CADTH

CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

Niraparib (ZEJULA)

(GlaxoSmithKline Inc.)

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.

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Abbreviations

AE	adverse event
AIC	Akaike information criterion
BIA	budget impact analysis
BIC	Bayesian information criterion
BRCA-Mut	breast cancer gene mutation
BRCA-wt	breast cancer gene wild type
CAD	Canadian Dollar
EOCD	Edinburgh Ovarian Cancer Database
EQ-5D	European Quality of Life Scale, 5 Dimensions
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
LY	life year
NVRD	no visible residual disease
OS	overall survival
PFLY	progression-free life year
PFS	progression-free survival
PPS	post-progression survival
QALY	quality-adjusted life year
QoL	quality of life
TTD	time-to-treatment discontinuation
VRD	visible residual disease
WTP	willingness-to-pay

Executive Summary

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

Table 1: Submitted for Review

Item	Description
Drug Product	Niraparib (Zejula), 100 mg capsule in cartons of 56 or 84 capsules
Submitted Price	Niraparib: $131.79 per 100 mg capsule
Indication	For the monotherapy maintenance treatment of female 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.
Health Canada Approval Status	NOC
Health Canada review pathway	Standard review
NOC Date	October 2nd, 2020
Reimbursement Request	As per indication.
Sponsor	GlaxoSmithKline Inc.
Submission History	Previously Reviewed: Yes 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. Recommendation date: September 3, 2020 Recommendation: Recommended on the condition that cost-effectiveness is improved to an acceptable level.[1]

NOC = notice of compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of Economic Evaluation	Cost-utility analysis Partitioned survival model
Target Population	Patients with newly-diagnosed, advanced epithelial ovarian, fallopian tube and peritoneal cancer who are in a complete or partial response to first-line platinum-based chemotherapy.
Treatment	Niraparib
Comparators	Base-case analysis (*overall population*; i.e., PRIMA ITT population and stage III patients with no visible residual disease [NVRD]): active surveillance Scenario analyses: • PRIMA *ITT population* (i.e., excludes stage III patients with NVRD): active surveillance • *Breast cancer gene mutation (BRCA-mut) population*: active surveillance, olaparib
Perspective	Canadian publicly-funded health care payer
Outcomes	QALYs, LYs, PFLYs
Time Horizon	20 years
Key Data Sources	• PRIMA trial for overall survival (OS), progression-free survival (PFS), and quality of life data (i.e., EQ-5D-5L) to inform the ITT population and a subset of the overall and BRCA-mut population • PAOLA-1 trial to inform the inclusion of stage III patients with NVRD in the overall population and BRCA-mut population
Submitted Results for Base Case	ICER = $42,704 per QALY ($113,143 inc. costs; 2.65 inc. QALYs) <u>Scenario analyses:</u> • *ITT population*: ICER = $60,050 per QALY ($102,504 inc. costs; 1.71 inc. QALYs) • *BRCA-mut population:* Niraparib dominated by olaparib (equally effective [0.00 inc. QALYs] but more expensive [inc. costs= $21,907])
Key Limitations	• The PRIMA trial only enrolled a small proportion of patients with stage III NVRD ovarian cancer following neoadjuvant chemotherapy and interval debulking surgery and excluded patients with stage III disease and NVRD following primary debulking surgery. To model the base-case, the sponsor estimated the comparative effectiveness using data from the PAOLA-1 trial and adjusted the PRIMA efficacy outcomes for niraparib to represent the inclusion of stage III NVRD patients. The sponsor's approach to incorporate the effects of treatment on stage III NVRD patients is uncertain as treatment effect between trials were naively incorporated despite differences in the patient population between PRIMA and PAOLA-1. Therefore, cost-effectiveness for niraparib in the overall population is unknown. • The sponsor did not explore cost-effectiveness of niraparib in the subgroup of patients with a wild type BRCA gene (BRCA-wt) despite an expected differential treatment efficacy exists between BRCA subgroups. Interpretation of the ITT population is limited given the included comparators do not fully reflect current clinical Canadian practice. Patient who are BRCA-mut would receive olaparib while patients who are BRCA-wt would be managed by active surveillance. In order to correctly model the ITT population, combining the subgroup analyses according to BRCA status (i.e., BRCA-wt and BRCA-mut populations) would be required. • Given the immaturity of the OS data in the PRIMA trial, the sponsor used an indirect approach to derive the mean OS associated with niraparib. This approach was associated with substantial uncertainty. The sponsor justified a 2:1 mean OS to mean PFS ratio based on Study 19, which varied in terms of baseline characteristics and line of treatment when compared with the PRIMA trial. The approach further depends on confidence in the difference in mean PFS for niraparib and active surveillance. As this was derived using parametric survival distributions that extrapolated PFS beyond the trial period, this adds a further source of uncertainty to the mean OS benefit estimate.

Component	Description
	• The sponsor's chosen parametric survival functions overestimated the percentage of patients remaining progression-free and who were alive beyond the PRIMA trial period for active surveillance according to the clinical experts consulted by CADTH. This overestimation of PFS and OS for active surveillance potentially favours niraparib given the indirect methods used to derive niraparib OS. • For patients who have achieved long-term remission (i.e., progression free after 10 years), the sponsor's model assumed mortality rates based on the Canadian general population. This does not accurately reflect the expected long-term mortality risk for patients with ovarian cancer and would bias results in favour of niraparib. • The time horizon did not fully capture the lifetime of the patient. For interventions that have differential effects on mortality, a lifetime time horizon is more appropriate.
CADTH Reanalysis Results	• CADTH base-case re-analyses were based on the ITT population. CADTH was unable to address the multiple methodological limitations associated with the approach to model the overall population and, as such, no re-analyses were conducted on the overall population. CADTH reanalyses included: reducing the mean OS to mean PFS ratio for niraparib; using alternate progression-free and overall survival extrapolations for active surveillance; adjusting mortality for patients in long-term remission; and adopting a lifetime time horizon. • *ITT population*: ICER = $128,557 per additional QALY gained ($103,869 inc. costs; 0.81 inc. QALYs) • *BRCA-mut population*: as aligned with the sponsor's results, niraparib remained dominated by olaparib (i.e., niraparib was more costly and less effective than olaparib). • Based on the absence of clinical data to inform cost-effectiveness for niraparib in BRCA-wt patients, the CADTH ICER estimate for the ITT population is likely an underestimation due to the differential treatment efficacy in BRCA subgroups and the exclusion of a relevant treatment comparator which dominates niraparib in the BRCA-mut subgroup.

BRCA-mut = breast cancer gene mutation; BRCA-wt = breast cancer gene wild type; EQ-5D-5L = European Quality of Life Scale, 5 Dimensions; inc = incremental; ITT = intention to treat; LY = life years; NVRD = no visible residual disease; OS = overall survival; PFLY = progression free life years; PFS = progression-free survival; QALY = quality-adjusted life year.

Conclusions

In the PRIMA study, patients with advanced ovarian cancer following response on front-line platinum-based chemotherapy, the difference in mortality between niraparib compared to active surveillance was not statistically significant over a maximum 29 months for the primary analysis (data cutoff - May 2019). The OS data was immature. For the BRCA-mut subgroup, an indirect treatment comparison was considered infeasible due to the absence of relevant trials. The sponsor's assumption of equivalent comparative efficacy between niraparib and olaparib in BRCA-mut patients is uncertain.

A key limitation with the sponsor's submitted evidence is the limited comparative clinical information for niraparib and active surveillance in stage III patients with no visible residual disease. To inform the overall population reflecting the full Health Canada indication, the sponsor naïvely adjusted the results from PRIMA and PAOLA-1. CADTH considered the use of a naïve comparison not to be appropriate. As such, the cost-effectiveness of niraparib for the treatment of stage III NVRD ovarian cancer and for the full Health Canada indication is unknown.

CADTH was unable to assess the differential efficacy of niraparib in the BRCA-wt subgroup due to the absence of OS data specific to BRCA-wt patients and, as such, cost-effectiveness in the BRCA-wt subgroup could not be assessed. Given the differential treatment efficacy expected, the cost-effectiveness of niraparib in the ITT population remains highly uncertain as the preferred approach to derive the aggregate incremental cost-effectiveness ratio (ICER) for the full ITT population would have been to weight the ICER of each subgroup by their respective prevalence.

Despite the limitations noted above, CADTH undertook reanalyses in the ITT population and addressed the following limitations: reducing the mean OS to mean PFS ratio for niraparib (a major driver in the economic analysis); using alternate progression-free and

overall survival extrapolations for active surveillance to reflect clinical practice; adjusting mortality for patients in long-term remission to incorporate cancer-adjusted mortality; and adopting a lifetime time horizon. In the CADTH base case reanalyses, reflecting the ITT population studied in the PRIMA trial, results were consistent with those submitted by the sponsor: niraparib was both more effective (gain of 0.81 QALYs) and more costly (cost expenditure of $103,869) when compared to active surveillance, with an ICER of $128,557 per additional QALY gained. Niraparib remains dominated by olaparib (i.e., niraparib was equally effective but more expensive) in the BRCA-mut subgroup in a CADTH scenario reanalysis.

Given that a BRCA-wt subgroup analysis was not provided, it is important to note that the approach taken to model the ITT population only reflects a comparison to active surveillance. The CADTH ICER estimates for the ITT population is likely an underestimation due to the exclusion of a relevant treatment comparator (i.e., olaparib) which was found to dominate niraparib in the BRCA-mut subgroup. Although CADTH determined that a price reduction of 60% would be required for niraparib to be considered cost-effective at a WTP threshold of $50,000 per QALY when compared to active surveillance only, a higher price reduction may be required when considering the treatment mix currently used in clinical practice.

Based on the sponsor's submitted budget impact analysis, the total budget impact of reimbursing niraparib under the full Health Canada indication was estimated to be $[redacted] over the first three years, when markups and dispensing fees are included. CADTH re-analysis of the sponsor's submitted BIA suggests that the estimated budget impact of introducing niraparib after first-line platinum-based chemotherapy would be $115,729,579 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: Submitted Budget Impact Analysis and CADTH Appraisal

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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