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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

OLAPARIB (LYNPARZA)

(AstraZeneca Canada Inc.)

Indication: As monotherapy for the treatment of adult patients with mCRPC and deleterious or suspected deleterious germline and/or somatic mutations in the HRR genes BRCA or ATM who have progressed following prior treatment with a NHA.

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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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Table of Contents

CADTH

List of Tables

Abbreviations

AE	adverse event
ATM	ataxia-telangiectasia mutated
BRCA1	breast cancer 1 gene
BRCA2	breast cancer 2 gene
FDA	Food and Drug Administration
HR	hazard ratio
HRRm	homologous recombination repair mutation
ICER	incremental cost-effectiveness ratio
icNHA	investigator's choice of new-hormonal agent
ITC	indirect treatment comparison
LY	life year
mCRPC	metastatic castration-resistant prostate cancer
OS	overall survival
PFS	progression-free survival
PSA	prostate-specific antigen
QALY	quality-adjusted life-year
rPFS	radiographic progression-free survival
RPSFTM	rank-preserving structural time failure model
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	Olaparib (Lynparza), tablet
Submitted price	Olaparib, 50 mg, 100 mg, and 150 mg oral tablets: $65.89 per tablet
Indication	Treatment of adult patients with metastatic castration-resistant prostate cancer and deleterious or suspected deleterious germline and/or somatic mutations in the homologous recombination repair genes BRCA or ATM who have progressed following prior treatment with a new hormonal agent. BRCA or ATM mutations must be confirmed before olaparib treatment is initiated.
Health Canada approval status	NOC
Health Canada review pathway	Standard
NOC date	August 21, 2020
Reimbursement request	As per indication
Sponsor	AstraZeneca Canada Inc.
Submission history	Previously reviewed: Yes <u>Ovarian Cancer (2nd line) – 2016:</u> Indication: As monotherapy maintenance treatment of adult patients with platinum-sensitive relapse BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy. Recommendation: Does not recommend reimbursement of olaparib as monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy.[1] <u>Ovarian Cancer - 2017 (resubmission)</u> Indication: As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic) epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response to platinum-based chemotherapy. Recommendation: Reimburse under the following conditions - For olaparib monotherapy maintenance treatment of adult patients with platinum-sensitive relapsed BRCA-mutated (germline or somatic as detected by approved testing) high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who have completed at least two previous lines of platinum-based chemotherapy and are in radiographic response (complete or partial response) to their most recent platinum-based chemotherapy regimen as per the SOLO-2 trial.[2] <u>Newly Diagnosed Ovarian Cancer – 2019</u> Indication: As monotherapy for the maintenance treatment of adult patients with newly diagnosed advanced BRCA-mutated high-grade epithelial ovarian, fallopian tube or primary peritoneal cancer who are in response (complete response or partial response) to first-line platinum-based chemotherapy, until disease progression or up to 2 years if no evidence of disease. Patients must have confirmation of BRCA mutation (identified by either germline or tumour testing) before olaparib treatment is initiated. Recommendation: Reimburse under the following conditions - For the maintenance treatment of adult patients with newly diagnosed, advanced, BRCA-mutated (germline or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to first-line platinum-based chemotherapy, as per SOLO-1 trial.[3]

ATM = ataxia-telangiectasia mutated; BRCA = breast cancer; NOC = Notice of Compliance.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partition-Survival model
Target population	Adult patients with metastatic castration-resistant prostate cancer and deleterious or suspected deleterious germline and/or somatic mutations in homologous recombination repair mutation (HRR-mutated [HRRm]) mCRPC (BRCA1/BRCA2/ATM) who have progressed following prior treatment with a new hormonal agent (NHA)
Treatment	Olaparib
Comparator	• Investigator's choice of new-hormonal agent (icNHA; i.e., abiraterone acetate or enzalutamide) • cabazitaxel • docetaxel
Perspective	Canadian publicly funded health care payer
Outcome	Quality-adjusted life years (QALYs)
Time horizon	10 years
Key data source	Overall survival (OS), radiographic progression-free survival (rPFS), and time-to-treatment discontinuation (TTD) data for olaparib and the icNHA were obtained from the PROfound trial. Hazard ratios derived from the sponsor conducted indirect treatment comparison (ITC) were applied to the OS and rPFS curves of the icNHA arm to model the comparative clinical efficacy of cabazitaxel and docetaxel.
Submitted results for base case	The sequential ICER for: • Olaparib versus docetaxel: $160,912 per QALY ($54,710 incremental costs; 0.34 incremental QALYs)[a]
Key limitations	• The OS for icNHA is uncertain due to methods used to account for treatment switching that occurred in the PROfound trial. Specifically, the assumption that switchers would achieve the full treatment effect as those who were initially assigned to olaparib may not be clinically appropriate. The CADTH clinical experts indicated that patients crossed over to olaparib after experiencing progression and therefore may not receive the full treatment benefit as pre-progression patients. Due to the lack of clinical data available to inform the OS of non-switchers, the true OS benefit for patients receiving only icNHA remains unknown. • The comparative efficacy estimates of olaparib versus cabazitaxel and docetaxel are highly uncertain due to clinical heterogeneity between trials (e.g., HRR genotype status, proportion of patients with visceral metastases, etc.) and potential effect modifiers were not considered. • Long-term parametric extrapolations of OS and rPFS within the submitted economic evaluation do not align with clinical expectations of the anticipated treatment effects of olaparib beyond the trial period. The extrapolation of OS beyond the trial period following radiographic progression was highly uncertain. • Health state utilities were adjusted to incorporate additional time-to-death disutilities in the final year of death. As a large portion of patients who progress will be in the last year of life adding an additional disutility may double count the disutility associated with post progression survival • Total drug acquisition costs of olaparib and icNHA were likely underestimated due to the sponsor's use of rPFS data to model treatment discontinuation. Clinical experts noted that TTD data available in the profound trial are more appropriate as they reflect several criteria used to determine treatment discontinuation, as some patients may remain on treatment for a short period beyond radiographic disease progression.
CADTH reanalysis results[b]	• Due to issues with the probabilistic sampling of OS and TTD extrapolations, only deterministic results are presented for all CADTH reanalyses. • CADTH conducted a reanalysis which included: selecting alternative parametric distributions for rPFS, TTD, and OS for olaparib and icNHA; modeling treatment discontinuation based on TTD

Component	Description
	data; applying health state utilities based on patients' progression status only; and applying trial-based utilities for progression. • CADTH found the sequential ICER for olaparib versus docetaxel was $459,527 per QALY. CADTH's base case reanalyses align with the sponsor's conclusions that olaparib was not cost-effective at a willingness-to-pay threshold of approximately $50,000 per QALY. A price reduction of 71% for olaparib would be required to achieve an ICER less than $50,000 per QALY. • The CADTH base case is reliant on estimates from the sponsor's ITC regarding the comparative efficacy versus docetaxel and cabazitaxel. If this evidence is deemed unreliable then olaparib should be priced no more than the lowest cost comparator to ensure cost-effectiveness at any willingness to pay threshold.

ATM = ataxia-telangiectasia mutated; BRCA = breast cancer; HRR = homologous recombination repair; icNHA = investigator's choice of new-hormonal agent; mCRPC = metastatic castration-resistant prostate cancer; NHA = new hormonal gent; OS = overall survival; PFS = progression-free survival. QALYs = quality-adjusted life-years; rPFS = radiographic progression-free survival; TTD = time to treatment discontinuation.

Note: Cabazitaxel was dominated (i.e., more costly and less effective) by docetaxel in both the sponsor and CADTH base case and was excluded from the sequential ICER calculations.

[a] CADTH-calculated sequential analyses based on the sponsor's base case results.

[b] All CADTH reanalysis results, including price reduction and other scenario analyses are reported deterministically.

Conclusions

Based on the clinical review of the evidence, olaparib demonstrated a statistically significant benefit in rPFS and OS compared to the icNHA. However, the comparative effectiveness of olaparib relative to other commonly used treatments remains uncertain due to the absence of high-quality evidence, as noted in the CADTH clinical review. CADTH was also unable to address the cost-effectiveness of olaparib according to genotype carrier status (i.e., BRCA1/2 and ATM).

Given issues with the sponsor's probabilistic sampling, CADTH undertook deterministic reanalyses of the economic model to address several limitations, including: a more clinically plausible extrapolation for overall survival (OS), radiographic progression-free survival (rPFS), and time to treatment discontinuation (TTD); and the use of trial-based utility estimates according to progression only. Based on CADTH reanalyses, the incremental cost-effectiveness ratio (ICER) for olaparib versus docetaxel was $459,527 per QALY gained; a 71% price reduction for olaparib is required to achieve an ICER of less than $50,000 per QALY. The analyses were primarily driven by the incremental benefit expected with olaparib over the model's time horizon compared to docetaxel and icNHA.

However, the CADTH estimation of cost-effectiveness of olaparib compared to cabazitaxel and docetaxel remains uncertain due to the lack of head-to-head comparative effectiveness and limitations identified with the sponsor submitted indirect treatment comparison (ITC). The CADTH base case is reliant on estimates from the sponsor's ITC regarding the comparative efficacy versus docetaxel and cabazitaxel. As noted by CADTH clinical experts, there is no robust evidence to ascertain which of the agents (i.e., olaparib, docetaxel, cabazitaxel, or radium-223) has superior efficacy. Given the high degree of clinical uncertainty, to ensure cost effectiveness at any willingness-to-pay threshold, a further price reduction may be required so that olaparib costs no more than the lowest cost comparator.

Based on the CADTH reanalyses, the budget impact from the introduction of olaparib is expected to be $3,975,749 in year 1, $11,156,238 in year 2, and $13,898,668 in Year 3. The total three-year budget impact for reimbursing olaparib was therefore $29,030,654. CADTH reanalyses suggest that the estimated impact of introducing olaparib would be higher than the sponsor's assessment which estimated the budget impact to be $25,669,238 over 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 BIA 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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