019 and S-020). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Dec 18. RCM No.: 2020-2432.

[g] Gao, T. Label and Labeling Review for Zejula (NDA 208447/S-018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 May 27. RCM No.: 2020-1026.

[h] Gao, T. Label and Labeling Review for Zejula (NDA 208447/S-017). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 Feb 5. RCM No.: 2020-109.

[i] Gao, T. Label and Labeling Review for Zejula (NDA 208447/S-007 and NDA 208447/S-011). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 Aug 16. RCM No.: 2018-1375.

[j] Gao, T. Label and Labeling Review for Zejula (NDA 208447). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Feb 15. RCM No.: 2016-2454-1.

[k] Gao, T. Label and Labeling Review for Zejula (NDA 208447). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 Jan 12. RCM No.: 2016-2454.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[l] along with postmarket medication error data, we reviewed the following Zejula labels and labeling submitted by GlaxoSmithKline.

- Container labels received on June 30, 2022
- Professional samples container labels received on June 30, 2022
- Prescribing Information and Patient Information (Image not shown) received on June 30, 2022, available from \\CDSESUB1\EVSPROD\nda214876\0020\m1\us\114-labeling\1141-draft\draft-proposed.docx

G.2 Label and Labeling Images

Container labels

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[l] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: December 12, 2022

To: Rashida Redd, BA, Regulatory Project Manager,
Division of Oncology 1 (DO1)

From: Adesola Adejuwon, PharmD, MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

CC: Rachael Conklin, MS, RN, RAC, Team Leader, OPDP

Subject: OPDP Labeling Comments for ZEJULA (niraparib) tablets, for oral use

NDA: 214876

Background:
In response to DO1's consult request dated August 15, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI) and carton and container labeling for the original NDA submission for ZEJULA (niraparib) tablets, for oral use (Zejula).

PI/PPI:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on November 28, 2022, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI, and comments were sent under separate cover on December 12, 2022.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on June 30, 2022, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Adesola Adejuwon at 240 402 5773 or Adesola.Adejuwon@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	December 12, 2022
To:	Rashida Redd, BA Regulatory Health Project Manager **Division of Oncology 1 (DO1)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Ruth Mayrosh, PharmD Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Adesola Adejuwon, PharmD, MBA Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	ZEJULA (niraparib)
Dosage Form and Route:	tablets, for oral use
Application Type/Number:	NDA 214876
Applicant:	GlaxoSmithKline, LLC

1 INTRODUCTION

On June 30, 2022, GlaxoSmithKline, LLC re-submitted for the Agency's review an original New Drug Application (NDA) 214876 for ZEJULA (niraparib) tablets. The purpose of this submission is to propose a new tablet formulation.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology 1 (DO1) on August 15, 2022 for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ZEJULA (niraparib) tablets.

2 MATERIAL REVIEWED

- Draft ZEJULA (niraparib) tablets PPI received on June 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 28, 2022.
- Draft ZEJULA (niraparib) tablets Prescribing Information (PI) received on June 30, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on November 28, 2022.
- Approved ZEJULA (niraparib) capsules labeling dated July 27, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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