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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

NIRAPARIB (ZEJULA)

GlaxoSmithKline Inc.

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

Version: Final
Publication Date: September 3, 2020
Report Length: 18 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

AE	adverse event
AIC	Akaike Information Criteria
AICc	Akaike Information Criteria with correction
AQPP	Association québécoise des pharmaciens propriétaires
BIA	budget impact analysis
BIC	Bayesian Information Criteria
CDR	CADTH Common Drug Review
CGP	clinical guidance panel
CSR	Clinical study report
EQ-5D-5L	European Quality of Life Five Dimensions Five Levels
gBRCA	germline breast cancer susceptibility gene
HRD	homologous recombination deficiency
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
KM	Kaplan-Meier
LY	life-year
OS	overall survival
PAG	Provincial Advisory Group
PARP	poly (ADP-ribose) polymerase inhibitor
PBCT	platinum-based chemotherapy
PFS	progression-free survival
PPS	post-progression survival
PSROC	platinum-sensitive recurrent ovarian cancer
QALY	quality-adjusted life-year
RCS	restricted cubic spline
RMST	restricted mean survival time
TOMT	time on maintenance treatment
TTD	time to treatment discontinuation
WTP	willingness-to-pay

Executive Summary

The executive summary is comprised of two tables (Table 1: Background and; Table 2: Economic Evaluation) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Niraparib (Zejula), 100 mg capsules
Submitted price	Niraparib, 100 mg capsule: $131.79
Indication	Monotherapy for the maintenance treatment of female adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in a complete or partial response to platinum-based chemotherapy.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	June 27, 2019
Reimbursement request	As per indication
Sponsor	GlaxoSmithKline Inc.
Submission history	Previously reviewed: No

NOC = Notice of Compliance

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Decision analytical model with three states (progression-free disease, progressed-disease and death) that estimates mean progression-free and overall survival for each treatment
Target population	Platinum-sensitive, recurrent ovarian cancer (PSROC) patients with high-grade serous histology who are in response to their most recent PBCT
Treatment	Niraparib
Comparators	Primary analysis (full population): Active surveillance Secondary analyses: • Non-gBRCA population: Active surveillance • gBRCA population: Active surveillance, and olaparib
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Seven years
Key data source	Mean PFS and TOMT were estimated from the NOVA trial [1] OS for active surveillance and niraparib were estimated from Study 19 [2]
Submitted results for base case and key scenario analyses	Primary analysis (full population): ICER=$76,458 per QALY vs. active surveillance Secondary analyses: • Non-gBRCA population: ICER=$77,280 vs. active surveillance • gBRCA population: Niraparib dominated by olaparib
Key limitations	• The model was inappropriate as it estimated the mean number of years of PFS and PPS, and multiplied these means by the utility and costs to estimate cost-effectiveness. It did not incorporate transitions between health states at different time points as would a typical partitioned survival analysis. The sponsor's approach inadequately accounted for the shape of the parametric functions for PFS, TTD and OS as it effectively assumes that mean PFS, TTD and OS are normally distributed for the purpose of estimating costs and benefits. • The sponsor's method of deriving the OS associated with niraparib was highly uncertain. As there is limited evidence for niraparib on OS, the sponsor derived mean OS with niraparib as the mean OS with placebo (from Study 19 which compared olaparib with placebo) plus the mean PFS benefit of niraparib compared with placebo (from NOVA) multiplied by the OS benefit to PFS benefit ratio (assumed to be 2:1, based on Study 19 [i.e. 2 months of OS benefit for every month of PFS benefit]). This is a critical limitation as this assumption underpins the sponsor's model. It remains unknown if there is an OS benefit associated with niraparib. • The comparative clinical effects between niraparib and olaparib are uncertain in the gBRCA population as it was assumed that niraparib and olaparib were equal in terms of PFS, OS and TOMT. The clinical guidance report identified several limitations in the sponsor's ITC/NMA (the network size was small, there was no closed loop and there were potential sources of heterogeneity across included trials in terms of study design and baseline characteristics). While the results of the ITC/NMA must be interpreted with caution due to the identified limitations, the sponsor's assumption of equal efficacy for PFS between niraparib and olaparib may be reasonable, based on the ITC/NMA findings. The sponsor also referenced two ITCs from conference proceedings that remain unpublished as full peer-reviewed literature, which concluded there was no difference in efficacy between niraparib and olaparib in terms of PFS. No evidence was submitted to support the assumption that TOMT and OS would be the same for niraparib and olaparib. • The sponsor's chosen parametric survival functions overestimated the percentage of patients remaining progression-free beyond the NOVA trial period for both niraparib and active

Component	Description

	surveillance according to the clinical experts consulted by CADTH. This overestimation of PFS potentially favours niraparib.
	• There were concerns regarding the selection of parametric functions of various outcomes.
	  ○ The choice of parametric functions for TTD resulted in more patients in the non-gBRCA population remaining on active surveillance than in the gBRCA population in the post-trial period. The clinical experts consulted by CADTH expected that the gBRCA patients would remain on treatment for longer.
	  ○ The choice of parametric survival functions for OS with active surveillance likely overestimated the percentage of patients alive beyond the trial period (of Study 19) according to clinical experts consulted by CADTH.
	• The sponsor's time horizon was not reflective of a patient's lifetime (up to when OS≤1%). At the sponsor time horizon of 7 years, 7% of patients receiving active surveillance in the non-gBRCA and 13% in the gBRCA populations were still alive.
	• The implementation of niraparib dose reductions led to illogical average daily doses (i.e., doses that were not in increments of 100 mg, which is the smallest strength size supplied). This could not be resolved due to limitations in the model structure. Additionally, a calculation error for the dose of niraparib used in cycle five and beyond was corrected.

CADTH reanalysis results	• CADTH reanalyses included changing the OS to PFS benefit ratio from 2:1 to 1:1; selecting alternative parametric functions for PFS, TTD and OS; adopting a lifetime time horizon (13 years); and, correcting the niraparib dose for cycle five and beyond. • Non-gBRCA population: ICER=$194,360 compared with active surveillance. (0% probability of being cost-effective at WTP of $50,000 per QALY) • gBRCA population: Niraparib remained dominated by olaparib (0% probability of being cost-effective at WTP of $50,000 per QALY). • Price reductions of 76% and 61% in the non-gBRCA and gBRCA populations respectively would be required for niraparib to be considered cost-effective at a WTP of $50,000 per QALY, compared with active surveillance.

gBRCA = germline breast cancer susceptibility gene; ICER = incremental cost-effectiveness ratio; ITC: indirect treatment comparison; LY = life-year; NMA: network meta-analysis; OS = overall survival; PBCT = platinum-based chemotherapy; PFS = progression-free survival; PPS = post-progression survival; PSROC = platinum-sensitive recurrent ovarian cancer; QALY = quality-adjusted life-year; TOMT = time on maintenance treatment; vs = versus; WTP = willingness-to-pay

Conclusions

CADTH undertook reanalyses of the sponsor's economic submission to address some of the identified limitations: reanalyses included assuming a 1:1 ratio of overall survival (OS) benefit to progression-free survival (PFS) benefit when estimating mean OS for niraparib; selecting alternative parametric distributions to extrapolate PFS, time to treatment discontinuation and OS beyond the provided trial data; adopting a lifetime horizon of 13 years; and, correcting the dose of niraparib used in cycle five and beyond. Based on CADTH reanalyses, the ICER for niraparib compared with active surveillance was $194,360 per QALY gained in the non-gBRCA population. In the gBRCA population, results remained unchanged as niraparib remained dominated by olaparib (i.e., niraparib is as effective as olaparib but more costly). Price reductions of 76% and 61% would be required for niraparib to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained in the non-gBRCA and gBRCA populations, respectively, when compared with active surveillance.

In the gBRCA population, substantial uncertainty remains regarding the assumption of equal efficacy between niraparib and olaparib: identified limitations in the sponsor's indirect treatment comparison (ITC) / network meta-analysis (NMA) impact the interpretation of PFS; TOMT was not included in the ITC/NMA; and, there is no data to demonstrate that niraparib and olaparib are equal in terms of OS. Given that the OS data in the NOVA trial was immature and not utilized in the sponsor's pharmacoeconomic model, and that the derivation of mean OS for niraparib was based on data from Study 19, an olaparib drug trial, the OS estimates used in the model for both the gBRCA and non-gBRCA population are highly uncertain. The current OS data for niraparib is immature and not informative, therefore no reliable conclusions regarding niraparib's effect on OS can be drawn at this time. It remains unknown whether there is

an OS benefit associated with niraparib, compared with active surveillance. There is no data to support that niraparib and olaparib will be equal in terms of OS as no direct or indirect treatment comparisons have compared the OS outcome.

CADTH conducted scenario analyses to explore alternative assumptions for OS, all of which had a significant influence on the model results. In the non-gBRCA population, ICERs ranged from $100,346 to $348,338 for niraparib compared with active surveillance depending on the approach to estimate mean OS for niraparib. In the gBRCA population, niraparib remained more expensive than olaparib, due to the assumptions of equal efficacy used in the model.

Based on the sponsor's submitted budget impact analysis, the total incremental cost is estimated to be [redacted] for a combined population (gBRCA and non-gBRCA) over the first 3 years [redacted] in Year 1, [redacted] in Year 2, and [redacted] in Year 3). The CADTH reanalysis suggests that the budget impact of introducing niraparib to the market was underestimated in the sponsor's results. CADTH estimated the budget impact in the combined population to be $7,165,065 in Year 1, $11,666,332 in Year 2 and $15,670,846 in Year 3 which is equal to a cumulative total of $34,502,243 over the first three years.

Stakeholder Input Relevant to the Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information

Economic Review

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 1: Cost Comparison Table

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 2: Submission Quality

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 3: Additional Information on the Submitted Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

Appendix 5: Additional Information on the Submitted BIA

This section outlines the technical details of the pCODR Economic Guidance Panel's evaluation of the economic evidence that is summarized in the executive summary. In accordance with the *Disclosure of Information Guidelines for the CADTH Pan-Canadian Oncology Drug Review*, this section is not eligible for disclosure. It was provided to the pCODR Expert Review Committee (pERC) for their deliberations and the participating drug programs for their information.

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