pCODR EXPERT REVIEW COMMITTEE (pERC)
INITIAL RECOMMENDATION

The CADTH pan-Canadian Oncology Drug Review (pCODR) was established by Canada's provincial and territorial Ministries of Health (with the exception of Quebec) to assess cancer drug therapies and make recommendations to guide drug reimbursement decisions. The pCODR process brings consistency and clarity to the assessment of cancer drugs by looking at clinical evidence, cost-effectiveness, and patient perspectives.

Providing Feedback on This Initial Recommendation
Taking into consideration feedback from eligible stakeholders, the pCODR Expert Review Committee (pERC) will make a Final Recommendation. Feedback must be provided in accordance with *pCODR Procedures*, which are available on the pCODR website. The Final Recommendation will be posted on the pCODR website once available, and will supersede this Initial Recommendation.

Drug: Larotrectinib (Vitrakvi)

Submitted Reimbursement Request: For the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion. Additional criteria: Age ≥ 1 month; ECOG score of ≤ 3; Tumour harbouring NTRK1, NTRK2 or NTRK3 gene fusion confirmed by a validated diagnostic testing method; Patients eligible for larotrectinib should have no satisfactory alternative treatments or have progressed following treatment.

Submitted by: Bayer Inc.

Manufactured by: Bayer Inc.

NOC/c Date: July 10, 2019

Submission Date: February 25, 2019

Initial Recommendation Issued: August 29, 2019

Approximate per Patient Drug Costs, per Month (28 Days)	Larotrectinib costs $5,988.89 per bottle for a bottle of 56 capsules (25 mg strength) capsules; $17,966.67 for a bottle of 56 capsules (100mg strength); $8,555.56 per 100 mL oral solution (20 mg/mL). In adults and at the recommended dose of 100 mg twice per day, larotrectinib costs $641.67 using 2 x 100 mg capsule or $855.56 using 8 x 25 mg capsule per day. In children and at the recommended dose of 100 mg/m^2 up to a maximum of 100 mg twice daily, i.e., maximum 200 mg daily, larotrectinib costs a maximum of $855.56 per day. In both adults and pediatric patients, larotrectinib may cost from $17,966.76 to $23,955.57 per 28-day cycle depending on the formulation used.

pERC RECOMMENDATION

☐ **Reimburse**
☒ **Reimburse with clinical criteria and/or conditions[a]**
☐ **Do not reimburse**

[a] If the condition(s) cannot be met, pERC does not recommend reimbursement of the drug for the submitted

pERC conditionally recommends the reimbursement of larotrectinib (Vitrakvi) for the treatment of adult and pediatric patients with locally advanced solid tumours that have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion (This recommendation pertains only to adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma [STS], and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma), without a known acquired resistance mutation, that are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options, only if the following conditions are met:

- Cost-effectiveness being improved to an acceptable level
- Feasibility of adoption (budget impact and access to testing) is addressed

Patients should have good performance status and treatment should be continued until unacceptable toxicity or disease progression.

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reimbursement request.	pERC made this recommendation because it concluded that there may be a net clinical benefit of larotrectinib based on a clinically significant benefit in overall response rate (ORR) and a generally safe and a manageable toxicity profile. In making this recommendation, pERC acknowledged the uncertainty in the evidence presented but agreed that treatment with larotrectinib would be most impactful for adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma given the high frequency of the NTRK gene fusion, the significant need for treatment options, and the substantial burden of disease in these tumour types. pERC further recognized that the patient populations to whom this recommendation applies would be small (i.e., relatively uncommon cancers). pERC agreed that larotrectinib aligns with patient values as it improves symptom control, provides better disease control, has a manageable toxicity profile, and provides patients with ease of administration. In all other solid tumours that have an NTRK gene fusion, pERC does not recommend the reimbursement of larotrectinib. pERC made this recommendation because it was not satisfied that there is a net clinical benefit based on the available evidence. While pERC noted that there is a need for treatment in these settings and that the overall clinical data suggest that larotrectinib may have a clinically meaningful ORR, there was considerable uncertainty regarding the prognostic impact of the NTRK gene fusion and the magnitude of clinical benefit across all tumour types. pERC had considerable concern about the quality of the limited data submitted. The Committee noted that there was a high level of uncertainty in the clinical effect estimates (PFS and overall survival) and cost estimates used in the submitted economic evaluations. This led to a wide range of incremental cost-utility estimates, all of which pERC considered unacceptable. Therefore, larotrectinib could not be considered cost-effective at the submitted price. pERC also highlighted that the submitted budget impact of larotrectinib was underestimated and the actual budget impact of implementing larotrectinib would be substantial. Therefore, pERC had concerns about the capacity of jurisdictions to implement larotrectinib particularly due to the NTRK testing requirements that would be needed.
POTENTIAL NEXT STEPS FOR STAKEHOLDERS	**Ensuring Evidence-Based Clinical Effectiveness and Cost-effectiveness** pERC noted that the confirmation of Health Canada regulatory approval for larotrectinib was conditional pending the results of trials to verify its clinical benefit. Given the substantial uncertainty in the magnitude of clinical benefit and cost-effectiveness with larotrectinib, pERC agreed that any additional evidence that could be collected through the regulatory process should be made available to jurisdictions and CADTH-pCODR to better inform the true effectiveness and cost-effectiveness of larotrectinib. pERC noted that this approach would help facilitate the equitable and timely access to promising treatments for patients while ensuring that publicly funded treatments are supported by rigorous evidence that demonstrates clinical and economic effectiveness and safety. **Pricing Arrangements to Improve Cost- Effectiveness and Budget Impact** Given that there may be a net clinical benefit of larotrectinib in advanced adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma and who have an NTRK gene fusion, compared with available treatment options, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of larotrectinib to an acceptable level. Due to the high cost of the drug, the considerable uncertainty in the incremental

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clinical and cost-effectiveness of larotrectinib, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness.

Accessibility to Testing for NTRK Gene Fusion Status
pERC agreed that NTRK gene fusion status is required prior to initiating treatment with larotrectinib. The Committee noted that it would be ideal for jurisdictions to have the NTRK mutation testing (RNA-based next generation sequencing [NGS] testing, incorporation of NTRK gene fusion to existing testing panels and/or immunohistochemistry followed by RNA-based testing) at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation for larotrectinib.

Factors Affecting Budget Impact and Adoption Feasibility
pERC noted that the budget impact of larotrectinib is likely to be high as the implementation of testing for the NTRK gene fusion and number of patients to be tested to identify the NTRK gene fusion has a large budget impact, particularly in more commonly occurring cancers where the NTRK gene fusion frequency is low, such as STS.

Possibility of Resubmission to Support Reimbursement in Broader Population
pERC acknowledged that the SCOUT and NAVIGATE trials are currently ongoing with estimated primary completion dates in 2022 and 2023, respectively. pERC noted that final results from these trials could form the basis of a resubmission to pCODR when the full data are available. pERC also encouraged the provision of new and more robust data that may better inform the historical outcomes of patients with the NTRK gene fusion (e.g., Voyager-1 trial) and/or the prognostic ability of the NTRK gene fusion to predict patient outcomes and overall survival.

Please note: Provincial Advisory Group (PAG) questions are addressed in detail in the Summary of pERC Deliberations and in a summary table in Appendix 1.

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SUMMARY OF pERC DELIBERATIONS

NTRK gene fusions are observed in variable frequencies across a spectrum of pediatric and adult solid tumours. There is some uncertainty regarding exact frequencies of the NTRK gene fusion across tumour types with estimates for incidence ranging from 0.1 to 1% in more commonly occurring cancers like non-small cell lung cancer (NSCLC) to 100% in less frequently occurring cancers like mammary analogue secretory carcinoma of the salivary gland. Generally, the NTRK gene fusion does not co-exist with other oncogenic driver mutations. Given the lack of data assessing the prognostic relevance of the NTRK gene fusion across cancer types, pERC had difficulty determining the burden of illness and need for treatment specifically targeting patients with the NTRK gene fusion. pERC further agreed that robust evidence is required to fully establish the role of the NTRK gene fusion in cancer prognosis. pERC acknowledged that among patients with tumour types that have a high frequency of the NTRK gene fusion, have no other known resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options, there is more certainty in the burden of illness and the need for new and effective treatment options. On the balance of these factors, pERC agreed that there may be a need for new and effective treatment options in such patient populations.

pERC's *Deliberative Framework* for drug reimbursement recommendations focuses on four main criteria:	
CLINICAL BENEFIT	PATIENT-BASED VALUES
ECONOMIC EVALUATION	ADOPTION FEASIBILITY

pERC deliberated on the results of a pooled analysis from the LOXO-TRK-14001, SCOUT, and NAVIGATE trials which evaluated larotrectinib in adult and pediatric patients with advanced or metastatic solid tumours. The primary outcome in the pooled analysis reported high overall response rates of 81% with the median duration of response not being reached as of the latest data cut. PFS was 28.3 months at the latest data cut while overall survival, only available for an earlier data cut, was not mature. pERC agreed that the pooled ORR results are large and impressive while the overall survival (OS) and PFS results are difficult to interpret given the methodological limitations of pooling patient populations with varying survival distributions. Although acknowledging the challenges of interpreting the results by tumour type, with sample sizes for these subgroups ranging from n = 1 to n = 28, pERC noted that ORRs were high in some tumour types, while in others (e.g., with an n = 1), ORR was 0%. pERC recognized that due to small sample sizes a lack of a response in some tumour types could be due to chance, however, in the absence of data on predictive relevance of NTRK and more robust clinical data across tumour types, pERC could not conclude that there is a clear benefit with larotrectinib across all NTRK positive solid tumours. pERC also considered the health-related quality of life (HRQoL) data collected and agreed that the improvements reported are difficult to interpret given the exploratory nature of the analysis. pERC further deliberated on the toxicity profile of larotrectinib and agreed that the low incidence of adverse events demonstrated that larotrectinib is well tolerated by patients.

In deliberating on the results of the pooled analysis, pERC had various discussions on the interpretability of the evidence within a setting that lacked evidence supporting or refuting the prognostic ability of the NTRK gene fusion, lacked historical evidence demonstrating outcomes in patients with the gene fusion, had various limitations in trial design including and not limited to heterogeneous patient populations in the pooled analysis and lack of evidence supporting the surrogacy of ORR for PFS and or OS. pERC noted that patients could be replaced in the NAVIGATE trial due the absence of any radiological disease assessments after the initiation of larotrectinib. Although there was no information on the number of patients that were replaced, pERC expressed concern that this may have introduced bias by selecting patients who had a better compliance or outcomes. Following a lengthy discussion on how meaningful the results of the pooled analyses were across all patients within the pooled analysis and the broader population of patients with the NTRK gene fusion, pERC was unable to generalize the overall trial results across all tumour types. pERC agreed that further evidence is required on the efficacy and safety of larotrectinib and on the prognostic impact of the NTRK gene fusion to aid in determining the generalizability of the trial results. In an effort to help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness and safety, pERC considered potential subgroups of patients with the NTRK gene fusion that may have more certainty of benefit

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despite the associated limitations of the evidence. Based on this discussion, pERC identified patients with tumours that harbour a high frequency of the NTRK gene fusion, have tumours with no other known resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options among the population of patients who may have more certainty of clinical benefit with larotrectinib treatment. Among the patients included in the pooled analysis, pERC agreed that these criteria applied specifically to adult or pediatric patients with soft tissue sarcoma, adult or pediatric patients with salivary gland tumours and pediatric patients with cellular congenital mesoblastic nephroma and infantile fibrosarcoma. pERC acknowledged the promising results in all other tumour types included in the pooled analysis but agreed that the limitations associated with the trial which had an impact on the interpretability of the results and the uncertainty in the prognostic impact of the NTRK gene fusion could not be overcome to determine that there was a net clinical benefit across all tumour types harbouring an NTRK gene fusion. pERC encouraged the provision of new and more robust data in these populations that may better inform the historical outcomes of patients with the NTRK gene fusion (e.g., Voyager-1 trial), prognostic ability of the NTRK gene fusion and/or the efficacy and safety of larotrectinib in patients with the NTRK gene fusion (e.g., more mature data from the ongoing SCOUT and NAVIGATE trials which are part of the regulatory requirement of the conditional Health Canada approval).

pERC considered the generalizability of the trial results. Although the pooled analysis only recruited patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of 0 to 2, pERC noted that the decision to restrict treatment based on PS should be left to the treating oncologist. Therefore, pERC concluded that patients with a good PS should be eligible for larotrectinib. pERC also supported the time-limited availability of larotrectinib for patients who fit the reimbursement population, as outlined by pERC, and are currently receiving an alternative treatment option.

pERC deliberated on input from patient advocacy groups and noted that patients value a targeted treatment that improves symptom control, has better disease control, allows for a better quality of life, and provides patients with ease of administration. Input from patient groups indicated that patients have variable experiences with disease and treatment options. Key symptoms identified by patient input varied from no symptoms to those having symptoms that significantly affect day-to-day life. The most difficult symptoms experienced by patients were fatigue, pain, incontinence, shortness of breath, headaches, dizziness, and swelling. Among patients who had experience with larotrectinib, all patients indicated that it offered clinically meaningful responses. All patients said improvements happened quickly — some symptoms resolving within days of starting larotrectinib. All patients said larotrectinib helped them maintain high quality of life (QoL) with disease related symptoms being significantly improved or managed better than on previous therapies. Patients expressed that all side effects were tolerable and minor. Based on the impact of larotrectinib on symptom control, its ability to provide better disease control, manageable toxicity profile and ease of administration, pERC agreed that larotrectinib aligned with patient values.

pERC deliberated on the cost-effectiveness of larotrectinib compared with available drugs. pERC acknowledged the difficulties in determining the cost-effectiveness of larotrectinib across a heterogeneous group of tumours and focused its deliberations on the main factors that impact the incremental cost-utility ratio (ICUR). First, pERC noted that the uncertainty in the presence of a survival benefit and the magnitude of such benefit will have an impact on the ICUR. pERC discussed that the OS and PFS results from the pooled analysis are difficult to interpret and there is no evidence supporting the surrogacy of ORR for PFS and/or OS. Based on these considerations, pERC agreed that it is unclear if larotrectinib confers a survival benefit in patients with NTRK-positive solid tumours. pERC further agreed that there was considerable uncertainty in the magnitude of the survival benefit modelled within individual tumour types as demonstrated in the 95% confidence interval (incorporated by the Economic Guidance Panel [EGP]) around each tumour-specific survival curve. Secondly, pERC noted that costs associated with testing and drug acquisition costs will have an impact on the ICUR. pERC discussed that the cost of testing had a substantial impact on the ICUR particularly when the incidence of the NTRK gene fusion is low or when there was a low-cost comparator option. In considering the cost-effectiveness of patients included in pERC's reimbursement recommendation, pERC noted that models for adult and pediatric patients with salivary gland tumours, pediatric patients with IFS and pediatric patients with CMN were not available while cost-effectiveness analyses were available for the adult and pediatric populations for STS. pERC however noted that the EGP's re-analysis estimates, for the available modelled populations, exceeded $400,000/QALY in most scenarios and were unlikely to be below $250,000/QALY in all scenarios. Despite the absence of tumour-specific models for part of the population in pERC's recommendation and based on factors that most impact the incremental cost-utility ratio (ICUR), pERC agreed that larotrectinib for the treatment of adult and pediatric patients with salivary gland tumours,

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adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma, is not cost-effective at the submitted price and according to EGP re-analyses.

pERC considered the feasibility of implementing a reimbursement recommendation for larotrectinib and discussed that the additional cost of testing and incidence rate of NTRK gene fusion could result in a potentially large budget impact. Based on the EGP's re-analysis, pERC noted that for tumours with low incidence of the NTRK gene fusion, the budget impact is lower and disproportionately spent on testing rather than treatment. Among tumours where the NTRK gene fusion is more common, the budget impact is greater and driven more by the cost of treatment (rather than by screening). pERC agreed that it would be ideal for jurisdictions to have the NTRK mutation testing (RNA-based NGS testing, incorporation of NTRK gene fusion to existing testing panels and/or immunohistochemistry followed by RNA-based testing) at the time of diagnosis to manage both the patient population and the budget impact of a reimbursement recommendation. pERC further agreed that the implementation of testing for the NTRK gene fusion will likely have a large budget impact, particularly in more commonly occurring cancers where the NTRK gene fusion frequency is (eg. STS population).

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EVIDENCE IN BRIEF

The CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) deliberated upon:

- A pCODR systematic review.
- Other literature in the Clinical Guidance Report that provided clinical context.
- An evaluation of the manufacturer's economic model and budget impact analysis.
- Guidance from the pCODR clinical and economic review panels.
- Input from seven patient advocacy groups (Canadian Cancer Survivor Network [CCSN], Colorectal Cancer Canada [CCC], Lung Cancer Canada [LCC], Neuroblastoma Canada [NC], Ontario Parents Advocating for Children with Cancer [OPACC], Sarcoma Cancer Foundation Canada [SCFC], and Thyroid Cancer Canada [TCC"]).
- Input from registered clinicians [one single clinician, and four joint clinician inputs, comprising of 26 oncologists and one pharmacist from Colorectal Cancer Canada (CCC; 11 clinicians), the Pediatric Oncology Group of Ontario (POGO; five clinicians), LCC; seven clinicians), and Cancer Care Ontario (CCO; three clinicians and one pharmacist)].
- Input from pCODR's PAG.

OVERALL CLINICAL BENEFIT

pCODR review scope

The purpose of the review is to evaluate the safety and efficacy of larotrectinib (Vitrakvi) in the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring a NTRK gene fusion.

Health Canada has issued marketing authorization for the use of larotrectinib for the treatment of adult and pediatric patients with solid tumours that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options. The marketing authorization was issued with conditions, pending the results of trials to verify its clinical benefit. pERC agreed that any additional evidence that may be collected through the fulfillment of this regulatory requirement should be made available to jurisdictions and CADTH-pCODR to better inform the true effectiveness and cost-effectiveness of larotrectinib.

Studies included: Pooled analysis of select patients from three separate non-randomized trials with different designs

The pCODR systematic review was based on a pooled analysis of three, open-label, single-arm trials of larotrectinib (LOXO-TRK-14001, a phase I adult dose escalation and expansion trial; SCOUT, a phase I/II pediatric trial; and NAVIGATE, a phase II basket trial in adults and adolescents) in adult and pediatric patients with advanced or metastatic solid tumours.

The pCODR review also provided contextual information on two topics.

- Prognostic relevance of the NTRK gene fusion in patients with solid tumours: A literature search was conducted and did not identify any relevant information that addressed the prognostic relevance of the NTRK gene fusion across tumour types.
- Testing for Neurotrophic Receptor Tyrosine Kinase (NRTK) Gene Fusion.

Patient populations: Heterogeneous patient population across three trials informing the pooled analysis

Key eligibility criteria of the three trials included:

- LOXO-TRK-14001: adult patients (≥ 18 years of age), with ECOG performance score of 0 to 2, and locally advanced or metastatic solid tumours that had progressed, were nonresponsive to available therapies, were unfit for standard chemotherapy, or for which no standard or available curative therapy existed. NTRK gene fusion status was not among the inclusion criteria. In the dose escalation phase, patients received increasing dose levels of larotrectinib (50 mg daily to 200 mg twice daily) until the dose-limiting toxicity in cycle 1, or until the maximum tolerated dose was reached. Patients in the expansion cohorts were treated at the maximum tolerated dose, or at a dose level deemed by the sponsor to provide significant TRK inhibition. The primary end point of the study was the safety

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of larotrectinib (including dose-limiting toxicity) and identification of the maximum tolerated dose. Secondary end points included overall response rate (ORR) and duration of response (DOR). A total of 72 patients were enrolled into the trial. Patient enrolment is complete.

- LOXO-TRK-15003 (SCOUT): pediatric patients (infants, children, and adolescents one month old to 21 years old) with locally advanced or metastatic solid tumours or central nervous system (CNS) tumours that had relapsed, progressed, or had inadequate response to available therapies. Patients were required to have a Karnofsky (for patients aged ≥ 16 years) or Lansky (for patients aged <16 years) performance score of at least 50. Larotrectinib was administered in increasing doses in the phase I dose escalation phase (based on age and body surface area (BSA) in two cohorts and using a BSA-based dose for three additional cohorts). A starting dose of 100 mg twice daily was used in the phase I expansion and phase II based on previous testing in adults. Larotrectinib was administered orally twice daily, based on 28-day cycles. The primary end point of the phase I dose escalation component was the safety of larotrectinib, including dose-limiting toxicity. ORR (per RECIST version 1.1), PFS, OS, and assessment of pain and HRQoL were conducted in the phase I expansion and phase II stage of the trial. A total of 37 patients were recruited on the trial. Patient enrolment is ongoing.
- LOXO-TRK-15002 (NAVIGATE): nine cohorts of adolescent and adult patients with solid tumours harbouring NTRK fusions (NSCLC, thyroid cancer, sarcoma, colorectal cancer, salivary gland cancer, biliary cancer, primary CNS tumour, all other solid tumour types with evaluable but not measurable disease; and patients with an NTRK gene fusion identified in a lab where certification of the lab cannot be confirmed by the sponsor - all the testing was performed in a Clinical Laboratory Improvement Amendments–certified (or equivalent) laboratory). Patients were required to have an ECOG PS ≤ 3, or Karnofsky performance score of at least 50 for patients with CNS tumours. Larotrectinib was administered at 100 mg orally in patients with a BSA ≥ 1 m^2, or 100 mg/m^2 orally twice daily for children and adolescents with a BSA < 1 m^2, up to a maximum of 100 mg twice daily based on 28-day cycles. The primary end point of the trial was ORR, as determined by an independent radiology review committee using RECIST (version 1.1) or RANO criteria. Secondary end points included: investigator-assessed ORR, DOR, PFS, OS, and safety. HRQoL was measured as an exploratory end point. A total of 75 patients were recruited on the trial. Patient enrolment is ongoing.

In all three trials, treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal.

The pooled analyses included adult and pediatric patients who were enrolled across the three larotrectinib studies if they met the following criteria: documented NTRK gene fusion as determined by local testing; non–central nervous system primary tumour with one or more measurable lesions at baseline that could be assessed according to RECIST, version 1.1; and received one or more doses of larotrectinib. A total of 122 adult and pediatric patients with NTRK gene fusion cancer were included in the efficacy analysis population with an additional 70 patients included for the safety analysis. Patient ages ranged from 1.2 months to 80 years, with a median of 41 years. The majority of patients had an ECOG performance score of 0 or 1; and 45% of patients had received two or more prior systemic anti-cancer therapies. A total of 15 different tumour types were included with sample sizes ranging from n = 28 (adult STS) to n = 1 (appendix, CMN, pancreas and unknown primary site of tumour).

Key efficacy results: Variable ORR across subgroups by tumour type, inability to interpret PFS and OS results

The key efficacy outcome deliberated on by pERC included ORR, which was the primary end point of the pooled analysis. As of the 30-July-2018 data cut-off date, ORR was 81% (95% CI, 72% to 88%) in the pooled analysis; with 17% of patients achieving a complete response and 63% achieved a partial response. The median time to response was 1.8 months. At the data cut-off, 84% of responding patients (73% of all patients) remained on treatment or had undergone surgery with curative intent. The ORR results varied across the subgroups by tumour types, and NTRK gene fusion or major NTRK isoforms. ORR was however consistent across other subgroups based on baseline disease characteristics (ECOG status and metastatic cancer status) and number of prior treatment regimens. pERC agreed that the ORR results are large and impressive. Although acknowledging the challenges of interpreting subgroup results with very few patient numbers, pERC noted that the high ORR rates were variable when considering ORR by tumour type, with a 0% ORR in some tumours with n=1.

Key secondary endpoints in the pooled analysis included PFS and OS. At the 30-July-2018 data cut-off date, after a median follow-up of 19.6 months, the median PFS was 28.3 months (95% CI, 9.9 to not

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estimable). The submitter acknowledged that this estimate was "not statistically stable due to a low number of progression events, as evidenced by the wide confidence interval." OS results were only available for an earlier analysis performed at the 19-February-2018 data cut-off (extended primary data set; n = 73), where 86% of patients were still alive and 14% had died. After a median follow-up of 14.8 months, the median OS had not been reached. At 12 months, the probability of survival was estimated to be 90%. pERC agreed that the OS and PFS results are difficult to interpret given the methodological limitations of pooling patient populations with varying survival distributions.

Patient-reported outcomes: Difficult to interpret improvements given exploratory assessment

HRQoL and health utilities were exploratory end points in the NAVIGATE and SCOUT trials while these were not measured in the LOXO-TRK 14001 trial. The minimally importance difference was defined as a change in score of ≥10 points for EORTC QLQ-C30, ≥ 4.5 points for PedsQL-Core score, and ≥ 10 points for the EQ-5D-5L visual analogue scale (VAS).

Of the 40 adult patients who completed EORTC QLQ-C30 questionnaire, 70% had an improvement in global health scores, with 60% reporting improvements that reached or exceeded the minimally important difference of 10 points. Among evaluable patients, 41% had an improvement in EORTC QLQ-C30 global health score that lasted for at least two consecutive cycles. EORTC QLQ-C30 global health score improvements were reported for all tumour types. Within the EQ-5D measure, 73% had an and improvement in VAS health score, with 60% reporting a post-baseline score that reached or exceeded the MID of 10 points. Among evaluable patients, 51% had an improvement in VAS health score that lasted for at least two consecutive cycles.

Of the 17 pediatric patients who completed the PedsQL-Core questionnaire, 88% had improvement in PedsQL total scores, with 76% reporting a best post-baseline score that reached or exceeded the MID of 4.5 points. Among evaluable patients, 65% reported improvements that lasted for at least two consecutive cycles. PedsQL total score improvements were observed across tumour types.

pERC considered the HRQoL data collected and agreed that the improvements reported are difficult to interpret given the exploratory nature of the analysis. pERC acknowledged that there is additional difficulty in interpreting HRQoL improvements in pediatric patients which range in age from ≥ two years to < 18 years.

Limitations: Extensive limitation in interpretability of available evidence

pERC considered the extensive limitations associated with the evidence base supporting the use of larotrectinib in adult and pediatric patients harbouring an NTRK gene fusion. pERC first noted a lack of historical evidence to determine prognostic impact of the gene fusion. pERC acknowledged that the NTRK gene fusions are rare and the natural history of the disease has not been well characterized to date. An independent search conducted by the CADTH-pCODR review team and confirmation from the submitter noted that there is no literature available that demonstrated the impact of NTRK gene fusion on patients' outcomes across tumour types. pERC also noted a lack of data on comparative efficacy and safety among cancers for who there are established standards of care (e.g., targeted therapies or immunotherapies).

Secondly, pERC considered heterogeneity in the design of the trials used to inform patients included in the pooled analysis. These included different phases of studies combined (a phase I adult trial [LOXO-TRK 14001], a phase I/II pediatric trial [SCOUT], and a phase II basket trial [NAVIGATE] in adults and adolescents); different primary outcomes across trials (safety and tolerability of larotrectinib as a primary objective in the LOXO-TRK 14001 and SCOUT studies, while the primary objective of the NAVIGATE trial was efficacy of larotrectinib based on best overall response rate); different requirements for outcome measurement where assessment of ORR was based on investigators in the LOXO-TRK 14001 and SCOUT trials while an independent committee assessed ORR in the NAVIGATE trial; and differences in eligibility criteria where the presence of a confirmed NTRK fusion was mandated before enrolment in the NAVIGATE trial; while NTRK-positive status was not a requirement in the LOXO-TRK 14001 and SCOUT trials with prospective confirmation of TRK gene fusions in the two latter trials. pERC agreed that the between-study heterogeneity creates considerable difficulty in pooling results across the three trials.

Lastly, pERC noted that pooling data across tumour types may lead to inflated type I error if the treatment effect is heterogeneous across different tumour types. pERC discussed that analysis of the data by subgroups from the three trials (integrated analysis; n = 122) indicated that ORR results varied across

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tumour types. The reported ORR benefit ranged from 100% in thyroid cancer, gastrointestinal stromal tumour (GIST), and CMN to 0% in appendix, pancreas and breast cancers, and cholangiocarcinoma. Furthermore, traditional survival analysis methods such as Kaplan-Meier curves rely on the assumption that a single survival distribution can be used to estimate the survival of all study patients. Given this, there is considerable difficulty in interpreting results which pool data on survival outcomes (i.e., PFS and OS) across different tumour types.

pERC noted that patients could be replaced in the NAVIGATE trial due the absence of any radiological disease assessments after the initiation of larotrectinib. Although there was no information on the number of patients that were replaced, pERC expressed concern that this may have introduced bias by selecting patients who had a better compliance and/or outcome.

Overall, pERC had a fulsome discussion in determining how meaningful the results of the pooled analyses were across all patients within the pooled analysis and broader population of patients with the NTRK gene fusion. pERC agreed that further evidence is required to confirm efficacy and safety of larotrectinib in the broader population and further evidence addressing the predictive impact of the NTRK gene fusion. Based on this, the Committee was unable to generalize the overall trial results across all patients with an NTRK gene fusion. In an effort to help facilitate the equitable and timely access to promising treatments for patients while ensuring that treatments considered for public reimbursement adhere to a level of rigour that sufficiently demonstrates effectiveness and safety, pERC considered potential subgroups of patients with the NTRK gene fusion where a clear unmet need exists despite the associated limitations of the evidence. pERC identified patients whose tumours harbour a high frequency of the NTRK gene fusion, have tumours with no other known resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options among the population of patients who may have more certainty of clinical benefit with larotrectinib treatment. Among the patients included in the pooled analysis, pERC agreed that these criteria applied specifically to adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. pERC acknowledged the promising results in all other tumour types included in the pooled analysis but agreed that the limitations associated with the trial which had an impact on the interpretability of the results and the uncertainty in the predictive impact of the NTRK gene fusion could not be overcome. pERC could not conclude that there was a net clinical benefit across all tumour types harbouring an NTRK gene fusion. pERC encouraged the provision of new and more robust data in these populations that may better inform the historical outcomes of patients with the NTRK gene fusion (e.g., Voyager-1 trial), prognostic ability of the NTRK gene fusion and/or the efficacy and safety of larotrectinib in patients with the NTRK gene fusion (e.g., more mature data from the ongoing SCOUT and NAVIGATE trials which are part of the regulatory requirement of the Health Canada approval).

Safety: Low incidence of toxicity, well tolerated

pERC discussed the toxicity profile of larotrectinib. Among the 207 patients included in the safety analysis data set, the majority of the reported adverse events (AEs) were grade 1 or 2. Treatment-related Grade 3 or 4 AEs occurred in less than 5% of patients. The most common Grade 3 or 4 AEs included anemia, increase in liver enzyme (alanine transaminase, ALT and aspartate transaminase, AST) levels, and nausea. [redacted] out of the [redacted] patients ([redacted]) in the integrated analysis set required dose reductions due to AEs, and [redacted] maintained tumour regression on a reduced dose. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 1, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*). [redacted] patients discontinued larotrectinib due to an AE. pERC deliberated on the toxicity profile of larotrectinib and agreed that the low incidence of AEs demonstrated that larotrectinib is well tolerated by patients. (*Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until December 1, 2019 or until notification by manufacturer that it can be publicly disclosed, whichever is earlier*).

Need and burden of illness: Uncertainty in the burden of illness and need for treatments targeting the NTRK gene fusion

NTRK gene fusions are observed in variable frequencies across a spectrum of pediatric and adult cancers. There is some uncertainty regarding exact frequencies of the NTRK gene fusion in tumours with estimates for incidence ranging from 0.1 to 1% in more commonly occurring cancers like NSCLC to 100% in less

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frequently occurring cancers like mammary analogue secretory carcinoma of the salivary gland. Generally, the NTRK gene fusion does not co-exist with other driver mutations, with small studies reporting co-localization with PD-L1 gene alteration, EGFR and MET amplification and others in a smaller proportion of patients. pERC discussed the absence of literature assessing the prognostic relevance of the NTRK gene fusion in cancer and the absence of evidence demonstrating historical outcomes of patients harbouring the NTRK gene fusion. pERC therefore agreed that, until more robust evidence is made available, the Committee has recommended reimbursement of larotrectinib for specific tumour types based on the balance of clinical considerations. pERC supported the collection of robust evidence to establish the role of the NTRK gene fusion in the prognosis of disease and agreed that when such data are available, it should be made available to jurisdictions and CADTH-pCODR. pERC acknowledged that among select patients who harbour a high frequency of the NTRK gene fusion, have no other known resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment option, there may be more certainty of a burden of illness and need for new and effective treatment options that target a known mutation (NTRK gene fusion in this instance). On the balance of these factors, pERC agreed that there may be a need for new and effective treatment options in such patient populations.

Registered clinician input: Sequencing and need of larotrectinib dependent on tumour type; need for more evidence in some tumour types, testing an important consideration

Input was received from one single clinician and four joint clinician inputs comprising 26 oncologists and one pharmacist from the following groups: Colorectal Cancer Canada (CCC; 11 clinicians), the POGO; five clinicians), LCC; seven clinicians), and CCO; three clinicians and one pharmacist).

Clinicians noted that a variety of drugs are currently used in patients with NTRK-positive solid tumours. Including conventional cytotoxic drugs in subsets of pediatric malignancies harbouring the NTRK gene fusion, chemotherapy and immunotherapy in lung cancer. Some of these therapies were stated to have fewer side effects and lead to better QoL compared with cytotoxic chemotherapy (e.g., immunotherapies). Clinicians also noted that large randomized controlled trials with patients harbouring the NTRK gene fusion are unlikely to be conducted. CCO clinicians stated that a phase I study with one breast cancer patient is insufficient evidence to extrapolate the use of larotrectinib to breast cancer patients. CCO therefore agreed that there is no unmet need for larotrectinib in patients with breast cancer.

While acknowledging the limited data available, clinicians identified that for patients with colorectal, pancreas or cholangiocarcinoma, larotrectinib offers a significant improvement beyond current standard options based on its route of administration and lack of chemotherapy related toxicity. For other settings including GIST and hepatocellular carcinoma, larotrectinib would be an additional treatment option along with available standard drugs (sunitinib, imatinib and regorafenib in GIST and sorafenib and regorafenib in HCC). A number of groups including LCC, POGO and the single clinician input highlighted the benefit of larotrectinib as related to its safety profile. Tolerability and duration of disease control were stated to be remarkable across the board, showing superiority over cytotoxic chemotherapy regimens and immunotherapy, which can be associated with significant immune mediated AEs.

Generally, clinicians noted that for patients in whom the NTRK gene fusion occurs with high frequency and for whom upfront therapy of choice remains surgical resection and includes potential for significant morbidity (IFS, cellular CMN, secretory breast cancer [SBC] and mammary analogue secretory carcinoma of the salivary gland [MASC]), patients should be considered candidates for larotrectinib if low intensity/low toxicity cytotoxic therapy (such as vincristine and dactinomycin) are insufficient to control disease and allow resection. Clinicians further noted that larotrectinib should be prioritized over traditional cytotoxic drugs with higher potential late effects such as anthracyclines or alkylators. For patients where the NTRK gene fusion occurs with low frequency, clinician's decision on treatment with larotrectinib varied by disease prognosis. For patients in whom prognosis is poor (i.e., high grade gliomas, metastatic sarcoma, metastatic papillary thyroid cancer) larotrectinib therapy should be considered as part of front-line therapy. For patients in whom prognosis is good, clinicians noted that larotrectinib be reserved as a second-line therapy until evidence showing equivalent or better than current front-line therapy is available.

There was no consensus from input received by clinicians on the sequencing of larotrectinib compared with currently available drugs. Generally, clinicians prefer to use larotrectinib in front line for pediatric

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populations. Among gastrointestinal solid tumours (colorectal, pancreatic, hepatocellular carcinoma and cholangiocarcinoma), clinicians indicated a preference to use larotrectinib first line and beyond.

All clinicians agreed that patients eligible for larotrectinib would need to present with solid tumours harbouring the NTRK gene fusion. Clinicians further noted that there is no routine testing for NTRK currently available, and that testing is not funded although it is anticipated that availability of NTRK testing will increase over the next five years given the increasing number of targeted therapies, and the declining cost of NGS testing. A variety of tests to identify the NTRK gene fusion were stated. A number of clinician groups noted that testing for the NTRK gene fusion is likely to be added to existing NGS panels (e.g., colorectal cancer, lung cancer). Ideally identification of the NTRK gene fusion would occur during diagnosis of the patient's tumour, or during testing for other mutations. However, there was no consensus on the timing of testing.

pERC reflected on the clinician input and agreed that the reimbursement population should be limited to adult and pediatric patients with salivary gland tumours, adult patients with STS and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. pERC further supports the provision of more robust data to help inform the efficacy and safety of larotrectinib in the broader population. pERC's recommended population for reimbursement of larotrectinib is in alignment with input from registered clinicians which noted that candidates for larotrectinib should include patients in whom the NTRK gene fusion occurs with high frequency and for whom upfront therapy of choice remains surgical resection and includes potential for significant morbidity.

PATIENT-BASED VALUES

Values of patients with NTRK-positive solid tumours: Symptom control, disease control, better QoL, ease of administration

pERC deliberated upon on collaborative input from seven patient groups, most of which was collected through US institutions or patients in the US with experience using larotrectinib. pERC noted that patients value a treatment that improves symptom control, has better disease control, allows for a better QoL, and provides patients with ease of administration. Input from patient groups indicated that patients have variable experiences with disease and treatment options. Key symptoms identified by patient input varied from no symptoms to those having symptoms that significantly affect day-to-day life. The most difficult symptoms experienced by patients were fatigue, pain, incontinence, shortness of breath, headaches, dizziness, swelling. Patient respondents reported that larotrectinib is a targeted agent which offered improvement in cancer symptoms, better disease control, manageable toxicities, ease of administration and maintenance of a high level of quality of life.

The prognosis of cancer in some patients, especially in lung cancer, was described as feeling like a death sentence. Sarcoma patients experience an invasive and aggressive disease, affecting both children and young adults. Treatment with surgery for these patients can lead to loss of limbs and long rehabilitation.

All patients providing input had previous treatment with chemotherapy, surgery, radiation, immunotherapies, and/or targeted therapies. Patients indicated that they had exhausted other options. Soft tissue sarcoma patients described having a struggle to find effective treatments. Chemotherapy in lung cancer and sarcoma patients was described to have many well-documented side effects ranging from minimal to debilitating effects including nausea, vomiting and extreme fatigue. Chemotherapy also requires multiple hospital visits for administration, treatments for toxicities and delayed effects. Patients noted that immunotherapies have fewer side effects (or are better managed) and provide better QoL than chemotherapy. Lastly, patients acknowledged that targeted therapies have created a new paradigm for lung cancer patients. Some patients described going into debt to access treatments, including incurring the loss of homes, marriages, careers, experiencing depression, and reduced QoL.

Caregivers indicated that the illness and treatment limit their and the patients' QoL. The poor prognosis and stigma of lung cancer leads to worry, isolation, anxiety and depression. Furthermore, the surgeries and rehabilitation for sarcoma affect marriages and career prospects of younger patients.

Patient values on treatment: better QoL, better survival, improved symptom control, ease of administration

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Patients' expectations of the new treatment include better QoL while managing disease. Lung cancer patients expressed a desire for better survival rates, improved symptoms and an easier form of treatment, while sarcoma patients often experience quick disease progression and without long-term effective treatments, expressed a desire for reduction in pain, increase in mobility, and ease of breathing.

Among the 14 patients (one pediatric and 13 adults) who had experience with larotrectinib, all indicated that larotrectinib offered clinically meaningful responses to cancer (resolved completely, significantly or to a great extent) according to scans. The sarcoma patients (SCFC) were several years beyond their treatment and had not experienced any disease regression or reappearance of tumours. All patients also said improvements happened quickly — some symptoms resolving within days of starting larotrectinib. All said larotrectinib helped them maintain high QoL with disease related symptoms being significantly improved or managed better than on previous therapies. Side effects experienced by patients while on larotrectinib included elevated ALT/AST levels, tinnitus, swollen ankles, withdrawal-like symptoms, overstimulation, fatigue, sensitivity to light, and flu-like symptoms. Patients expressed that all side effects were tolerable and minor. Despite the absence of robust clinical evidence to guide pERC's deliberation, the Committee commended the substantial collaborative work undertaken by patient groups, including extensive interviews, which helped pERC better understand the impact of treatment, the nature of the side effects and the ways in which larotrectinib contrasts with other treatments.

ECONOMIC EVALUATION

Economic model submitted: Cost-effectiveness and cost-utility analysis based on six tumour-specific models and one model pooling all patients

The EGP assessed the submitted cost-effectiveness and cost-utility analyses of larotrectinib for the treatment of adult and pediatric patients with locally advanced or metastatic solid tumours harbouring an NTRK gene fusion.

Seven separate analyses were included in the submitted base case. One model was based on the pooled analysis comparing larotrectinib with standard chemotherapy in individual settings, hereafter referred to as best supportive care (BSC) for each of the 14 tumour types included in the analysis from three clinical trials informing the efficacy and safety outcomes. Notably, the six other tumour-specific analysis were available assessing larotrectinib in subgroups of patients with colorectal cancer (CRC - comparators: trifluridine plus tipiracil; BSC); NSCLC - comparators: pembrolizumab plus platinum; nivolumab; BSC); melanoma (comparator: BSC); thyroid cancer (comparators: lenvatinib; BSC); adult soft tissue sarcoma (STS - comparator: BSC); and pediatric STS (comparator: BSC).

Although requested by the EGP, the submitter was unable to provide a model for salivary gland tumours, despite this tumour type having the largest sample size in the clinical trials (n = 13). The submitter explained that there was insufficient information on the natural history of salivary gland tumours, a lack of reference data for other relevant inputs, and a lack of information on the selection of an appropriate comparators in this setting to build a site-specific model. For all other cancers, the submitter further clarified that a consistent range of cost-effectiveness results was demonstrated and, given the limitations of the data, there is a diminishing value gained with additional models.

Basis of the economic model: Key costs underestimated, limited evidence informing survival curves for intervention arm

Key costs included were drug acquisition cost, diagnostic testing costs, non-treatment health care costs (surveillance and active follow-up for the "progression free and responsive to treatment," "progression free, but not responding to treatment/stable disease," and "progressed disease" states and terminal care) and cost of AEs. pERC noted that non-treatment health care costs, testing costs and likely AE costs were underestimated in the submitted models.

Key clinical effect estimates considered in the various analyses included OS, PFS, utilities, and disutilities associated with AEs. The efficacy and safety evidence for larotrectinib came from an integrated analysis of three studies (LOXO-TRK-14001, LOXO-TRK-15002 or NAVIGATE, LOXO-TRK-15003 or SCOUT). Kaplan-Meir data for PFS and OS were based on tumour-specific subgroup survival curves. pERC noted that uncertainty in tumour-specific larotrectinib survival curves was not captured in the probabilistic analysis for 15 cycles (trial data) and hence, in some situations 100% PFS and OS were assumed certain despite

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very small sample sizes and short follow-up period. This was modified in the EGP re-analysis. The efficacy and safety for the comparators (where available) came from representative studies selected by the submitter to characterize the range of potential outcomes associated with the comparators. The comparator arms were not composed of patients selected based on the NTRK gene fusion status. No formal quantitative indirect treatment comparison was performed.

Drug costs: High cost of treatment

In adults and at the recommended dose of 100 mg twice per day, larotrectinib costs $641.67 using 2 x 100 mg capsule or $855.56 using 8 x 25 mg capsule per day. In children and at the recommended dose of 100 mg/m^2 up to a maximum of 100 mg twice daily, i.e., maximum 200 mg daily, larotrectinib costs a maximum of $855.56 per day with the oral solution. In both adults and pediatric patients, larotrectinib may cost from $17,966.76 to $23,955.57 per 28-day cycle depending on the formulation used.

The following comparators were considered in the submitted economic evaluation. Costs are based on a 28-day cycle:

- CRC: Trifluridine/tipiracil ($6,219.96), BSC (5-fluorouracil-oxaliplatin-leucovorin, $4,693).
- NSCLC: Pembrolizumab plus Platinum ($11,733), Nivolumab ($8,213), BSC (docetaxel-pemetrexed-topotecan, $4,065).
- Melanoma: BSC (dacarbazine-temozolomide-carboplatin-paclitaxel, $2,721).
- Thyroid: Lenvatinib ($6,184), BSC (doxorubicin-cisplatin, $800).
- Adult STS: BSC (Doxorubicin plus ifosfamide, $1,039).
- Pediatric STS: BSC (Vincristine-dactinomycin-cyclophosphamide — VAC, $95)
- GIST: BSC (Imatinib-sunitinib, $4,465).
- Other sarcoma: BSC (doxorubicin, $933).
- MASC: BSC (Doxorubicin-5-fluorouracil-cisplatin-vinorelbine-oxaliplatin-carboplatin-paclitaxel-docetaxel-methotrexate-ifosfamide-gemcitabine, $1,342).
- Cholangiocarcinoma: BSC (gemcitabine-cisplatin-5-fluorouracil, $344).
- Breast: BSC (capecitabine -epirubicin-doxorubicin-fulvestrant, $1,589).
- Appendix: BSC (capecitabine-5-fluorouracil-irinotecan-raltitrexed -oxaliplatin-leucovorin-folinic acid, $3,225).
- Pancreatic: BSC (5-fluorouracil-gemcitabine, $181)

Clinical effect estimates: Considerable uncertainty in survival estimates and cost inputs

pERC deliberated on the cost-effectiveness of larotrectinib compared with available drugs. Among the seven models provided to evaluate the cost-effectiveness of larotrectinib, pERC noted that the model with the results of the full pooled analysis violated a number of modelling and statistical assumptions which caused the pCODR EGP to reject this analysis. pERC agreed with the EGP and only considered the tumour-specific models for its deliberations. pERC noted that the evidence informing the available models (n = 4 in some instances), created considerable uncertainty in the submitted and EGP's re-analysis estimates. pERC further noted that the available tumour-specific models did not address all the specific patient populations included in the reimbursement population defined by the Committee. pERC also acknowledged the rationale provided by the submitter indicating that a consistent range of cost-effectiveness results were demonstrated across the seven models provided and, given the limitations of the data, there is an expectation that the value of insight to be gained with any additional site-specific models diminishes.

Given the difficulties in determining the cost-effectiveness of larotrectinib, pERC's deliberations were focused on the main factors that impact the incremental cost utility ratio (ICUR). First pERC noted that the uncertainty in the presence of a survival benefit and the magnitude of such benefit will have a big impact on the ICUR. pERC discussed that the OS and PFS results from the pooled analysis are difficult to interpret and there is no evidence supporting the surrogacy of ORR for PFS and/or OS. Based on these, pERC agreed that it is unclear if larotrectinib confers a survival benefit in patients with NTRK-positive solid tumours. pERC further agreed that there was considerable uncertainty in the magnitude of the survival benefit modelled within individual tumour types as demonstrated in the 95% confidence interval (incorporated by the EGP) around each tumour-specific survival curve. Secondly, pERC noted that costs associated with testing or drug acquisition costs will have a big impact on the ICUR. pERC discussed that the cost of testing had a substantial impact on the ICUR particularly when the incidence of the NTRK gene fusion is low or when there was a low-cost comparator option.

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In specifically considering the cost-effectiveness of patients included in pERC's reimbursement recommendation, pERC noted that cost-effectiveness analysis were available for the adult patients with STS and pediatric populations for STS but were not available for adult and pediatric patients with salivary gland tumours and pediatric patients with IFS and CMN. pERC however noted that the EGP's re-analysis estimates, for the available modelled populations, exceeded $400,000/QALY in most scenarios and were unlikely to be below $250,000/QALY in all scenarios. Despite the absence of tumour-specific models and based on the factors that most impact the ICUR, pERC agreed that larotrectinib for the treatment of adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma, is not cost-effective based on EGP re-analyses and at the submitted price.

ADOPTION FEASIBILITY

Considerations for implementation and budget impact: Potentially large budget impact due to testing implementation

pERC considered the feasibility of implementing a reimbursement recommendation for larotrectinib and noted that incorporation of testing costs for all cancer sites, duration of larotrectinib therapy, the frequency of testing, and the frequency of NTRK gene fusion had the biggest impact on the budget impact analysis. Based on the EGP's re-analysis, pERC noted that for tumours with lower incidence of the NTRK gene fusion, the budget impact is lower and disproportionately spent on testing compared to treatment. Among tumours where the NTRK gene fusion is more common, the budget impact is greater and driven more by the price of treatment (rather than by screening).

pERC agreed that it would be ideal for jurisdictions to have the NTRK mutation testing (RNA-based NGS testing, incorporation of NTRK gene fusion to existing testing panels and/or immunohistochemistry followed by RNA-based testing) at the time of diagnosis to manage the budget impact of a reimbursement recommendation. pERC further agreed that the implementation of testing for the NTRK gene fusion and number of patients to be tested to identify the NTRK fusion protein will likely have a large budget impact, particularly in more commonly occurring cancers where the NTRK gene fusion frequency is low. Given that there may be a net clinical benefit of larotrectinib in adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma, compared with available treatment options, jurisdictions will need to consider pricing arrangements and/or cost structures that would improve the cost-effectiveness of larotrectinib to an acceptable level. Due to the high cost of the drug, the considerable uncertainty in the incremental clinical and cost-effectiveness of larotrectinib, pERC concluded that a substantial reduction in drug price would be required to improve cost-effectiveness.

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ABOUT THIS RECOMMENDATION

The pCODR Expert Review Committee

Recommendations are made by the CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) following the pERC Deliberative Framework. pERC members and their roles are as follows:

Dr. Maureen Trudeau, Oncologist (Chair)
Dr. Catherine Moltzan, Oncologist (Vice-Chair)
Daryl Bell, Patient Member Alternate
Dr. Kelvin Chan, Oncologist
Lauren Flay Charbonneau, Pharmacist
Dr. Matthew Cheung, Oncologist
Dr. Winson Cheung, Oncologist
Dr. Henry Conter, Oncologist
Dr. Avram Denburg, Pediatric Oncologist
Dr. Leela John, Pharmacist
Dr. Anil Abraham Joy, Oncologist
Dr. Christine Kennedy, Family Physician
Dr. Christian Kollmannsberger
Dr. Christopher Longo, Health Economist
Cameron Lane, Patient Member
Valerie McDonald, Patient Member
Dr. Marianne Taylor, Oncologist
Dr. W. Dominika Wranik, Health Economist

All members participated in deliberations and voting on the Initial Recommendation, except:

- Drs. Henry Conter, Avram Denburg, Christian Kollmannsberger, and Dominika Wranik who were not present for the meeting.
- Valerie McDonald who was excluded from voting due to a conflict of interest.

Avoidance of conflicts of interest

All members of the pCODR Expert Review Committee must comply with the *pCODR Conflict of Interest Guidelines*; individual conflict of interest statements for each member are posted on the pCODR website and pERC members have an obligation to disclose conflicts on an ongoing basis. For the review of larotrectinib (Vitrakvi) for NTRK solid tumours, through their declarations, one member had a real, potential or perceived conflict and based on application of the *pCODR Conflict of Interest Guidelines*, both of these members was excluded from voting.

Information sources used

pERC is provided with a pCODR Clinical Guidance Report and a pCODR Economic Guidance Report, which include a summary of patient advocacy group and PAG input, as well as original patient advocacy group input submissions, to inform its deliberations. pCODR guidance reports are developed following the pCODR review process and are posted on the pCODR website. Please refer to the pCODR guidance reports for more detail on their content.

Consulting publicly disclosed information

pCODR considers it essential that pERC recommendations be based on information that may be publicly disclosed. All information provided to the pCODR Expert Review Committee for its deliberations was handled in accordance with the *pCODR Disclosure of Information Guidelines*. Bayer Inc., as the primary data owner, did not agree to the disclosure of clinical data, therefore, this information has been redacted in this recommendation and publicly available guidance reports.

Use of this Recommendation

This Recommendation from pERC is not intended as a substitute for professional advice, but rather to help Canadian health systems leaders and policy-makers make well-informed decisions and improve the quality of health care services. While patients and others may use this Recommendation, it is for informational and educational purposes only, and should not be used as a substitute for the application of clinical judgment respecting the care of a particular patient, for professional judgment in any decision-making process, or for professional medical advice.

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APPENDIX 1: CADTH PAN-CANADIAN ONCOLOGY DRUG REVIEW EXPERT REVIEW COMMITTEE RESPONSES TO PAG IMPLEMENTATION QUESTIONS

PAG Implementation Questions	pERC Recommendation
• Guidance on the use of larotrectinib in patients with poor PS (i.e., ECOG > 2, LPS < 40%, and KPS < 50%).	• Although the pooled analysis only included patients with an ECOG PS of 0 to 2, even though ECOG 3 patients were eligible for the NAVIGATE trial, pERC agreed that the decision to restrict treatment based on PS should be left to the treating oncologist. Therefore, pERC concluded that patients with a good PS should be eligible for larotrectinib.
Time limited need: • A time limited need for reimbursement in patients that are identified to harbour a NTRK gene fusion and currently on other treatments.	• pERC supported the time limited availability of larotrectinib for patients who fit the reimbursement population, as outlined by pERC, and are currently on an alternative treatment option.
Treatment setting and sequencing: • Guidance on larotrectinib place in therapy. • Optimal sequencing of larotrectinib with other treatment options (i.e., would use be after all other treatment options are exhausted)? • What would patients receive after progression on larotrectinib?	• Based on the recommended patient population, patients who qualify for treatment with larotrectinib will include adult and pediatric patients with salivary gland tumours, adult or pediatric patients with soft tissue sarcoma (STS), and pediatric patients with cellular congenital mesoblastic nephroma or infantile fibrosarcoma. pERC agreed that these patients will have no satisfactory treatment options. • Decision on treatment following progression should be based on disease-related considerations, clinician discretion and patient factors.
Testing concerns: • Information on the turnaround time for NTRK gene fusion testing. • Guidelines on criteria for testing and whether all patients should be tested. • Expected number of patients eligible for larotrectinib (i.e., anticipated number of patients requiring testing per year, with tumours harbouring a NTRK gene fusion, and who would receive larotrectinib treatment). • Timing of testing and whether patients should be tested at diagnosis or at relapse.	• Based on input from the Clinical Guidance Panel addressing testing concerns, pERC noted that depending on the scope of testing and the jurisdiction, immunohistochemical testing turnaround time ranges from 2 to 5 calendar days while the turnaround time for NGS testing (including RNA-based NGS testing) ranges from 2 to 4 weeks. • pERC noted that patients must have confirmed NTRK-positive status before starting larotrectinib treatment. Based on CGP input, for cases with a high likelihood of NTRK fusion (IFS and CMN) RNA-based NGS testing should be performed. • pERC noted that there is no prospective, population-based study to accurately determine the number of patients to be tested. pERC anticipates that jurisdictions will need to determine the volume of testing during implementation. Generally, pERC agreed that the number of patients to be tested will be low given that the annual number of patients with STS. Infantile fibrosarcoma, CMN and salivary gland tumours are small. • Based on input from registered clinicians, pERC noted that identification of the NTRK gene fusion would ideally occur during diagnosis of the patient's tumour, or during testing for other mutations.

CGP = Clinical Guidance Panel; CMN = cellular congenital mesoblastic nephroma; ECOG PS = Eastern Cooperative Oncology Group Performance Status; IFS = infantile fibrosarcoma; KPS = Karnofsky Performance Score; LPS = Lansky Performance Score; NGS = next generation sequencing; NTRK = neurotrophic tyrosine receptor kinase; PAG = Provincial Advisory Group; pERC = CADTH pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee; RNA = ribonucleic acid; STS = soft tissue sarcoma.

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