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CADTH DRUG REIMBURSEMENT REVIEW

Pharmacoeconomic Report

ENTRECTINIB (ROZLYTREK)

(Hoffmann-La Roche Ltd.)

Indication: For the first-line treatment of patients with ROS1 positive locally advanced or metastatic non-small cell lung cancer.

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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
ALK	anaplastic lymphoma kinase
CUA	cost-utility analysis
FISH	fluorescence in situ hybridization
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
IHC	immunohistochemistry
KM	Kaplan-Meier
LY	life-year
MAIC	matching-adjusted indirect comparison
NSCLC	non-small cell lung cancer
OS	overall survival
pCODR	Pan-Canadian Oncology Drug Review
PSM	partitioned survival model
PFS	progression-free survival
QALY	quality-adjusted life-year
ROS1	c-ros oncogene 1
SE	standard error
TKI	tyrosine kinase inhibitor
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	entrectinib (Rozlytrek), 100 mg and 200 mg capsules
Submitted price	entrectinib, 200 mg, capsule: $95.33 per capsule entrectinib, 100 mg, capsule: $47.66 per capsule
Indication	Treatment of patients with ROS1 positive locally advanced or metastatic NSCLC not previously treated with crizotinib
Health Canada approval status	NOC
Health Canada review pathway	Standard review
NOC date	May 05, 2020
Reimbursement request	As monotherapy for the first-line treatment of patients with ROS1-positive locally advanced or metastatic non-small cell lung cancer
Sponsor	Hoffmann-La Roche Limited
Submission history	Previously reviewed: No

NOC = Notice of Compliance; NSCLC = non-small cell lung cancer; ROS1 = c-ros oncogene 1 receptor tyrosine kinase gene.

Table 2: Summary of Economic Evaluation

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Treatment-naïve patients with ROS1-positive locally advanced or metastatic NSCLC. The target population aligns with the sponsor's reimbursement request but does not align with the Health Canada approved indication.
Treatment	Entrectinib
Comparators	(1) Crizotinib (2) Chemotherapy with pemetrexed + cisplatin or carboplatin followed by pemetrexed maintenance (chemotherapy)
Perspective	Canadian publicly funded health care payer
Outcomes	Quality adjusted life years (QALYs), life years (LYs)
Time horizon	10 years
Key data source	• Progression-free survival (PFS) and overall survival (OS) data for entrectinib: integrated data from 3 single-arm trials (N=94): ALKA-372-001, STARTRK-1 and STARTRK-2; forming the Overall ROS1 NSCLC Efficacy Evaluable Analysis Set • Hazard ratios (HRs) for PFS and OS for entrectinib versus crizotinib: propensity-score analysis based on Overall ROS1 NSCLC Efficacy Evaluable Analysis Set and the Flatiron database • HR for PFS and OS for crizotinib versus chemotherapy: PROFILE 1014
Submitted results for base case	Results from a sequential analysis showed that the ICER of entrectinib was $78,019 per QALY gained compared with chemotherapy. Crizotinib was ruled out by extended dominance by chemotherapy and entrectinib.
Key limitations	• The clinical efficacy of entrectinib is uncertain. The individual studies were all open-label, single-arm unblinded trials. Furthermore, considerable heterogeneity was noted between the individual studies and, by pooling, no adjustments were conducted to account for the heterogeneity. • Comparative clinical efficacy for entrectinib compared with crizotinib or chemotherapy was based on multiple different data sources including a propensity score analysis from the Flatiron database and naïve comparison to the PROFILE 1014 trial. The CADTH clinical review highlighted several concerns with the internal validity of the approach given the substantial heterogeneity across the study designs and the populations, and the omission of important prognostic variables in the propensity scoring method. This introduced significant uncertainty into the indirect comparisons that could not be sufficiently explored and integrated into the economic analysis. It was therefore considered inappropriate to perform and interpret the results sequentially. • The predicted OS curve for entrectinib in the sponsor's model lacked face validity and was not aligned with the observed survival expected for this patient population. Overall survival was overestimated according to the clinical experts consulted on this review. • The sponsor's assumptions regarding the distribution of patients receiving subsequent treatments were not reflective of current Canadian practice. As the proportion of patients receiving a tyrosine kinase inhibitor after entrectinib or crizotinib was overestimated, this would consequently increase subsequent treatment costs. • The sponsor did not include the cost of ROS1 testing. As ROS1 testing is not routinely available, the introduction of entrectinib is expected to be associated with an increase in testing costs.
CADTH reanalysis results	• Given the inconclusiveness of the comparative clinical evidence, the cost-effectiveness of entrectinib is unknown. CADTH undertook exploratory reanalyses to correct the sponsor's model using best available evidence, but the validity and interpretability of the results are limited by the comparative evidence. • In light of the lack of direct comparative clinical efficacy information for entrectinib compared to chemotherapy or crizotinib, CADTH's exploratory re-analyses incorporated the relative efficacy

Component	Description
	(PFS and OS) for entrectinib compared to crizotinib based on a matched adjusted indirect comparison to the PROFILE 1001 trial and included the cost of ROS1 testing. Compared to chemotherapy, the ICER of entrectinib was $91,447 per QALY. Entrectinib was associated with an ICER of $119,460 per QALY compared to crizotinib. However, these analyses should be viewed only as exploratory given the absence of any direct comparative clinical data for entrectinib. • Sensitivity analyses were conducted which demonstrated that the submitted economic model was sensitive to changes in the assumed OS benefit for entrectinib relative to crizotinib; the survival models used to extrapolate the long-term OS for entrectinib; and, the assumptions regarding treatment waning.

ICER = incremental cost-effectiveness ratio; HR = hazard ratio; LY = life-year; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression free survival; QALY= quality-adjusted life-year; ROS1 = c-ros oncogene 1 receptor tyrosine kinase gene.

Conclusions

Several major limitations could not be sufficiently addressed by CADTH, including the lack of direct comparative clinical data and concerns about the quality of the submitted real-world data and the propensity score analysis. Given the inconclusiveness of the comparative evidence, a CADTH base case could not be derived to estimate the cost-effectiveness of entrectinib compared with crizotinib or chemotherapy.

In an exploratory analysis, assuming confidence in the comparative clinical evidence that were estimated from a matching-adjusted indirect comparison to the PROFILE 1001 trial and in which incorporated the costs of ROS1 testing, entrectinib is associated with an ICER of $119,460 per QALY compared with crizotinib, and an ICER of $91,447 per QALY compared to chemotherapy. If no difference in OS and PFS is assumed between entrectinib compared with crizotinib, entrectinib would be dominated by crizotinib (i.e., entrectinib is more costly and equally effective). Since the comparative clinical evidence is limited to pairwise comparisons, all comparators could not be considered together within this exploratory analysis to identify the cost-effective therapy(ies) among these three treatments.

Results from CADTH re-analyses were highly sensitive to the relative OS benefit for entrectinib compared to crizotinib; the survival model used to extrapolate long-term OS for entrectinib; and, the assumptions regarding treatment waning. Furthermore, limited data on long-term PFS and OS leads to uncertainty in the cost-effectiveness of entrectinib given that 46% of the incremental QALYs were accrued beyond the trial in comparison to chemotherapy and crizotinib respectively. Together, combined with the concerns in the comparative clinical effects of entrectinib, the cost effectiveness estimates should be viewed as exploratory.

Based on the sponsor's submitted budget impact analysis, the total budget impact was estimated to be $1,022,214 over the first three years. CADTH re-analysis of the sponsor's submitted BIA suggests that the estimated budget impact of introducing entrectinib would be $2,635,483 over the first three years.

The Health Canada indication for entrectinib is for the treatment of patients with ROS1 positive locally advanced or metastatic non-small cell lung cancer (NSCLC) not previously treated with crizotinib. The modelled population within the economic analysis focused on treatment-naïve ROS1-positive locally advanced or metastatic NSCLC patients. Uncertainty remains to the cost-effectiveness and budget impact of entrectinib in the full Health Canada indication.

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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