7.05 LAROTRECTINIB,
Capsule 25 mg (as sulfate)
Capsule 100 mg (as sulfate)
Oral solution 20 mg per mL (as sulfate), 50 mL, 2
Vitrakvi®,
Bayer Australia Ltd

1 Purpose of submission

1.1 The standard re-entry submission requested a General Schedule Authority Required (Written) listing of larotrectinib for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) or soft tissue sarcoma (STS) harbouring neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions.

1.2 As was the case for the previous submission, listing was requested on the basis of a cost-effectiveness analysis versus standard of care (SoC).

1.3 The key changes in the requested listing from the previous submission (Larotrectinib Public Summary Document [PSD], November 2021 PBAC Meeting with March 2022 Addendum) were:

- the resubmission requested listing for two tumour types (NSCLC and STS) whereas in the previous submission, listing was requested for four tumour types (NSCLC, STS, thyroid cancer, and colorectal cancer [CRC]).
- the proposed listing in the resubmission is line-agnostic which allows treatment with larotrectinib in the first-line setting. In the previous submission, the proposed positioning of larotrectinib was in the refractory setting which required that the condition must have relapsed, or be refractory to, at least one prior therapy AND with no suitable alternate therapy available.

1.4 There are currently no generic small gene panel tests which cover multiple tumour types, and tumour specific panel tests only for NSCLC (Medicare Benefits Schedule [MBS] items 73437, 73438 and 73439, implemented on 1st November 2023), STS (MBS items 73376 and 73374) and glioma (MBS item 73429). The resubmission requested PBS listing for the tumour types for which there is funded testing available. The pre-subcommittee response (PSCR) noted that there are currently no TRK inhibitors listed on the PBS for NSCLC and STS patients, therefore these patients will be identified with an actionable driver mutation but have no PBS reimbursed access to an effective treatment option.

1.5 The resubmission invited the PBAC to also consider the inclusion of patients with glioma-like central nervous system (CNS) tumours in the listing given their poor prognosis, limited treatment options, and paucity of available data (N=13) in the

larotrectinib studies. Glioma-like CNS tumours are rare (0.5-1%) but have a devastating impact on patient survival and quality of life (QoL).

1.6 Table 1 summarises the components of the overall clinical claim addressed by the resubmission.

Table 1: Key components of the clinical issue addressed by the resubmission[a]

Component	Description
Population	Patients with locally advanced or metastatic NSCLC or STS[b] solid tumours and confirmed *NTRK* fusion
Intervention	Larotrectinib 100 mg twice daily for adults
Comparator	SoC represented by the following for the two[b] specified tumour types: NSCLC – Docetaxel STS – Pazopanib[c]
Outcomes	Treatment: Overall response rate, duration of response, overall survival, progression free survival, safety.
Clinical claim	In patients with locally advanced or metastatic NSCLC or STS[b] solid tumours and confirmed *NTRK* fusion, treatment with larotrectinib is superior in terms of efficacy and comparable safety[d] when compared to SoC.

Source: Adapted from Table 1.2 of the resubmission, and the Larotrectinib PSD, November 2021 PBAC Meeting, with March 2022 Addendum

CRC = colorectal cancer; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic receptor tyrosine kinase; R/R = refractory/relapsed; SoC = standard of care; STS = soft tissue sarcoma.

Key changes from the original submission have been underlined as follows:

[a]The previous submission was an integrated codependent resubmission with components relevant to both testing for *NTRK* fusions and treatment. The PBAC recommended listing for other requested tumour types such as paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (Larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum).

[b]For the adult low frequency population, the resubmission specified only two tumour types (NSCLC and STS) compared to four tumour types (NSCLC, STS, thyroid cancer, and CRC) requested in the previous submission. In addition, for the adult low frequency metastatic or locally advanced cancer population, the previous submission positioned larotrectinib where surgical resection was likely to result in severe morbidity and have R/R disease with no suitable alternate therapy. The requested listing in this resubmission is line-agnostic.

[c]The nominated comparator for STS patients changed from dacarbazine in the previous submission to pazopanib in the current resubmission.

[d]The therapeutic conclusion in Section 2.8 of the resubmission was that larotrectinib had a comparable safety profile relative to SoC.

2 Background

Registration status

2.1 Larotrectinib was granted provisional approval by the TGA on 7 September 2020 (extension granted until 7 September 2024) for the treatment of adult and paediatric patients with locally advanced or metastatic solid tumours that:

- have a neurotrophic tyrosine receptor kinase (*NTRK*) gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have either progressed following treatment or who have no satisfactory alternative therapy.

The decision to approve this indication was made on the basis of objective response rate (ORR) and duration of response (DOR) from single arm clinical studies. The

sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine.

2.2 The resubmission noted that full TGA approval is anticipated in September 2027.

2.3 The provisional indication does not support use of larotrectinib as first-line therapy for patients with NTRK fusion positive locally advanced or metastatic solid tumours. The Food and Drug Administration (FDA) approved indication for larotrectinib is similar to the TGA provisionally approved indication.

2.4 Current updated international clinical practice guidelines for locally advanced or metastatic NTRK fusion positive NSCLC appear to vary. The National Comprehensive Cancer Network (NCCN) guidelines note that TRK inhibitors (larotrectinib and entrectinib) are preferred as first-line treatment[1]. The European Society for Medical Oncology (ESMO) guidelines recommend larotrectinib for patients who have no satisfactory treatment options. Specifically, the ESMO recommends platinum-doublet chemotherapy with or without immune checkpoint inhibitors (ICIs) as first-line therapy for NSCLC tumours with a mesenchymal-epithelial transition (MET) amplification, *NTRK* gene fusion, human epidermal growth factor receptor 2 (HER2) mutation, and epidermal growth factor receptor (EGFR) exon 20 mutation[2].

2.5 In the previous submission, the clinical management algorithms proposed for adults with low fusion frequency cancers positioned larotrectinib for patients who had progressed on first-line SoC, second-line SoC, and subsequent lines of therapy, until patients have no other suitable therapies available.

2.6 The intended clinical management algorithm in the resubmission, for *NTRK* fusion positive locally advanced or metastatic NSCLC, positioned larotrectinib as first-line therapy for patients who are 'inappropriate' for immunotherapy ± chemotherapy. Other eligible patients will receive larotrectinib after progression on immunotherapy ± chemotherapy.

2.7 The requested line-agnostic listing does not specify that patients should be 'inappropriate' (or unsuitable) for immunotherapy ± chemotherapy to be eligible for larotrectinib in the first-line setting. In addition, 'inappropriate' is open to interpretation. For example, should larotrectinib gain a line-agnostic listing, a patient may be considered as inappropriate for immunotherapy ± chemotherapy to be consistent with evolving guidelines which recommend use of targeted therapy in an early treatment setting for NSCLC (although the patient may not necessarily be intolerant to or contraindicated for immunotherapy ± chemotherapy).

2.8 The current clinical management algorithm for *NTRK* fusion positive STS in the resubmission indicates that patients are treated with an anthracycline (doxorubicin) ± ifosfamide chemotherapy in the first-line setting, and those who progress on first-line

[1] NCCN Guidelines Version 5.2023. Non-Small Cell Lung Cancer, NSCLC -32.

[2] Hendriks L, et al (2023). Oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*;34(4):339-57.

therapy are eligible for pazopanib. The intended clinical management algorithm positions larotrectinib to displace pazopanib to a later-line setting. This is not in line with the requested line-agnostic listing. The ESC noted the current NCCN guidelines recommend use of larotrectinib and entrectinib as preferred regimens in the first line treatment setting if NTRK fusion is identified.

2.9 Resistance to larotrectinib can develop over time and is a probable contributory factor in patients with primary progressive disease. Mechanisms of acquired resistance in patients with larotrectinib-treated NTRK fusion positive tumours, include the emergence of NTRK kinase domain mutations or bypass tract activation. Early clinical data indicate that particular on-target resistance mechanisms might be overcome by next generation TRK inhibitors, such as selitrectinib and repotrectinib[3].

Previous PBAC consideration

2.10 This is the third submission seeking PBS listing of larotrectinib for adult patients with locally advanced or metastatic NSCLC and STS tumours harbouring *NTRK* fusions.

2.11 Two previous submissions were lodged as integrated co-dependent submissions for consideration by the PBAC and the MSAC which led to the implementation of a PBS listing for paediatric patients, and adult patients with high frequency *NTRK* fusion tumours (specifically mammary analogue secretory carcinoma [MASC] and secretory breast carcinoma).

2.12 The following summarise the PBAC outcomes relating to the previous submission for larotrectinib (Larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum).

2.13 At its November 2021 meeting, the PBAC deferred making its decision on whether to recommend the listing of larotrectinib for *NTRK* fusion tumours that are either unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery, or limb amputation to achieve a complete surgical resection (para 7.1).

2.14 The PBAC noted that the updated evidence was indicative of a larger treatment effect in patients with high frequency *NTRK* fusion tumours compared to those with low frequency *NTRK* fusion tumours. However, the PBAC noted that the number of patients across the studies remained small and the updated data remained immature with median overall survival (OS) not being reached for all tumour types combined (para 7.7).

2.15 The Economics Sub Committees (ESCs) considered the uncertainty around how larotrectinib would be used in the adult low *NTRK* frequency subgroup in clinical practice, given the availability of effective later-line treatment options, and the limited evidence to support a treatment benefit of larotrectinib. The ESCs noted that the

[3] Hong DS, et al (2020). Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *The Lancet Oncology*;21(4):531-40

clinical need for larotrectinib in the adult low NTRK frequency population before last-line therapy was less justifiable (para 2.4).

2.16 At its meeting in November 2021, the MSAC supported the creation of new MBS items for *NTRK* fusion testing to determine eligibility for treatment with larotrectinib in all paediatric patients, and adult patients with high-frequency *NTRK* fusion cancer types (para 8.2). The MSAC also considered that the two cancer types with high frequency of *NTRK* fusion in adults, MASC of the salivary gland and secretory breast carcinoma, should be specified in the item descriptor (para 8.4).

2.17 The PBAC subsequently recommended the listing of larotrectinib for paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (MASC and secretory breast carcinoma), noting that the MSAC supported funding the co-dependent *NTRK* fusion testing (para 10.1).

2.18 The PBAC did not recommend the listing of larotrectinib for adult patients with low frequency *NTRK* fusion tumours as the incremental cost-effectiveness ratio (ICER) for this population remained high and uncertain, and that there is less unmet clinical need given the effective alternative treatments available (para 7.12).

2.19 Table 2 summarises relevant PBAC concerns raised in the previous submissions for larotrectinib and how these were addressed in the resubmission.

Table 2: Relevant PBAC concerns in previous submissions for larotrectinib and how these were addressed in the resubmission

Matters of concern	How the resubmission addressed it
The PBAC noted that the evidence was indicative of a larger treatment effect in patients with high frequency *NTRK* fusion tumours compared to those with low frequency *NTRK* fusion tumours. However, the PBAC noted that the number of patients across the studies remained small and the updated data remained immature with median OS not being reached for all tumour types combined (para 7.7, November 2021 PSD with March 2022 Addendum).	Listing was only requested for NSCLC and STS with a request from the sponsor for PBAC to consider including patients with *NTRK* fusion glioma-like CNS tumours given their poor prognosis, limited treatment options, and limited data. Not adequately addressed. Even at the updated July 2022 data cut-off and after pooling across the larotrectinib studies, the number of patients across the studies remained small (NSCLC [n=25] and STS [n=30]) and the OS data remained immature.
The PBAC noted the TGA-approved registration was for patients who have either progressed following treatment or have no satisfactory alternative therapy. The PBAC advised that a criterion restricting treatment to patients with prior treatment or patients who are not suitable for other treatments should be included in the PBS restriction (para 7.3, November 2020 PSD).	Not addressed. The requested listing was line-agnostic which allows use of larotrectinib in the first-line setting. Note that in the November 2021 submission, the proposed PBS restriction for adult low frequency tumours was amended to R/R disease with no suitable alternate therapy.
Concerns regarding the SoC comparators mainly related to the appropriateness and applicability of the SoC data, the transitivity of the populations, and whether these factors favoured larotrectinib in the naïve indirect comparisons (para 5.5, November 2021 PSD with March 2022 Addendum).	Not adequately addressed. The evidence remains restricted to the refractory setting and not applicable to a line-agnostic setting as proposed in the requested listing. In addition, the indirect comparisons were between single arms of heterogeneous studies and were descriptive for OS and PFS outcomes. The risk of bias and confounding is high and can favour either larotrectinib or SoC.

Matters of concern	How the resubmission addressed it
The SoC comparators nominated for the specified tumour types were dacarbazine and placebo/BSC for STS, trifluridine/tipiracil for CRC, docetaxel and placebo for NSCLC, and lenvatinib for thyroid cancer. These comparators and their corresponding studies represent heavily pre-treated patient populations that have progressed on several lines of therapy, or for whom, there are no alternative therapies. Their applicability will be limited if larotrectinib is used earlier than intended (para 5.9, November 2021 PSD with March 2022 Addendum).	Not adequately addressed. Docetaxel remains the SoC comparator for NSCLC. The nominated SoC comparator for STS has changed from dacarbazine/BSC in the previous submission to pazopanib in the resubmission. The PBAC concern remains outstanding as these comparators represent the refractory patient population and their applicability will be limited if larotrectinib is used earlier in the first-line setting. This issue also applies to the larotrectinib data which were sourced from studies in the refractory setting.
The PBAC considered the claim of superior effectiveness compared to SoC for the low frequency adult and paediatric populations was not sufficiently supported (para 7.12, November 2020 PSD).	Not adequately addressed and this concern remains outstanding. The claim of superiority for the low frequency NSCLC and STS tumour types was based on descriptive indirect comparisons and data from a small number of patients.
Price reduction to achieve an ICER within the range of $55,000 to < $75,000 /QALY to $75,000 to < $95,000 /QALY (para 7.16, November 2021 PSD with March 2022 Addendum).	The resubmission maintained the price of larotrectinib in the resubmission and the ICERs presented exceeded $95,000 to < $115,000 /QALY gained. The presentation of higher ICERs compared to what the PBAC had previously advised was not acknowledged in the resubmission.
A shorter time horizon (para 7.16, November 2021 PSD with March 2022 Addendum)	The time horizon in the model base-case was reduced to 10 years, based on the extended follow-up time for OS (of all patients) in the pooled dataset (40 months). This was not well justified and remains considerably longer than what the PBAC has previously accepted for in the later-line setting (5 years) for both NSCLC (para 6.57 larotrectinib PSD, November 2021 PBAC meeting and para 6.06 pembrolizumab PSD, March 2019 PBAC meeting) and STS (para 6.30, eribulin PSD, November 2016 PBAC meeting).
More conservative extrapolations (para 7.16, November 2021 PSD with March 2022 Addendum)	The resubmission did not use the most conservative PFS and OS extrapolations.
Likely overestimated uptake of larotrectinib (para 7.17, November 2021 PSD with March 2022 Addendum)	The resubmission assumed [redacted]% uptake in the eligible population. This remains an overestimation.

Source: Larotrectinib PSD November 2020, Table 3, Larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum, and Sections 1-4 of the resubmission.

BSC = best supportive care; CNS = central nervous system; CRC = colorectal cancer; ePAS = extended primary analysis set; ICER = incremental cost-effectiveness ratio; *NTRK* = neurotrophic tyrosine receptor kinase; NSCLC = non-small cell lung cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PFS = progression-free survival; PSD = public summary document; QALY = quality adjusted life year; R/R = relapsed/refractory; SoC = standard of care; STS = soft tissue sarcoma

3 Requested listing

3.1 Suggestions and additions proposed by the Secretariat are added in italics and suggested deletions are crossed out with strikethrough.

Essential elements of the requested listing (initial pack – first 3 months of therapy)

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Larotrectinib, 100 mg, oral capsules	56	2	Published $12,537.13 Effective $[redacted]	VITRAKVI®, Bayer Australia Ltd
Larotrectinib, 25 mg, oral capsules	56	2	Published $3,255.88 Effective $[redacted]	
Larotrectinib, 20 mg/ml, 2 × 50 ml, oral solution	1	2	Published $4,287.13 Effective $[redacted]	

Source: Table 1-8 of the resubmission

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required (in writing-*legacy)* ~~only via~~ Postal/HPOS upload~~)~~ *or Online PBS Authorities immediate assessment*
Administrative Advice: *For a patient who has received non-PBS-subsidised supply of this drug, apply under an 'Initial treatment' phase listing provided that they meet all stated PBS eligibility criteria.*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: *Special Pricing Arrangements apply.*
Administrative Advice: *Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).* *Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au* *Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos)* *Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos* *Or mailed to:* *Services Australia* *Complex Drugs* *Reply Paid 9826* *HOBART TAS 7001*
Indication: ~~Locally advanced or metastatic Non-small cell lung cancer or Soft Tissue Sarcoma~~ *Solid tumours (of certain specified types)* with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
Treatment Phase: Initial treatment
Clinical criteria:
The condition must be confirmed to be positive for a neurotrophic tropomyosin receptor kinase (NTRK) gene fusion prior to treatment initiation with this drug through a pathology report from an Approved Pathology Authority – provide the following evidence: (i) the date of the pathology report substantiating the positive NTRK gene fusion, (ii) the name of the pathology service provider, (iii) the unique identifying number/code linking the pathology test result to the patient; the recency of the pathology report may be of any date,
AND
Clinical criteria:
~~Patients must be diagnosed with a solid tumour~~
AND
Clinical criteria:
The condition must be non-small cell lung cancer confirmed through a pathology report from an Approved Pathology Authority (of any date); or

The condition must be soft tissue sarcoma confirmed through a pathology report from an Approved Pathology Authority (of any date).
AND
Clinical criteria:
The condition must be metastatic *disease*; OR
The condition must be both: (i) locally advanced, (ii) unresectable
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised anti-cancer therapy for this condition.
Treatment criteria:
Patient must not be undergoing treatment through this Initial treatment phase listing where the patient has developed disease progression while receiving this drug for this condition,
AND
Treatment criteria:
Patient must not receive more than 3 months of treatment under this restriction
Prescribing Instructions: *The authority application must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail, and must include:* *(a) details of the pathology report substantiating the positive NTRK gene fusion. The recency of the pathology report may be of any date.* *(b) details of the pathology report establishing the carcinoma type (non-small cell lung cancer or soft tissue sarcoma) being treated, if different to the pathology report provided to substantiate the NTRK gene fusion.* *All reports must be documented in the patient's medical records.*
Prescribing Instructions: *If the application is submitted through HPOS upload or mail, it must include:* *(i) a completed authority prescription form; and* *(ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).*

Essential elements of the requested listing (continuing pack)

Name, restriction, manner of administration, form	Maximum quantity (units)	No. of repeats	Dispensed price for maximum quantity	Proprietary name and manufacturer
Larotrectinib, 100 mg, oral capsules	56	5	Published $12,537.13 Effective $[redacted]	VITRAKVI®, Bayer Australia Ltd
Larotrectinib, 25 mg, oral capsules	56	5	Published $3,255.88 Effective $[redacted]	
Larotrectinib, 20 mg/ml, 2 × 50 ml, oral solution	1	5	Published $4,287.13 Effective $[redacted]	

Source: Table 1-9 of the resubmission

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☒Medical Practitioners
Restriction type: ☒Authority Required ~~(in writing only via post/HPOS upload)~~ *(Telephone/Electronic)*
Administrative Advice: *For a patient who has received non-PBS-subsidised supply of this drug, apply under an 'Initial treatment' phase listing provided that they meet all stated PBS eligibility criteria.*
Administrative Advice: *No increase in the maximum number of repeats may be authorised.*
Administrative Advice: *Special Pricing Arrangements apply.*
Administrative Advice:

Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
Indication: ~~Locally advanced or metastatic Non-small cell lung cancer or Soft tissue Sarcoma~~ *Solid tumours* with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
Treatment Phase: Continuing treatment
Clinical criteria:
~~Solid tumour with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion~~
~~**AND**~~
Clinical criteria:
The treatment must cease to be a PBS benefit upon radiographic progression
AND
Clinical criteria:
The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
Treatment criteria:
~~Patient must be undergoing continuing PBS-subsidised treatment commenced through an 'Initial treatment' listing~~
Patient must have previously received PBS-subsidised treatment with this drug for this condition.
Prescribing Instructions: *Where radiographic progression is observed, mark any remaining repeat prescriptions with the word 'cancelled'.*

3.2 The resubmission noted that a special pricing arrangement (SPA) is currently in place for the existing listing of larotrectinib and requested that the SPA be extended for this listing of larotrectinib. The effective prices proposed in the resubmission are identical to the effective prices for current larotrectinib listings, with initial scripts having a lower effective price than continuing scripts. The pre-PBAC response proposed a 33% reduction in the effective price of the 100 mg strength, with an effective ex-manufacturer price of $ for initial scripts and $ for continuing scripts.

3.3 The resubmission noted the following:

- The intent is to provide access to patients with locally advanced or metastatic NSCLC or STS tumours who have positive *NTRK* gene fusions. With the availability of gene panel testing, oncogenic driver mutations such as *NTRK* gene fusions could be detected at diagnosis prior to disease progression or in patients who have received previous therapy and experienced disease progression.
- The proposed PBS restriction wording is based on the existing PBS listings for larotrectinib but also considers the clinical evidence for the specific tumours requested where patients have progressive disease despite prior therapy.

3.4 The proposed PBS restriction allows for first-line treatment with larotrectinib, which is broader (or earlier) than the provisionally approved TGA indication which specifies that the tumours should be metastatic or where surgical resection is likely to result in severe morbidity and has either progressed following treatment or who has no satisfactory alternative therapy.

3.5 In the first-line setting, there are more effective treatment options (immunotherapy ± platinum doublet chemotherapy for NSCLC and anthracycline based chemotherapy for STS) than the comparators nominated in the resubmission (docetaxel for NSCLC

and pazopanib for STS). The larotrectinib studies were also conducted in the refractory setting. Thus, the evaluation considered there was misalignment between the populations in the larotrectinib and comparator studies and the requested line-agnostic listing. The pre-PBAC response noted that 24% of patients in the ePAS7 analysis received larotrectinib as a first-line treatment.

3.6 In the intended management algorithm for NSCLC presented in the resubmission, patients who are 'inappropriate' for immunotherapy ± chemotherapy will receive front-line therapy with larotrectinib. Other eligible patients will receive larotrectinib after progression on immunotherapy ± chemotherapy. The requested listing does not specify these conditions. Furthermore, the definition of 'appropriate' is open to interpretation. A patient may be considered as 'inappropriate' for immunotherapy ± chemotherapy (regardless of intolerance or contraindications) if larotrectinib becomes available and evolving clinical practice guidelines recommend targeted therapy in an earlier treatment setting before immunotherapy ± chemotherapy. The PSCR proposed inclusion of the clinical criteria "Patient must have received prior systemic treatment for this disease, OR Patient must have a condition that predisposes them to unacceptable risk of intolerance to other systemic therapies" to clarify the clinical use of larotrectinib. The ESC considered the revised proposed clinical criteria may be reasonable.

3.7 The resubmission stated that there were only 13 adult patients with glioma-like CNS tumours in the larotrectinib studies at the latest July 2022 data cut-off. The resubmission invited the PBAC to consider whether this group could be provided access to larotrectinib based on the availability of a panel test for this population, equity, the paucity of viable treatments, the scarcity of data to support a listing in this difficult-to-treat population, and the dire prognosis of this population. The ESC noted no clinical data was provided in the resubmission for this population and considered that the *ad hoc* inclusion of glioma-like CNS tumours in the listing would be unreasonable. The pre-PBAC reiterated the request to consider making larotrectinib available for patients with glioma-like CNS tumours, noting the rarity of *NTRK* gene fusions in this condition (0.5-1.0%) and low 5 year survival (~35%). The pre-PBAC noted the available clinical data for this population was included as an attachment to the resubmission.

3.8 The resubmission noted that compassionate access was being provided to some patients whilst the PBAC evaluation process was ongoing. Based on the proposed initiation and continuation criteria, no separate grandfather clause will be required for the three patients currently receiving compassionate access to larotrectinib, as per previous PBAC advice (para 10.4, larotrectinib PSD, November 2021 with March 2022 Addendum). The PBAC noted a separate grandfather restriction would not be required given that patients transitioning to PBS-subsidised treatment would meet the initial restriction criteria.

3.9 The PBAC agreed with the Secretariat that it would be appropriate for the listing to be Authority Required (In Writing) for initial scripts and Authority Required

(telephone/online PBS Authorities system) for continuing scripts, consistent with the current listing.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 The human *NTRK* genes consist of *NTRK1, NTRK2*, and *NTRK3* which are responsible for encoding the TRK proteins TRKA, TRKB, and TRKC, respectively, which play crucial roles in the development and function of the nervous system. However, a rearrangement involving one of the *NTRK* genes – known as *NTRK* gene fusion –can lead to oncogenic expression and, consequently, tumorigenesis. The resultant oncoprotein is typically a constitutively activated or overexpressed kinase, leading to activation of downstream oncogenic pathways.

4.2 Table 3 summarises *NTRK* gene fusion prevalence estimates by lung cancer tumour histology from an Australian systematic review study[4].

Table 3: *NTRK* gene fusion prevalence estimates by lung cancer tumour histology

Cancer type	*NTRK* gene fusion prevalence, %	95% CI, %
Lung	0.06	0.03, 0.10
Non-squamous non-small cell lung cancer	0.00	0.00, 0.40
Lung adenocarcinoma	0.09	0.03, 0.31
Lung squamous cell carcinoma	0.00	0.00, 0.73
Large cell neuroendocrine carcinoma	1.45	0.04, 7.81
Mucinous adenocarcinoma	1.39	0.03, 7.50
Small cell lung cancer	1.64	0.20, 5.80
EGFR, ALK, KRAS, ROS1 WT lung adenocarcinoma	3.30	0.69, 9.33
BRAF, KRAS, EGFR WT lung adenocarcinoma	0.27	0.01, 1.69
EGFR T790M 2nd generation TKI resistant non-small cell lung cancer	1.79	0.04, 9.55
EGFR mutation post TKI non-small cell lung cancer	0.10	0.03, 0.26

Source: Table 1-4 of the resubmission (Source for submission: O'Haire et al (2023).
ALK = anaplastic lymphoma kinase, *BRAF* = v-Raf murine sarcoma viral oncogene homolog B, *EGFR* = epidermal growth factor receptor, *KRAS* = Kirsten rat sarcoma viral oncogene homolog, *NTRK* = neurotrophic tropomyosin receptor kinase; *ROS1* = c-ros oncogene 1, TKI = tyrosine kinase inhibitor; WT = wild type.

4.3 The resubmission stated that *NTRK* gene fusions occur largely independently from other oncogenic drivers, and that despite the rarity of *NTRK* gene fusions, when present, they act as primary oncogenic drivers, making them critically relevant for therapeutic interventions.

4.4 STS represents a diverse group of tumours that arise from mesenchymal tissues, encompassing a wide range of histological subtypes. These can be broadly categorised based on their differentiation or origin: liposarcoma (adipose tissue), leiomyosarcoma (smooth muscle cells), rhabdomyosarcoma (striated muscle), synovial sarcoma

[4] O'Haire S et al (2023). Systematic review of *NTRK* 1/2/3 fusion prevalence pan-cancer and across solid tumours. *Scientific Reports*; 13(1):4116

(pluripotent mesenchymal cells), angiosarcoma (vascular; considered aggressive and often manifested in the skin, breast, or liver), and fibrosarcoma (fibroblasts).

4.5 STS prognosis is influenced by various factors. For instance, high-grade tumours have a worse prognosis, larger and deeper tumours correlate with poorer outcomes, truncal and retroperitoneal tumours have a worse prognosis compared to limb tumours.

4.6 *NTRK* gene fusions are relatively rare in STS but have been identified as significant drivers in specific subtypes. Prevalence estimates vary among different studies and occur in less than 1% of all STS (prevalence 0.69%; 95% confidence interval [CI]: 0.26, 0.85%).

4.7 Larotrectinib is an orally bioavailable, adenosine triphosphate (ATP)-competitive and highly selective tropomyosin receptor kinase (TRK) inhibitor, which was rationally designed to avoid activity with off-target kinase. The target for larotrectinib is the TRK family of proteins inclusive of TRKA, TRKB, and TRKC that are encoded by *NTRK1, NTRK2*, and *NTRK3* genes, respectively.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 For NSCLC, the nominated comparator was docetaxel which has not changed from the previous submission. The submission nominated entrectinib as a near-market comparator.

5.2 For STS, pazopanib was nominated as a new comparator in the resubmission compared to dacarbazine in the previous submission. The arguments presented in the resubmission for nominating pazopanib were that i) dacarbazine is no longer available on the PBS, ii) pazopanib is listed on the PBS for advanced (unresectable and/or metastatic) non-adipocytic STS, following previous treatment with anthracycline based chemotherapy, and iii) eribulin is only available on the PBS for liposarcoma. The ESC noted entrectinib could also be considered a near-market comparator for STS.

5.3 The nominated comparators in the resubmission represent SoC in the later-line treatment setting whereas the requested listing allows use of larotrectinib in the first-line setting for which there are more effective treatment options. These include immunotherapy ± platinum doublet chemotherapy for NSCLC and anthracycline-based chemotherapy for STS. If larotrectinib is used in the first-line setting, these front-line treatment options would be displaced to a later-line setting. The ESC considered that, with the proposed line agnostic restriction criteria, some use in the first-line treatment setting was likely in patients with identified *NTRK* fusions.

5.4 Worthy of note is that the clinical efficacy of ICIs for patients with *NTRK* fusion positive NSCLC remain unestablished and unknown[5]. There are several studies exploring the relationship between *NTRK* fusion and biomarkers for ICIs, including programmed cell death ligand 1 (PD-L1) expression, microsatellite instability, and tumour mutation burden (TMB), which had been identified as predictive biomarkers for ICIs[6,7]. Evidence can be found in 31 cases with *NTRK* fusions, where PD-L1 expression was detected in 23% of cases with *NTRK* fusions, but only two cases possessed high microsatellite instability (MSI-H)[8]. The association between *NTRK* fusion and TMB remains unclear in NSCLC.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinician stated that the clinical evidence for larotrectinib was as strong as for other oncogene driven NSCLC, expressed concern that patients with NSCLC can be identified with an actionable *NTRK* gene fusion but have no PBS reimbursed access to an effective treatment option, and was strongly supportive of a line-agnostic listing of larotrectinib.

Consumer comments

6.2 In addition to the input noted by the PBAC at the November 2021 meeting (para 6.2, larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum), the PBAC noted and welcomed the input from health care professionals (2) and organisations (3) via the Consumer Comments facility on the PBS website.

6.3 The PBAC noted the advice received from three organisations (Omico, Lung Foundation Australia, and the Medical Oncology Group of Australia [MOGA]) supporting the PBS listing of larotrectinib for the treatment of adults with locally advanced or metastatic NSCLC or STS harbouring *NTRK* gene fusions.

6.4 Omico and Lung Foundation Australia emphasised the need for novel targeted therapies such as larotrectinib to be available to patients with rare or less common cancers. In addition to describing the effectiveness of larotrectinib for NSCLC, the organisations highlighted the opportunity to match therapy with the characteristics of individual patients, and avoid unnecessary treatments and associated side effects.

[5] Liu F et al (2022). NTRK fusion in non-small cell lung cancer: Diagnosis, therapy, and TRK inhibitor resistance. *Frontiers in Oncology*. 2022;12:864666

[6] Sha D et al (2020). Tumor mutational burden as a predictive biomarker in solid tumors. *Cancer discovery*. 10(12):1808-25.

[7] Zhao P et al (2019). Mismatch repair deficiency/microsatellite instability-high as a predictor for anti-PD-1/PD-L1 immunotherapy efficacy. *Journal of Hematology & Oncology*; 12(1):1-14.

[8] Gatalica Z et al (2019). Molecular characterization of cancers with NTRK gene fusions. *Modern Pathology*. 32(1):147-53.

6.5 Comments from two health care professionals described the importance of patients having access to larotrectinib for its superior efficacy, tolerability and brain protection, compared with any other treatment, and that equity of access for patients with rare cancers should be a consideration in reimbursement decisions. They also commented that a home-based therapy such as larotrectinib can improve patients' quality of life and that of their families and carers.

6.6 The MOGA expressed its strong support for the larotrectinib submission, categorising it as one of the therapies of "highest priority for PBS listing" on the basis of the SCOUT and NAVIGATE trials. The PBAC noted that the MOGA presented a European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) for larotrectinib, which was limited to 3 (out of a maximum of 5, where 5 and 4 represent the grades with substantial improvement)[9].

Clinical studies

6.7 The studies included for larotrectinib in the resubmission have not changed from the previous submission (Study 20288 [formerly known as LOXO001], Study 20289 or NAVIGATE [formerly known as LOXO002], and Study 20290 or SCOUT [formerly known as LOXO003]). The resubmission presented pooled data across the three studies for larotrectinib (extended primary analysis set ePAS7) which corresponded to an updated July 2022 data cut-off (compared to the July 2020 data cut-off in the previous submission). The justification provided in the resubmission for pooling was because of the small patient numbers in the individual larotrectinib studies.

6.8 The ePAS7 consisted of 272 patients across all tumour types, 27 patients with lung cancer (25 patients with NSCLC), and 30 patients with STS. Although the SCOUT study was designed as a paediatric study, the study is ongoing and two patients with *NTRK* fusion positive STS have since had their 18th birthdays at the updated July 2022 data cut-off and were thus included in the adult STS cohort.

6.9 As the nominated comparator of docetaxel for NSCLC has not changed from the previous submission, the CheckMate 057 study presented in the previous submission has been retained in the current resubmission. CheckMate 057 compared nivolumab with docetaxel in patients with advanced non-squamous NSCLC who had failed prior first-line platinum-based chemotherapy. Patients were enrolled in CheckMate 057 regardless of *NTRK* fusion status.

6.10 The nominated comparator for STS has changed from dacarbazine in the previous submission to pazopanib. The resubmission included the PALETTE study which was not presented in the previous submission. The PALETTE study compared pazopanib with placebo in heavily pre-treated adult patients with progressive metastatic STS after at least one anthracycline-containing regimen, and a maximum of four prior lines of systemic therapy for metastatic disease.

[9] Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. Annals of Oncology 28:2340-2366, 2017

6.11 The key evidence provided in the resubmission to support the claim of superior effectiveness, in terms of OS and progression free survival (PFS), was based on a descriptive non-matched (unadjusted) indirect comparison between single arms. This involved updated pooled larotrectinib data versus i) single arm docetaxel data from CheckMate 057 for NSCLC, and ii) single arm pazopanib data from PALETTE for STS.

6.12 Details of the studies presented in the resubmission are provided in Table 4.

Table 4: Listing of the relevant studies included for the naive indirect comparisons

Trial ID/First Author	Protocol title/ Publication title	Publication citation
Larotrectinib single arm studies		
20288 (formerly known as LOXO-TRK-14001/LOXO-001)	CSR: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumours Interim CSR.	February 2020
	20288 CSR: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumours Interim CSR Update (data cutoff April 2021).	January 2022
20289 NAVIGATE (formerly known as LOXO-TRK-14002/LOXO-002)	20289 (NAVIGATE) CSR: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with *NTRK* Fusion-Positive Tumours Interim CSR.	February 2020
	20289 (NAVIGATE) CSR: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with *NTRK* Fusion-Positive Tumours. July 2020 update (data cutoff July 2022).	January 2023
20290 SCOUT[a] (formerly known as LOXO-TRK-15003/LOXO-003)	LOXO-TRK-15003 (SCOUT) CSR: A Phase 1/2 Study of the Oral TRK Inhibitor LOXO-101 in Pediatric Patients with Advanced Solid or Primary Central Nervous System Tumors. Update (data cutoff July 2022).	January 2023
Pooled/combined larotrectinib studies/exploratory analyses	Drilon A, Tan DSW et al. Efficacy and Safety of Larotrectinib in Patients with Tropomyosin Receptor Kinase Fusion – Positive lung cancers.	*JCO Precis Oncol* 2022; 6:e2100418
	Leyvraz S, Hong DS et al. Long-term efficacy and safety of larotrectinib in an integrated dataset of patients with TRK fusion cancer.	*Onc Res and Treat* 2021; 44:13
	McDermott RS, van Tilburg C et al. Efficacy and safety of larotrectinib in a pooled analysis of patients (Pts) with tropomyosin receptor kinase (TRK) fusion cancer with an extended follow-up.	*Ann Oncol* 2022; 33:S751-2.
Studies of SoC[b] by tumour types requested in the resubmission		
Docetaxel – NSCLC		
CheckMate 057 (Borghaei 2015)	Borghaei H, Paz-Ares L et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer	*NEJM* 2015; 373(17):1627-39.
Pazopanib – STS		
PALETTE	van der Graaf W, Blay J et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial.	*Lancet* 2012; 379(12):1879–86
	Le Cesne A, Bauer S et al. Safety and efficacy of Pazopanib in advanced soft tissue sarcoma: PALETTE (EORTC 62072) subgroup analyses.	*BMC cancer* 2019; 19(1):794
	Kasper B, Sleijfer S et al. Long-term responders, and survivors on pazopanib for advanced soft tissue sarcomas: sub analysis of two European Organisation for Research and Treatment of Cancer (EORTC) clinical trials 62043 and 62072.	*Ann Oncol* 2014; 25(3):719-24

Source: Table 2.3 of the resubmission.

NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tyrosine receptor kinase; SoC = standard of care; STS = soft tissue sarcoma

Blue shading represents information previously considered by the PBAC.

[a]The resubmission did not include this study in the master list of studies table, although two patients with STS from this study were included in the pooled ePAS7 dataset. Although the SCOUT study was originally a paediatric study, two patients with *NTRK* fusion positive STS have since had their 18th birthdays at the updated July 2022 data cutoff and they have been included in the pooled larotrectinib dataset.

[b]The SoC studies, CheckMate 057 and PALETTE, were randomised controlled trials but only the single docetaxel and pazopanib arms, respectively, were used in the indirect comparisons with larotrectinib.

6.13 The key features of the included evidence are presented in Table 5.

Table 5: Key features of the included evidence – indirect comparison between single arms

Studies	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Proposed medicine – Larotrectinib: ePAS7 (July 2022 data cutoff, Median follow-up for OS 39.4 months)						
Pooled analysis across all tumour types[a]	272	Single arm, OL	High	*NTRK* fusion positive. Refractory Failed chemo	OS, PFS, ORR, DOR	Not used
Lung cancer[c] NSCLC	27 25					PFS and OS used
STS	30					PFS and OS used
Comparator – Docetaxel in NSCLC (Minimum follow-up for OS 17.2 months)						
CheckMate 057	290	Single arm, OL [b]	High[b]	Unselected for *NTRK* fusion status. Refractory Failed chemo	OS, PFS, ORR, DOR	PFS and OS used
Comparator – Pazopanib in STS (Median follow-up for OS 14.9 months)						
PALETTE	246	Single arm, OL [b]	High[b]	Unselected for *NTRK* fusion status. Refractory Failed chemo	OS, PFS, ORR, DOR	Used

Source: Sections 2.2 to 2.6 of the resubmission.

DOR = duration of response; ePAS = extended primary analysis set; *NTRK* = neurotrophic tyrosine receptor kinase; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; STS = soft tissue sarcoma; OL = open label; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

[a]Pooled analysis from three larotrectinib studies (Studies 20288, 20289 [NAVIGATE], and 20290 [SCOUT])

[b]CheckMate 057 and PALETTE were randomised controlled trials but only the single docetaxel and pazopanib arms, respectively, were used in the indirect comparisons with larotrectinib. Hence the risk of bias was considered high for the indirect comparisons.

[c]Of the 27 patients, one patient had atypical carcinoid tumour of the lung and one patient had SCLC.

6.14 The risk of bias associated with the evidence was considered high given the open-label, single arm, and non-matched nature of the indirect comparisons and the limited reliability of the larotrectinib data which were based on a small number of patients.

6.15 The ESC considered there were notable differences in baseline demographics between the larotrectinib and comparator studies (Table 6) that made a comparison of outcomes problematic. In particular, the ESC noted the *NTRK* status in the comparator studies was unknown and there were differences in prior lines of cancer therapies across the studies.

Table 6: Baseline characteristics of patients from ePAS7 across the larotrectinib and docetaxel datasets.

Characteristic	NSCLC[a]		STS	
	Study 20288 (LOXO001), and Study 20289 (NAVIGATE) Larotrectinib (N=27)[a]	**CheckMate 057 Docetaxel (N=290)**	**Study 20288, Study 20289, and Study 20290 (SCOUT)[d] Larotrectinib (N=30)**	**PALETTE Pazopanib (N=246)**
Trial start year	**2015**	**2012**	**2015**	**2008**
NTRK status	Fusion only	Unselected (unknown)	Fusion only	Unselected (unknown)
Median age, years, (range)	52 (25-76)	64 (21-85)	40 (19-70)	57 (20-84)
Male, n (%)[b]	12 (44)	168 (58)	15 (50)	99 (40)
Race, n (%)[b]				
Caucasian	10 (37)	266 (92)	12 (40)	NR
Asian	13 (48)	8 (3)	4 (13)	
Other	4 (15)	16 (5)	14 (47)	
ECOG performance status, n (%)[b]				
0	9 (33)	85 (33)	13 (43)	113 (46)
1	15 (56)	194 (67)	13 (43)	133 (54)
2	1 (4)	-	4 (13)	-
3	2 (7)	-	-	-
Prior lines of anticancer treatment, n (%)[b]				
0	1 (4)	0 (0)	12 (40)	Reported for whole trial (N=372) but not by arm[c]. Prior systemic: 342 (93) ≥2: 207 (56) ≥3: 78 (21)
1	7 (26)	259 (89)	11 (36)	
2	8 (30)	31 (11)	2 (7)	
≥3	11 (41)	-	5 (17)	

Source: Table 2-33 of the resubmission.
ECOG = Eastern Cooperative Oncology Group; NR = reported; NTRK = neurotrophic tyrosine receptor kinase, NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; STS = soft tissue sarcoma.
Data cutoff July 2022
[a]Data were not presented exclusively for NSCLC patients.; Of the 27 patients, one patient had atypical carcinoid tumour of the lung and one patient had SCLC.
[b]Percentages based on N as the denominator.
[c]Sourced from van der Graaf 2012 (p1882).
[d]Two patients with STS from Study 20290 (SCOUT) were included in the pooled ePAS7 dataset. The SCOUT study was originally a paediatric study, two patients with NTRK fusion positive STS have since had their 18th birthdays at the updated July 2022 data cutoff.

Comparative effectiveness

Pooled OS data for larotrectinib (ePAS7)

6.16 Pooled OS results from the ePAS7 (N=272) across all tumour types:

- Based on the July 2022 data cutoff (median follow-up duration of 39.4 months), the pooled OS results remained immature. The median OS was not estimable (NE) (95% CI: 63.4 months, NE). The OS rates at 24 months, 36 months, and 48 months were 77% (95% CI: 72%, 82%), 72% (95% CI: 66%, 78%), and 65% (95% CI: 58%, 72%), respectively.

6.17 OS results from the ePAS7 by primary diagnosis or tumour type:

- Overall, there were small patient numbers for the majority of the tumour type cohorts which limited the reliability of the results.
- The median OS was 39.3 months for lung tumour type. Corresponding OS rates at 12 months, 24 months, 36 months, and 48 months were 89%, 67%, 57%, and 38%, respectively.
- The OS rates at 12 months, 24 months, 36 months, and 48 months were highest for infantile sarcoma (IFS) (100%, 98%, 98%, and 98%, respectively) and salivary gland (96%, 88%, 83%, and 72%, respectively) tumour types, and lowest for breast tumour type (80%, 55%, 41%, and 41%, respectively). The PBAC noted in its previous consideration of larotrectinib that the evidence was indicative of a larger treatment effect in patients with high frequency *NTRK* fusion tumours compared to those with low frequency *NTRK* fusion tumours, although the number of patients across the studies was small (para 7.7, larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum). IFS and breast cancer are considered high and low fusion frequency tumour types, respectively.
- For tumour types with at least 10 patients in a cohort, the median OS ranged from 29.4 months for CRC to 39.3 months for lung carcinoma; and the median OS was not reached in the STS, IFS, thyroid cancer and salivary gland tumour groups.
- The limited reliability of the data hampered the assessment of whether the treatment effect was consistent across different tumour types. Notwithstanding this, the OS results were indicative of a variation in the treatment benefit of larotrectinib across different tumour types. Consequently, interpreting the pooled results from the ePAS7 remains problematic.

Pooled PFS data for larotrectinib (ePAS7)

6.18 Based on the July 2022 data cutoff (median follow-up duration of 34.0 months), the median investigator assessed PFS was 27.5 months (95% CI: 19.2 months, 36.1 months). The corresponding PFS rates at 24 months, 36 months, and 48 months were 53% (95% CI: 46%, 59%), 43% (95% CI: 36%, 50%), and 37% (95% CI: 29%, 44%), respectively.

6.19 Based on the July 2022 data cutoff (median follow-up duration of 31.3 months), the median independent review committee (IRC) assessed PFS was 30.8 months (95% CI: 23.4 months, 36.1 months). The corresponding PFS rates at 24 months, 36 months, and 48 months were 56% (95% CI: 49%, 62%), 43% (95% CI: 36%, 51%), and 39% (95% CI: 31%, 47%), respectively.

Indirect comparison of effectiveness – Larotrectinib *versus* docetaxel in NSCLC

6.20 Table 7 summarises the key outcomes from the ePAS7 pooled dataset for larotrectinib and from CheckMate 057 for docetaxel. For larotrectinib, data are presented for all lung cancer patients (N=27) and for NSCLC patients only (N=25).

Table 7: Key efficacy outcomes for the larotrectinib and docetaxel datasets.

Outcomes	ePAS7 Larotrectinib		CheckMate 057 NSCLC Docetaxel N=290
	Pooled lung cancer[a], N=27	Pooled NSCLC[a] N=25	
PFS			
Investigator assessed, median (95% CI), months	22.1 (7.2, 38.3)	31.5 (7.2, 38.3)	4.2 (3.5, 4.9)
IRC assessed, median (95% CI), months	33.0 (11.3, NE)	33.0 (9.9, NE)	NR
OS[b]			
Median (95% CI), months	39.3 (17.2, NE)	39.3 (17.2, NE)	9.4 (8.1, 10.7)
ORR (CR + PR)			
Investigator assessed, n (%)	18 (66.7)	17 (68.0)	36 (12.4)
IRC assessed, n (%)	20 (74.1)	19 (76.0)	NR
DOR			
Investigator assessed, median (95% CI), months	29.7 (12.4, 36.5)	29.7 (17.4, 36.5)	5.6 (4.4, 6.9)
IRC assessed, median (95% CI), months	33.9 (9.5, NE)	33.9 (8.6, NE)	NR
TOT			
Median (95% CI), months	19.9 (11.1, 35.4)	NR	7.5 (6.4, 10.0)

Source: Table 2-34 and Table 2-36 of the resubmission

CI = confidence interval; CR = complete response; DOR = duration of response; ePAS = extended primary analysis set; IRC = independent review committee; NE = not estimable (not reached); NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; TOT = time on treatment.

[a]Two lung cancer patients in the ePAS7 analysis set had non-NSCLC disease (one patient with an atypical carcinoid tumour and one patient with small cell lung carcinoma).

[b]Data cutoff for ePAS7 July 2022. Median follow-up for OS in total ePAS7 was 39.4 months (follow-up duration specifically for lung cancer/NSCLC was not provided in the resubmission). Minimum follow-up for OS in CheckMate 057 was 17.2 months (p1362 of Borghaie 2015).

6.21 The resubmission concluded that for all outcomes: i) the results favoured larotrectinib over docetaxel with substantial differences for some outcomes, and ii) with no overlap in 95% CIs which provides strong evidence that the medians for PFS, OS, DOR and time on treatment (TOT) were larger for larotrectinib than for docetaxel.

6.22 Outcomes for larotrectinib were based on small patient numbers even after pooling (25 patients for NSCLC and 30 patients for STS). This limited the precision and hence the reliability of the efficacy estimates. A small number of additional patients may result in a substantial change to the outcome estimates reflecting the limited and uncertain nature of the available data.

6.23 There were substantial differences in efficacy endpoints favouring larotrectinib over docetaxel with relatively very poor outcomes in the docetaxel arm in terms of i) median OS (39.3 months versus 9.4 months), and ii) median investigator assessed PFS (22.1 months versus 4.2 months).

6.24 The robustness and reliability of the median PFS estimates for larotrectinib are uncertain given the large disparity between the investigator assessed and IRC assessed estimates in the lung cancer group (22.1 months and 33.0 months, respectively*).* The PSCR stated that an additional analysis revealed four patients in the NSCLC dataset

were deemed to have progressed according to the investigator but not by IRC and none the other way around. A total of three patients' durations were less than the median timepoints which causes the KM curve to drop and the median (the timepoint beyond which we expect 50% of patients to still be progression-free) to be reached sooner. The PSCR noted that the difference in medians is a consequence of the small sample size rather than an indication of lack of robustness or reliability.

6.25 Aside from investigator assessed median PFS, other outcomes were similar between the total lung cancer cohort and the NSCLC cohort in the larotrectinib ePAS7. This is expected as the majority of the lung cancer cohort were patients with NSCLC (25 of 27 patients).

6.26 The evidence may be indicative of a larger treatment effect associated with larotrectinib compared with docetaxel. However, the following issues warrant cautious interpretation of the data:

- The large differences in OS and PFS between the larotrectinib and docetaxel datasets, in a refractory NSCLC setting, raise concerns regarding whether the larotrectinib-treated and docetaxel-treated patient populations are comparable, and whether these differences in median OS and PFS estimates are a result of a selection bias.
- The larotrectinib studies are ongoing, and selection bias may arise if there is selective enrolment of patients with a better prognosis, or highly responding patients, or patients who may have received more effective therapies (such as immunotherapy + platinum doublet chemotherapy) in the first-line setting compared to the historical CheckMate 057 patient population. Patients enrolled in CheckMate 057 had disease that had progressed during or after a platinum-containing chemotherapy regimen. There was limited information provided on the types of prior systemic therapies administered in the larotrectinib dataset. The majority of disease-refractory patients in Australian clinical practice, if eligible, would have received first-line pembrolizumab ± platinum chemotherapy which is associated with improved PFS and OS benefit. Thus, the front-line therapeutic options for refractory patients enrolled in the CheckMate 057 trial may not be representative of those available for refractory patients in current clinical practice. The impact of this applicability issue is unknown.
- The indirect comparison between single arms was descriptive and it is unlikely that adjustment or matching would be feasible given the small number of larotrectinib patients. Baseline data indicated there were substantial heterogeneities in disease characteristics (e.g., *NTRK* status, prior lines of anticancer treatment and ECOG PS) and in demographics (e.g., age, gender and race) between the larotrectinib and docetaxel arms and the risk of bias and confounding is high.
- On-target resistance to larotrectinib can develop over time and is a probable contributory factor in patients developing disease progression upon treatment. Detailed information on whether patients received subsequent therapy with next

generation TRK inhibitors (such as selitrectinib and repotrectinib) to treat resistance to larotrectinib was not provided in the resubmission. At the July 2019 data cutoff (no data on subsequent therapies were provided for the July 2020 data cutoff), there were 41% (15/36) of patients in the larotrectinib NAVIGATE study who were administered either selitrectinib or entrectinib post progression (para 6.16, larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum). Second generation TRK inhibitors (such as repotrectinib and selitrectinib) are not currently TGA registered and thus any observed OS benefit associated with these second generation TRK inhibitors in the larotrectinib studies may not be realised in Australian clinical practice.

- The available evidence to support the comparative benefit of larotrectinib has limited applicability to the target population in the proposed listing. The proposed listing is line-agnostic but the larotrectinib and comparator studies were conducted in the refractory setting. Clinical practice guidelines are evolving with a trend towards recommendations for targeted therapy in the front-line setting. If larotrectinib is used in clinical practice as first-line therapy, pembrolizumab ± platinum doublet chemotherapy would be a more relevant comparator than docetaxel to larotrectinib. No comparative evidence for larotrectinib in the first-line setting was presented in the resubmission.

6.27 The resubmission presented an indirect treatment comparison with a near market comparator, entrectinib, for NSCLC. The resubmission noted that due to the differences in the patient composition of the datasets, it was difficult to make conclusions regarding the comparative effectiveness of larotrectinib and entrectinib in locally advanced or metastatic *NTRK* positive solid tumour patients.

Indirect comparison of effectiveness – Larotrectinib *versus* pazopanib in STS

6.28 Table 8 summarises the key outcomes in adult STS patients from the ePAS7 pooled dataset for larotrectinib and from the PALETTE trial for pazopanib.

Table 8: Key efficacy outcomes for the larotrectinib and pazopanib STS datasets

Outcomes	ePAS7 Larotrectinib STS Pooled N=30	PALETTE Pazopanib STS N=246
PFS		
Investigator assessed, median (95% CI), months	37.5 (6.8, NE)	4.6 (3.7, 4.8)
IRC assessed, median (95% CI), months	24.8 (3.6, NE)	NR
OS[a]		
Median (95% CI), months	60.2 (38.3, NE)	12.5 (10.6, 14.8)
ORR (CR + PR)		
Investigator assessed, n (%)	16 (53.3)	23 (9.0)
IRC assessed, n (%)	16 (50.0)	14 (6.0)
DOR		
Investigator assessed, median (95% CI), months	54.7 (7.2, NE)	NR
IRC assessed, median (95% CI), months	54.7 (23.0, NE)	NR
TOT		
Median (95% CI), months	15.7 (9.4, 43.0)	3.8 (3.2, 4.4)[b]

Source: Table 2-38, p96 of the resubmission

CI = confidence interval; CR = complete response; DOR = duration of response; ePAS = extended primary analysis set; IRC = independent review committee; NE = not estimable (not reached); NR = not reported; NSCLC = non-small cell lung cancer; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PR = partial response; TOT = time on treatment.

[a]Data cutoff for ePAS7 July 2022. Median follow-up for OS in total ePAS7 was 39.4 months (follow-up duration specifically for STS was not provided in the resubmission); Median follow-up for OS in pazopanib arm of PALETTE was 14.9 months (p1883 van der Graaf 2012)

[b]95% CI is an approximation based on the normal distribution, with a conservative estimate of the variance based on the interquartile range.

6.29 The resubmission noted that data on DOR in the pazopanib PALETTE trial were not provided in the publications available. The results for other outcomes favoured larotrectinib over pazopanib noting the small number of patients (N=30) in the larotrectinib dataset.

6.30 As was the case for NSCLC, there were substantial differences in efficacy outcomes favouring larotrectinib versus pazopanib with relatively very poor outcomes in the pazopanib arm (median OS: 60.2 months versus 12.5 months; median investigator assessed PFS: 37.5 months versus 4.6 months). These large differences in OS and PFS in the refractory setting also raise concerns regarding whether the patient populations are comparable in terms of disease severity and/or whether there is a high risk of selection bias.

6.31 There is concern regarding the robustness and reliability of the median PFS estimate for larotrectinib given the large disparity between the investigator assessed (37.5 months) and IRC assessed (24.8 months) estimates.

6.32 Notably, the disparity between the investigator assessed and IRC assessed median PFS estimates for STS (investigator estimate longer than IRC estimate) appears to be in the opposite direction to that observed for lung cancer (investigator assessed estimate was shorter than the IRC assessed estimate).

6.33 The resubmission also presented a formal unmatched, unadjusted indirect comparison of investigator assessed response (complete and partial combined) between larotrectinib and pazopanib arms. The results indicated that there was a statistically significant difference favouring larotrectinib over pazopanib (difference in response rate of 44% [95% CI: 26%, 62%]; p<0.001).

6.34 As was the case for the comparison between larotrectinib and docetaxel in NSCLC, the indirect comparison of larotrectinib with pazopanib in STS would need to be interpreted with caution:

- There is limited applicability of the data in the refractory setting to the line-agnostic proposed listing which allows use of larotrectinib in the first-line setting. As noted previously, evolving clinical practice guidelines recommend targeted therapy in the front-line setting. STS patients in the first-line setting would ideally be treated with chemotherapy including an anthracycline, which may represent a more appropriate comparator than pazopanib. No comparative evidence in the first-line setting was presented in the resubmission.
- The number of STS patients in the larotrectinib dataset was small (N=30), limiting the reliability of the results.
- The indirect comparisons of OS and PFS were descriptive, and between non-matched single arms. It is unlikely that matching would have been feasible given the small number of patients in the larotrectinib dataset. There was apparent heterogeneity in patient baseline characteristics across the larotrectinib and pazopanib STS datasets in terms of age, ECOG PS, *NTRK* status, and prior lines of therapy.
- There was no information provided on subsequent therapies with second generation TRK inhibitors to treat on-target resistance to larotrectinib. These therapies are not currently PBS-subsidised and thus any observed OS benefit in larotrectinib studies may not be realised in Australian clinical practice.

Comparative harms

Pooled safety data for larotrectinib (Overall safety analysis set)

6.35 The resubmission provided safety data from several safety analysis sets which included ePAS7 (N=272), an overall safety analysis set comprised of patients with or without *NTRK* gene fusions from the three larotrectinib studies[10] included in the resubmission who received ≥1 dose of larotrectinib (N=418), and a safety analysis set of patients with a documented *NTRK* gene fusion who received ≥1 dose of larotrectinib (TFCSAS; N=347).

[10] Study 20288 [formerly known as LOXO001], Study 20289 or NAVIGATE [formerly known as LOXO002], and Study 20290 or SCOUT [formerly known as LOXO003])

6.36 Table 9 summarises safety data from the overall safety analysis set based on the July 2022 data cutoff. Safety data presented in the previous submission, from the overall safety analysis set based on an earlier July 2020 data cutoff (Larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum), have been included for comparative purposes.

Table 9: Summary of overall safety analysis set for larotrectinib (regardless of the presence of *NTRK* fusions)

TEAE	Previous submission July 2020 data cutoff	Resubmission July 2022 data cutoff
	Overall safety set n=331	Overall safety set n=418
Patients with TEAE	320 (97%)	405 (97%)
Patients with TEAE related to larotrectinib	260 (79%)	333 (80%)
Patients with TEAE Grade 3 or 4	176 (53%)	239 (57%)
Patients with TEAE Grade 3 or 4 and related to larotrectinib	59 (18%)	81(19%)
Patients with TEAE and action taken of larotrectinib permanently discontinued	33 (10%)	47 (11%)
Patients with TEAE and action taken of larotrectinib permanently discontinued and related to larotrectinib	8 (2%)	9 (2%)
Patients with serious TEAE	129 (39%)	180 (43%)
Patients with serious TEAE and related to larotrectinib	20 (6%)	28 (7%)
Patients with fatal TEAE	21 (6%)	35 (8%)

Source: For previous data cutoff, Table 20, p40 of Larotrectinib PSD, November 2021 PBAC Meeting with March 2022 Addendum. For most recent data cutoff, Table 14.4.1, p6 of the Integrated Summary of Safety report, Attachment 2.6 accompanying the resubmission.
CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment emergent adverse event; *NTRK* = neurotrophic tyrosine receptor kinase; PSD = public summary document.
Blue shading represents information previously considered by the PBAC.
TEAEs were defined as adverse events that start on or after the first administration of larotrectinib. Related events are those judged by the Investigator as related to larotrectinib. Severity grade assignment based on CTCAE (v4.03): Grade 3 (severe), Grade 4 (life-threatening). Percentages are calculated based on the number of patients in the column heading as the denominator.

6.37 The overall safety profile was reasonably similar between the July 2020 and July 2022 data cut-offs. At the July 2022 data cutoff, 57% of patients had at least one Grade 3 or Grade 4 treatment emergent adverse event (TEAE). The proportion of patients with Grade 3 or Grade 4 TEAEs potentially related to larotrectinib was 19%. There were 47 patients (11%) who had TEAEs that led to permanent treatment discontinuation. Neurologic TEAEs were reported in 254 (61%) patients in the overall safety analysis set (Grade 1 [n=132; 32%], Grade 2 [n=71; 17%], with Grades 3, 4, and 5 events occurring in 42 [10%], 7 [2%], and 2 [<1%] patients, respectively). The available data indicated that the safety profile of larotrectinib was manageable. However, longer-term adverse event (AE) data from a larger larotrectinib-treated cohort are required to assess rare neurological or other relevant TEAEs to fully characterise the toxicity profile of larotrectinib.

Indirect comparison of safety – Larotrectinib *versus* docetaxel in NSCLC

6.38 The resubmission noted that safety data for larotrectinib were pooled across all tumour types in Studies 20288 and 20289 because i) only pooled results across different tumour types were available from Study 20288, ii) pooling the results provided a more adequate number of patients to reliably assess incidence of AEs, and

iii) it was reasonable to expect the safety profile of larotrectinib to be similar across different tumour types.

6.39 "Drug-related treatment-emergent events" were considered in the resubmission to be equivalent to what was described as "treatment-related events" in the CheckMate 057 trial.

6.40 Table 10 summarises the indirect comparison of safety between larotrectinib and docetaxel.

Table 10: Comparison of treatment-related AEs between larotrectinib and docetaxel

	Study 20288 and Study 20289 Larotrectinib (N=191)	CheckMate 057 Docetaxel (N=268)	Difference (95% CI)	p-value
Any AE	154 (81%)	236 (88%)	-7% (-14%, -1%)	0.034
Any Grade 3 or 4 AE	26 (14%)	144 (54%)	-40% (-48%, -32%)	<0.001
Fatigue	40 (21%)	78 (29%)	-8% (-16%, 0%)	0.052
Nausea	27 (14%)	70 (26%)	-11% (-19%, -5%)	0.002

Source: Table 2-35, p95 of the resubmission.
AE = adverse event; CI = confidence interval.
There were no Grade 5 treatment-related adverse events observed in patients treated with larotrectinib or docetaxel.
95% CIs were based on a normal approximation and p-values were based on Fisher's exact test

6.41 The resubmission concluded that results of the indirect comparison of safety were highly statistically significant which favoured larotrectinib over docetaxel.

6.42 The indirect comparison of safety presented in the resubmission was problematic given the single arm, non-matched, and non-blinded nature of the indirect comparison between heterogeneous patient populations. Moreover, the resubmission excluded AEs of special interest (AESI) associated with larotrectinib such as neurological AEs which are reflective of the mechanism of action of larotrectinib and are relevant in the assessment of benefit/risk. Moreover, the management of chemotherapy-related AEs has improved over time since the conduct of the historical CheckMate 057 trial (2012 to 2015)[11] with more frequent monitoring and earlier recognition of these events, and more effective prophylaxis and treatment in current clinical practice.

Indirect comparison of safety – Larotrectinib *versus* pazopanib in STS

6.43 Larotrectinib safety data were pooled across all tumour types in the 20288 and 20289 studies. Treatment-related AEs were referred to as "drug-related treatment-emergent" events, which were considered in the resubmission to be equivalent to what was described as "treatment-related" AEs in the PALETTE trial. "Treatment-emergent" events reported in larotrectinib studies were also considered equivalent to "on-therapy" events reported in the pazopanib study, which included all recorded events. Specific AE types for pazopanib in PALETTE were not presented separately for treatment-related AEs, only for all AEs. Thus, the resubmission presented an indirect

[11] https://classic.clinicaltrials.gov/ct2/show/NCT01673867

comparison of all types of AEs. Data on AEs by grade were not available for pazopanib for an indirect comparison.

6.44 Table 11 summarises the indirect comparison of safety between larotrectinib and pazopanib.

Table 11: Comparison of AEs between larotrectinib and pazopanib

	Study 20288 and Study 20289 Larotrectinib (N=191)	PALETTE Pazopanib (N=239)	Difference (95% CI)	p-value
Any AE	190 (99%)	237 (99%)	0% (-1%, 2%)	> 0.99
Fatigue	73 (38%)	155 (65%)	-27% (-36%, -17%)	<0.001
Nausea	51 (27%)	129 (54%)	-27% (-36%, -18%)	<0.001
Vomiting	32 (17%)	80 (33%)	-16% (-25%, -9%)	<0.001
Treatment-related AE only	154 (81%)	219 (92%)	-11% (-18%, -4%)	0.001

Source: Table 2-39 of the resubmission.
AE = adverse events. CI = confidence interval.
95% CIs were based on a normal approximation and p-values were based on Fisher's exact test

6.45 The resubmission concluded that the indirect comparison results were statistically significant for treatment-related AEs, for nausea and for fatigue, which favoured larotrectinib over pazopanib.

6.46 As was the case for NSCLC, the indirect comparison of safety between larotrectinib and pazopanib in STS was associated with several limitations including the single arm, non-matched, and non-blinded nature of the comparison, and the exclusion of neurological AESI that are specifically related to larotrectinib.

Benefits/harms

6.47 The basis of the evidence for effectiveness in the resubmission, in terms of PFS and OS, was a descriptive indirect comparison between single arms from heterogeneous studies, and the magnitude of the incremental benefit of larotrectinib versus the nominated comparators could not be reliably quantified. In terms of comparative safety, the claim in the resubmission was that larotrectinib had a comparable safety profile to SoC in NSCLC and STS. The indirect comparisons of safety were based on non-matched single arms with the exclusion of AESI associated with larotrectinib and the inclusion of specific AEs characteristic of the comparators. These indirect comparisons were not considered informative. Accordingly, a benefits/harms table has not been presented.

Clinical claim

6.48 The resubmission described larotrectinib as superior in terms of effectiveness and with a comparable safety profile compared with SoC in the proposed population with NSCLC or STS.

6.49 The ESC considered the claim of superior effectiveness was not adequately supported by the evidence presented in the resubmission. Collectively, the following limitations engender a high degree of uncertainty regarding the magnitude of the incremental

benefit associated with larotrectinib versus docetaxel in NSCLC and versus pazopanib in STS:

- The requested listing for larotrectinib in NSCLC and STS was line-agnostic which allows use of the medicine in the first-line treatment setting, whereas the evidence for larotrectinib and SoC was based on studies conducted in the refractory setting. No evidence was available to inform the incremental benefit of larotrectinib versus first-line SoC for advanced or metastatic NSCLC and STS. Evolving clinical practice guidelines show a trend towards recommending targeted therapy in an earlier treatment line for advanced disease which may possibly reflect the likely use of larotrectinib.
- The evidence was based on indirect comparisons between non-matched single arms from heterogeneous studies. For OS and PFS outcomes, the indirect comparisons were essentially descriptive and likely to be associated with a high risk of bias and confounding.
- Outcomes for larotrectinib were based on small patient numbers even after pooling (25 patients for NSCLC and 30 patients for STS). This limited the precision and hence the reliability of the efficacy estimates.
- There was lack of information on whether patients who had progressed on larotrectinib received subsequent second generation TRK inhibitors to treat on-target resistance to larotrectinib. These therapies are not currently available for this indication in Australian clinical practice. Consequently, any OS benefit observed in the larotrectinib studies may not be realised in current clinical practice.

6.50 The indirect comparisons presented in the resubmission to support the claim of comparable safety were between non-matched single arms which comprised of heterogeneous patient populations. Furthermore, the resubmission excluded AESI associated with larotrectinib such as neurological events whilst including AEs characteristic of chemotherapy and vascular endothelial growth factor (VEGF) inhibitors such as pazopanib. Overall, the ESC considered a reasonable conclusion based on the available data is that larotrectinib has a manageable safety profile, pending the availability of longer-term safety data, and that the safety profile of larotrectinib is different to that of docetaxel or pazopanib.

6.51 The PBAC considered the claim of superior effectiveness compared with the nominated comparators was reasonable but the magnitude of benefit remained highly uncertain. The PBAC considered the claim of comparable safety was reasonable.

Economic analysis

6.52 The resubmission presented separate modelled economic evaluations for the use of larotrectinib in *NTRK*-positive, locally advanced and unresectable, or metastatic, NSCLC and STS and was based on descriptive indirect comparisons of non-matched single arms from heterogeneous studies. This was changed from the previous

submission where additional adult low *NTRK* fusion frequency tumour types were included (colorectal and thyroid) and where results were weighted across the specified tumour types requested.

6.53 The types of economic evaluation presented were a cost-effectiveness analysis and cost-utility analysis with outcomes measured in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained. This was unchanged from the previous submissions. The key components of the economic evaluation are summarised in Table 12.

Table 12: Summary of model structure, key inputs and rationale

Component	Summary
Comparisons presented	Two separate analyses were presented: • larotrectinib vs docetaxel in patients with *NTRK*-positive locally advanced or metastatic NSCLC • larotrectinib vs pazopanib in patients with *NTRK*-positive locally advanced or metastatic STS
Type of analysis	Cost-utility analysis and cost-effectiveness analysis.
Outcomes	Life-years gained; quality-adjusted life years.
Time horizon	10 years in the model (compared to a median follow-up for OS of 40 months across all patients in the pooled ePAS7 dataset, not reported for the tumour type subgroups).
Methods used to generate results	Partitioned survival model.
Health states	PF, PP and Dead.
Cycle length	Weekly.
Transition probabilities	Health state allocation was derived from extrapolated time-to-event analyses of the lung cancer and STS subgroups of ePAS7 and comparator studies (CheckMate 057 for docetaxel and PALETTE for pazopanib).
Extrapolation method	KM data was used up until 12 months for PFS and up to 24 months for OS. The selection of these time points was inadequately justified in the resubmission. Parametric models were fitted to each treatment arm based on goodness of fit (AIC and BIC). 76% and 84% of the LYs (undiscounted) for NSCLC and STS were gained in the extrapolated period.
Utilities	Utility values were sourced from the CheckMate 057 trial for NSCLC (PF: 0.713 and PD: 0.688) and from the PALETTE trial for STS patients (PF: 0.674 and PD: 0.568). These were changed from the previous submission (PF: 0.80 and PD: 0.73).

Source: Table 3-1 of the submission.
AIC = Akaike information criterion; BIC = Bayesian information criterion; KM = Kaplan Meier; LY = life years; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival; PP= post progression; PF = progression-free; PFS = progression-free survival; STS = soft tissue sarcoma; QALYs = quality-adjusted life years
Blue shading represents information previously considered by the PBAC.

6.54 The PBAC previously advised that for adult low *NTRK* fusion frequency tumour types, given there would unlikely be sufficient data forthcoming to address the uncertainty around the effectiveness of larotrectinib, a further price reduction would be required to achieve a cost-effective price. The magnitude of the price reduction advised was to achieve an ICER within the range of $55,000 to < $75,000/QALY to $75,000 to < $95,000/QALY using more conservative extrapolations and a shorter time horizon. While the time horizon applied in the resubmission was reduced (from 15 years to 10 years), the resubmission did not apply the most conservative parametric extrapolations for OS and PFS, nor was a further price reduction proposed. The resulting incremental cost-effectiveness ratios (ICERs) presented ($135,000 to < $155,000 in NSCLC, and $95,000 to < $115,000 in STS) exceeded the range the PBAC

had previously considered cost-effective. The pre-PBAC response proposed a price reduction with resulted in an ICER of $95,000 to < $115,000 per QALY gained for NSCLC and $75,000 to < $95,000 per QALY gained for STS.

6.55 In addition to updating the larotrectinib data used in the model (from the July 2020 data cut to the July 2022 data cut), the main additional changes included in the resubmission's model were changing the comparator in STS to pazopanib (from dacarbazine previously) and excluding *NTRK* testing. A number of other changes were additionally made, including using tumour-specific health state utility values, excluding costs and disutility due to AEs and excluding terminal care costs. While the proposed AEMP for larotrectinib was unchanged in the resubmission, the average daily dose applied was increased from 188.6 mg per day to 200 mg. These changes were in general observed to increase the ICER relative to estimates and assumptions presented previously (see Table 19 and Table 20).

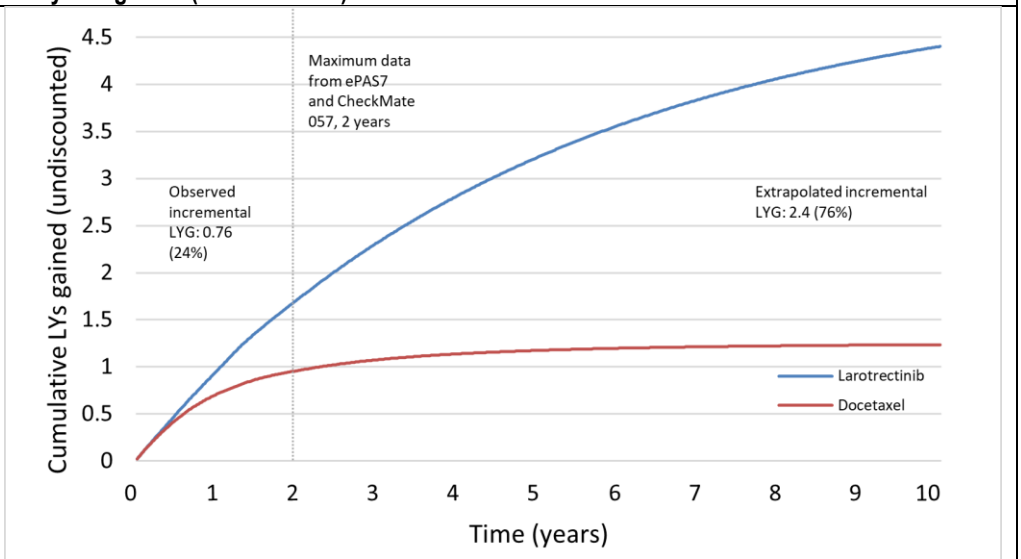
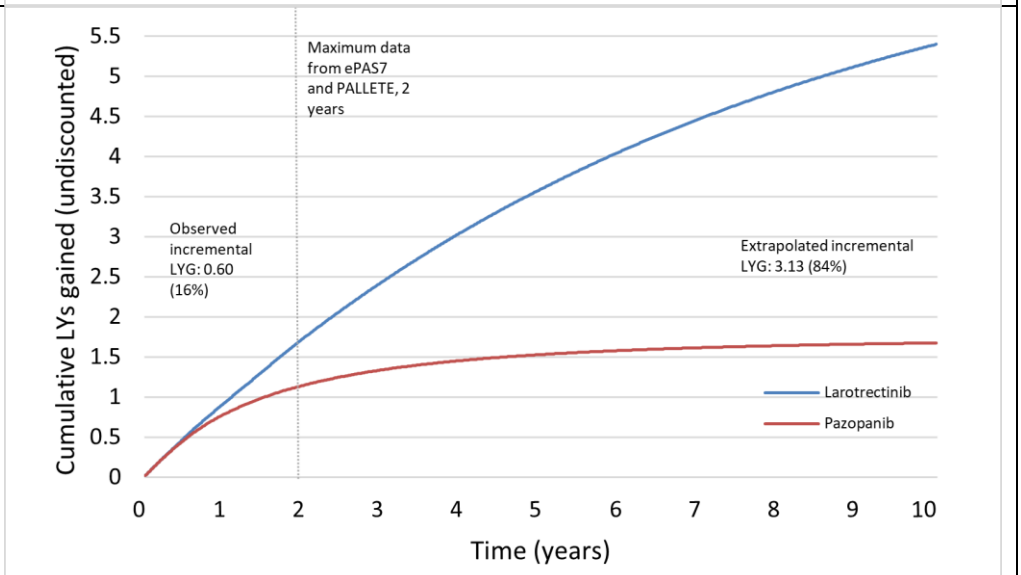
6.56 In each of the NSCLC and STS analyses, modelled costs and outcomes from larotrectinib or SoC treatment were generated through a partitioned survival analysis which allocated patients across three mutually exclusive health states: progression-free, progressed disease and dead. For patients treated with larotrectinib, health state allocation over the model time horizon was derived from the PFS and OS curves for the subgroups (lung and STS subgroups) of the ePAS7 pooled dataset. These subgroups were noted to include a small number of patients (≤ 30) and so are associated with substantial uncertainty. For docetaxel and pazopanib, health state allocation was derived from the survival curves from the Checkmate 057 and PALETTE trials respectively.

6.57 Observed Kaplan-Meier data for PFS and OS were used until 12 and 24 months respectively. The selection of these time points was not justified in the resubmission. Given that the PBAC Guidelines state a preference for observed data to be used until unreliable, the evaluation considered the application of the same truncation time point across tumour type and treatment received may not be reasonable. Given the small number of patients treated with larotrectinib and small number of events experienced, the use of only modelled data may be more appropriate. However, the analyses are not sensitive to this change.

6.58 Beyond these time points, survival data were extrapolated using parametric functions chosen based on the goodness of fit by AIC/BIC. Exponential models were chosen to extrapolate larotrectinib OS (in both NSCLC and STS), while log-normal models were used to extrapolate OS for docetaxel and pazopanib. The PBAC previously considered that the most conservative OS and PFS extrapolations should be used (para 6.73, larotrectinib PSD, November 2020 PBAC meeting). The most conservative extrapolations and best fitting models by visual inspection were Weibull and Gompertz for larotrectinib (for NSCLC and STS patients, respectively), and log-logistic for docetaxel and pazopanib. The ICERs are moderately sensitive to the use of the most conservative extrapolations (see Table 22 and Table 23).

6.59 Extrapolated survival data were used to determine health state membership over the modelled time horizon of 10 years. This was reduced from 15 years used previously. The resubmission justified the choice of time horizon based on the additional follow-up data in the pooled ePAS7 dataset (40 months median follow-up for OS). Follow-up times from the overall pooled dataset may have limited applicability to those of the subgroups of interest (NSCLC and STS). Further, the chosen time horizon remains substantially longer than what the PBAC have previously accepted in the later-line setting of NSCLC (para 6.57 larotrectinib PSD, November 2021 PBAC meeting; 6.06 pembrolizumab PSD, March 2019 PBAC meeting) and STS (para 6.30, eribulin PSD, November 2016 PBAC meeting), a shorter time horizon of 5 or 6 years may have been more appropriate. As depicted in Table 13, the majority of the life years (undiscounted) gained (76% for NSCLC and 84% for STS) were gained in the extrapolated period.

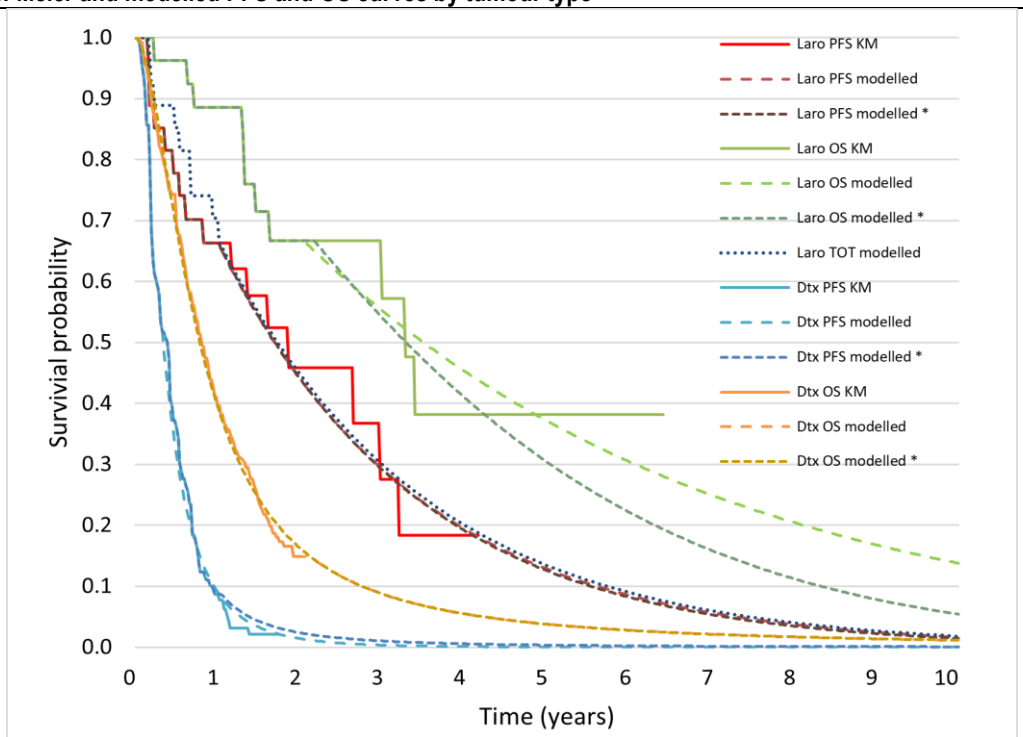
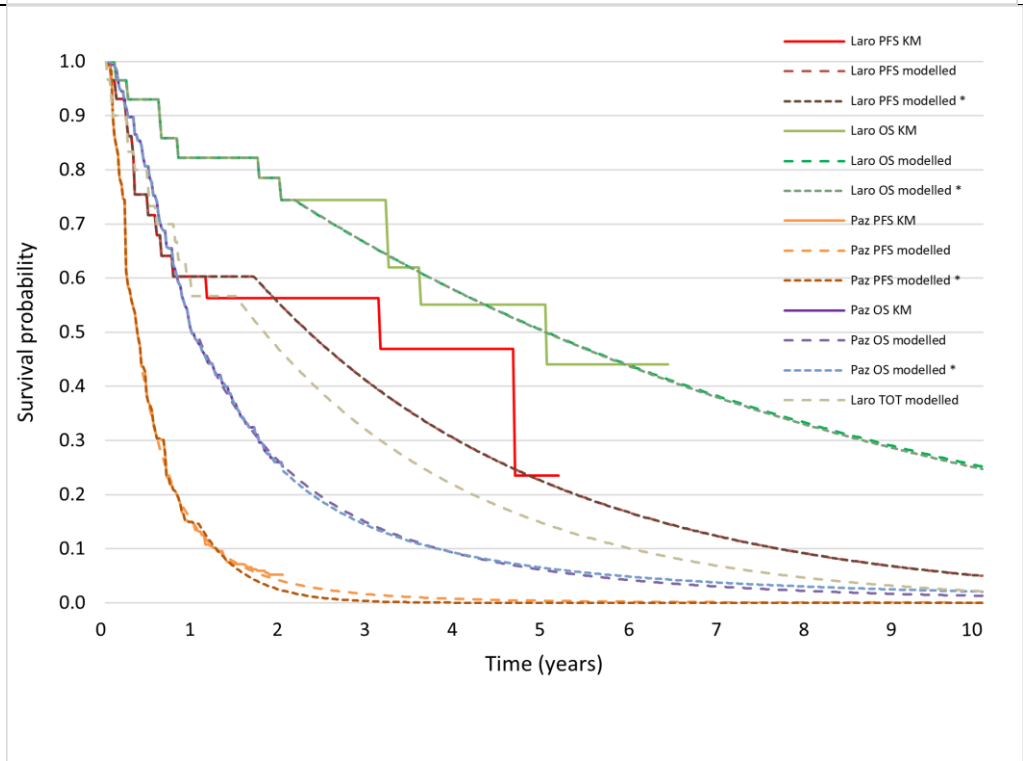
Table 13: Life-years gained over the modelled time horizon by tumour type

Tumour type	Life-years gained (undiscounted)
Adult *NTRK* positive NSCLC	
Adult *NTRK* positive STS	

Source: constructed during evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.
Lys = life-years; NSCLC = non-small cell lung cancer; STS = soft tissue sarcoma

6.60 A comparison of the observed Kaplan-Meier PFS and OS data, to the curves used in the model, by tumour type, are presented below in Table 14.

Table 14: Kaplan-Meier and modelled PFS and OS curves by tumour type

Adult *NTRK*-positive NSCLC Intervention: Larotrectinib Comparator: docetaxel	
Adult *NTRK*-positive STS Intervention: Larotrectinib Comparator: pazopanib	

* denotes the most conservative extrapolation (as identified in the evaluation)

Source: Constructed during the evaluation from "PFS_Est" and "OS_Est" worksheets of the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.

Dtx = docetaxel; KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; Laro = larotrectinib; OS = overall survival; Paz = pazopanib; PFS=progression-free survival; STS = soft tissue sarcoma; TOT = time on treatment

Note: PFS and OS KM data for docetaxel were truncated at 4 and 9 months, respectively, while PFS and OS KM data for pazopanib were truncated at 5 and 12 months, respectively (in line with publication).

6.61 The model did not employ a per-cycle transition probability to determine health state allocation over the modelled time horizon. Instead, the model used the minimum of the previous cycle's health state allocation and the observed data up until the truncation point (beyond which modelled data was used). This may not be appropriate and resulted in the apparent truncation point of larotrectinib OS in NSCLC extending to 2.2 years (compared to 2.0 years) and modelled larotrectinib PFS data exceeding the observed data in STS (as observed in the graphs presented in the above table).

6.62 The key drivers of the economic models are summarised in Table 15 and Table 16 for NSCLC and STS, respectively.

Table 15: Key drivers of the NSCLC model

Description	Method/Value	Impact (Revised base case: $[redacted][1]/QALY gained)
Incremental benefit of larotrectinib	Based on indirect comparison of single arm studies which contain major transitivity issues.	Likely high but not testable.
Time horizon	10 years. While this was reduced from the previous submission (15 years previously), the time horizon chosen was substantially longer than what the PBAC have previously accepted in the later-line setting of NSCLC (para 6.57 larotrectinib PSD, November 2021 PBAC meeting; 6.06 pembrolizumab PSD, March 2019 PBAC meeting).	High – favours larotrectinib. The ICER increases to $[redacted][2]/QALY when the time horizon decreased to 5 years.
Utility weights	PF = 0.713, PD = 0.688. The utility weights were lower than those applied in the previous submission (PF = 0.80, PD = 0.73) and in other submissions presented to the PBAC (PF=0.81, PD=0.72; para 6.48, atezolizumab PSD, July 2022 PBAC meeting)	Moderate – favours docetaxel. Applying alternate utility values leads to a reduction in the ICER ($[redacted][3]/QALY gained with previous submission estimates (similar to that for previously accepted PBAC values).
OS and PFS extrapolations	Parametric models were selected based on AIC/BIC values only (exponential models used for both OS and PFS for larotrectinib; log-normal models for both OS and PFS for docetaxel). The parametric models chosen in the resubmission were not the most conservative extrapolations which was inconsistent with previous PBAC advice (para 7.16, November 2021 PBAC Meeting with March 2022 Addendum).	Moderate – favours larotrectinib. When the most conservative extrapolations are chosen (OS: Weibull and Log-logistic; PFS: Gompertz and Log-logistic [for larotrectinib and docetaxel, respectively] the ICER increases to $[redacted][2]/QALY gained.

Source: compiled during the evaluation.

AIC/BIC = Akaike information criterion/Bayesian information criterion; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PF = progression-free; PFS= progression-free survival; QALY = quality-adjusted life year.

The redacted values correspond to the following ranges:

[1] *$135,000 to < $155,000*

[2] *$155,000 to < $255,000*

[3] *$115,000 to < $135,000*

Table 16: Key drivers of the STS model

Description	Method/Value	Impact (Revised base case: $[redacted][1]/QALY gained)
Incremental benefit of larotrectinib	Based on indirect comparison of single arm studies which contain major transitivity issue	Likely high but not testable.
Time horizon	10 years. While this was reduced from the previous submission (15 years previously), the time horizon chosen was substantially longer than what the PBAC have previously accepted in the later-line setting of STS (para 6.48, atezolizumab PSD, July 2022 PBAC meeting).	High – favours larotrectinib. The ICER increases to $[redacted][2]/QALY gained when the time horizon is decreased to 5 years.
Utility weights	PF = 0.674, PD = 0.568. The utility weights were lower than those applied in the previous submission (PF = 0.80, PD = 0.73) and in other submissions presented to the PBAC (PF=0.73, PD=0.67; Table 10, eribulin PSD, November 2016 PBAC meeting).	Moderate – favours pazopanib. Applying alternate utility values lead to a reduction in the ICER ($[redacted][3]/QALY gained using the previous submission estimates and $[redacted][3]/QALY gained using values from the eribulin submission.
OS and PFS extrapolations	Parametric models were selected based on AIC/BIC values only (exponential model used for OS and PFS for larotrectinib; log-normal models for both OS and PFS for pazopanib). The parametric models chosen in the resubmission were not the most conservative extrapolations which was inconsistent with previous PBAC advice (para 7.16, November 2021 PBAC Meeting with March 2022 Addendum).	Moderate – favours pazopanib. When the most conservative extrapolations are chosen (OS: Gompertz and Log-logistic; PFS: Exponential and Weibull [for larotrectinib and pazopanib, respectively], the ICER to $[redacted][1]/QALY gained.

Source: compiled during the evaluation.
AIC/BIC = Akaike information criterion/Bayesian information criterion; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PF = progression-free; PFS= progression-free survival; QALY = quality-adjusted life year; STS = soft tissue sarcoma
The redacted values correspond to the following ranges:
[1] *$115,000 to < $135,000*
[2] *$155,000 to < $255,000*
[3] *$95,000 to < $115,000*

6.63 The results of the economic evaluation for the two tumour types are presented in Table 17 and Table 18. The results were revised during the evaluation to apply the proposed dispensed prices of larotrectinib rather than AEMPs used in the resubmission base case. The STS analysis was further revised to correctly apply the cost of continuing larotrectinib scripts (rather than the cost of initial scripts across the course of treatment) [12]. The NSCLC analysis was further revised to apply a maximum of four cycles of docetaxel treatment, as per eviQ guidelines and as used in the previous submission. The PSCR accepted the model revisions applied by the evaluators. The resubmission did not present a stepped economic evaluation; this was conducted during the evaluation.

[12] The resubmission applied the costs of initial treatment across all cycles of treatment, instead of only to the first 12 cycles, in the STS model. This was corrected to apply the cost of continuing treatment for cycle 13 onwards (in line with the proposed listing).

Table 17: Results of the stepped economic evaluation for NSCLC (discounted)

Step and component	Larotrectinib	Docetaxel	Increment
Step 1: trial-based costs and outcomes (27 months)			
Costs	$	$6,236	$
LYG	1.82	0.98	0.84
Incremental cost/extra LYG gained			$ [1]
Step 2: extrapolated to 10 years			
Costs	$	$7,517	$
LYG	3.85	1.18	2.67
Incremental cost/extra LYG gained			$ [2]
Step 3: transformation into QALYs			
Costs	$	$7,517	$
QALYs	2.70	0.83	1.88
Incremental cost/extra QALY gained (base case)			**$** [3]
Previous submission [a]			
Costs	[redacted]	$58,199	$
QALYs	0.858	0.852	0.006
Incremental cost/extra QALY gained			**$** [2]

Source: tabulated during evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.

LYG = life year gained; NSCLC = non-small cell lung cancer; QALYs = quality-adjusted life years

Blue shading represents results previously considered by the PBAC.

Follow-up OS data for larotrectinib was available for NSCLC patients treated with larotrectinib for 77 months, while only 27 months of follow-up OS data was available for docetaxel. Therefore, the minimum duration of follow-up OS data was chosen for the stepped economic evaluation.

[a] In the previous submission, the analysis compared costs and outcomes in the tested population (i.e.,'NTRK testing and larotrectinib in NTRK+ and SoC in NTRK−' to 'No testing and SoC') and as such, the benefit of larotrectinib treatment was diluted. Costs in each model arm were driven by terminal care costs, which were excluded in the resubmission.

The redacted values correspond to the following ranges:

[1] *$155,000 to < $255,000*

[2] *$95,000 to < $115,000*

[3] *$135,000 to < $155,000*

Table 18: Results of the stepped economic evaluation for STS (discounted)

Step and component	Larotrectinib	Pazopanib	Increment
Step 1: trial-based costs and outcomes (48 months)			
Costs	$	$36,786	$
LYG	2.87	1.40	1.47
Incremental cost/extra LYG gained			$ [1]
Step 2: extrapolated to 10 years			
Costs	$	$38,333	$
LYG	4.61	1.57	3.04
Incremental cost/extra LYG gained			$ [2]
Step 3: utility weights applied			
Costs	$	$38,333	$
QALYs	2.91	0.95	1.95
Incremental cost/extra QALY gained (base case)			**$** [1]
Previous submission [a]			
Costs	$	$58,096	$
QALYs	1.023	0.985	0.037
Incremental cost/extra QALY gained			**$** [3]

Source: tabulated during evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.

LYG = life year gained; STS = soft tissue sarcoma; QALYs = quality-adjusted life years

Blue shading represents results previously considered by the PBAC.

For STS patients treated with larotrectinib, 77 months of follow-up OS data was available while only 48 months of follow-up OS data was available for patients treated with pazopanib. The minimum duration of follow-up OS data was chosen for the stepped economic evaluation.

[a] In the previous submission, the analysis compared costs and outcomes in the tested population (i.e.,'NTRK testing and larotrectinib in NTRK+ and SoC in NTRK−' to 'No testing and SoC') and as such, the benefit of larotrectinib treatment was diluted. Costs in each model arm were driven by terminal care costs, which were excluded in the resubmission.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$75,000 to < $95,000*

[3] *$55,000 to < $75,000*

6.64 The proposed price of larotrectinib is the same as the previous submission ($95,000 to < $115,000 per year of treatment). Further, the ICERs presented in this resubmission ($135,000 to < $155,000 for NSCLC and $115,000 to < $135,000 for STS) were considerably higher than those presented in the previous submission ($95,000 to < $115,000 for NSCLC and $55,000 to < $75,000 for STS). The stepped incorporation of changes from the previous submission results are presented in the tables below.

Table 19: Stepped incorporation of changes from the previous submission (NSCLC)

Analyses	Incremental cost ($)	Incremental QALY	ICER ($)
Previous submission subgroup base case ICER (revised)	[redacted]	**0.0060**	[redacted][1]
Adjustment of cycle length for model compatibility		0.0060	[redacted][1]
Patients enter model at point of treatment		2.9665	[redacted][1]
Exclude cost of testing		2.9665	[redacted][1]
Update data used in the model		2.2844	[redacted][1]
Update time horizon		2.0421	[redacted][1]
Update utility values		1.7879	[redacted][2]
Update larotrectinib dose and dispensing fees [a]		1.7879	[redacted][3]
Exclude terminal care costs		1.7879	[redacted][3]
Other minor model updates/changes [b] (resubmission base case)		**1.8773**	[redacted][3]
Base case including model corrections by evaluators		**1.8773**	[redacted][3]

Source: constructed from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the resubmission (November 2023) and the "A3.1+Larotrectinib_PBACMSAC_CEA_June21_resub_6June21" workbook provided with the previous submission (November 2021)

[a] The dose was updated to 200 mg (compared to 188.6 mg used previously); the dispensing fees was updated as the resubmission proposed a general schedule listing as opposed to a s100 listing in the previous submission.

[b] Other minor model updates/changes included: the exclusion of costs and outcomes associated with AEs, updated disease management costs, updated approach to costing subsequent treatment, updated docetaxel cost (and approach – weekly cost applied, rather than every third cycle), updated number of cycles in which initial larotrectinib script cost applies (12 from 14 previously) and updated application of discounting (applied per whole year, rather than partial year)

The redacted values correspond to the following ranges:

[1] *$95,000 to < $115,000*

[2] *$115,000 to < $135,000*

[3] *$135,000 to < $155,000*

Table 20: Stepped incorporation of changes from the previous submission (STS)

Analyses	Incremental cost ($)	Incremental QALY	ICER ($)
Previous submission subgroup base case ICER (revised)	[redacted]	**0.0373**	[redacted][1]
Adjustment of cycle length for model compatibility		0.0372	[redacted][1]
Patients enter model at point of treatment		3.3248	[redacted][1]
Exclude cost of testing		3.3248	[redacted][1]
Update data (and SoC cost) used in the model		2.7782	[redacted][1]
Update time horizon		2.2993	[redacted][2]
Update utility values		1.8246	[redacted][3]
Update larotrectinib dose and dispensing fees (noting that this was erroneous)[a]		1.8246	[redacted][3]
Exclude terminal care costs		1.8246	[redacted][3]
Other minor model updates/changes [b] (resubmission base case)		**1.9527**	[redacted][3]
Base case including model corrections by evaluators		**1.9527**	[redacted][4]

Source: constructed from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the resubmission (November 2023) and the "A3.1+Larotrectinib_PBACMSAC_CEA_June21_resub_6June21" workbook provided with the previous submission (November 2021)

[a] The dose was updated to 200 mg (compared to 188.6 mg used previously); the dispensing fees was updated as the resubmission proposed a general schedule listing as opposed to a s100 listing in the previous submission. Further, the cost of the initial script was applied to all scripts, instead of only the first 12 scripts (in line with the proposed listing).

[b] Other minor model updates/changes included: the exclusion of costs and outcomes associated with AEs, updated disease management costs, updated approach to costing subsequent treatment, updated docetaxel cost (and approach – weekly cost applied, rather than every third cycle), updated number of cycles in which initial larotrectinib script cost applies (12 from 14 previously) and updated application of discounting (applied per whole year, rather than partial year)

The redacted values correspond to the following ranges:

[1] *$55,000 to < $75,000*

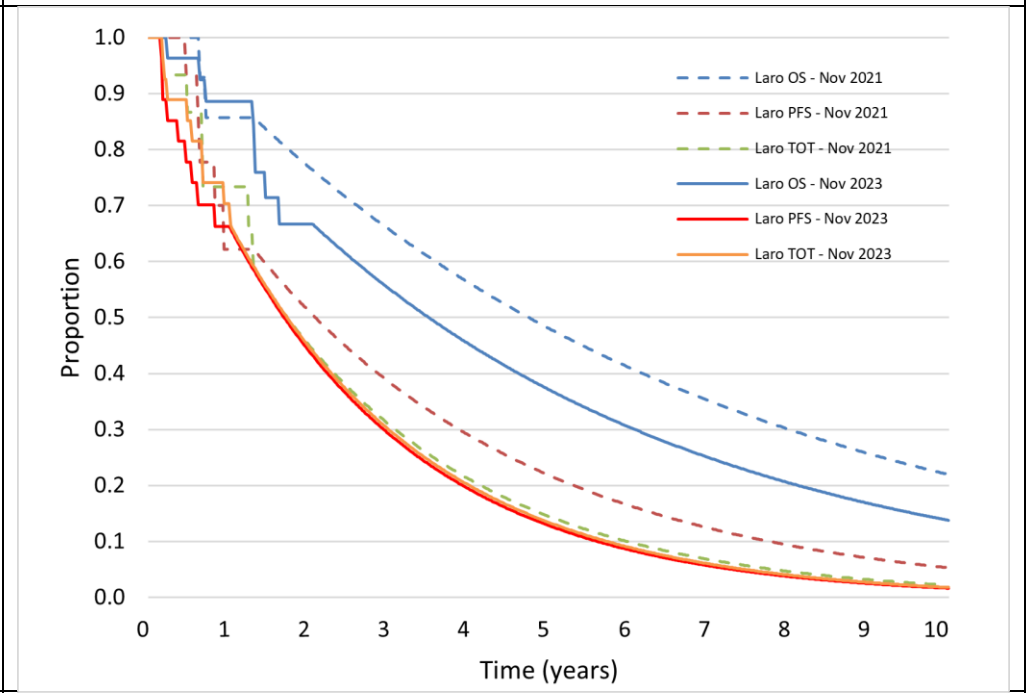
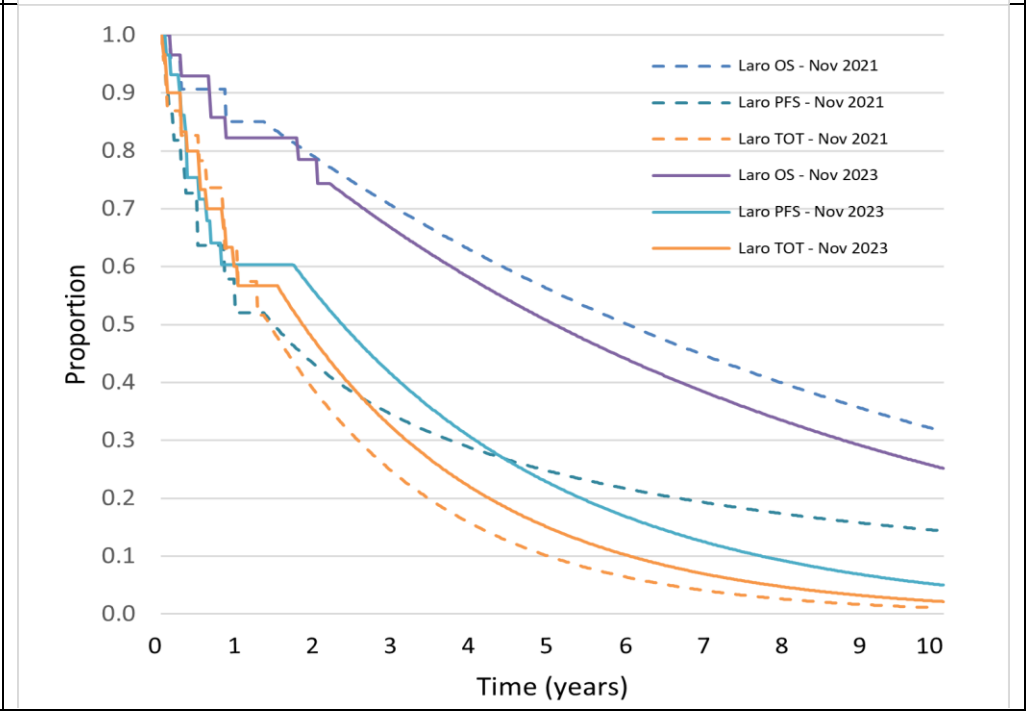
[2] *$75,000 to < $95,000*

[3] *$95,000 to < $115,000*

[4] *$115,000 to < $135,000*

6.65 The main change that led to a decrease in the ICER (compared to November 2021) was the exclusion of testing. The increases in the ICER were driven by the use of the updated data, reduction in time horizon, updated utility values, and to a lesser degree, the exclusion of terminal care costs. A comparison of the larotrectinib data used in the previous and current submission are presented in Table 21.

Table 21: Comparison of modelled survival curves between the previous and current resubmission by tumour type

Analysis	Survival curves
Adult *NTRK*-positive NSCLC	
Adult *NTRK*-positive STS	

Source: constructed from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the resubmission (November 2023) and the "A3.1+Larotrectinib_PBACMSAC_CEA_June21_resub_6June21" workbook provided with the previous submission (November 2021)

NSCLC = non-small cell lung cancer; NTRK = neurotrophic tyrosine receptor kinase; PFS = progression free survival; OS = overall survival; STS = soft tissue sarcoma; TOT = time on treatment.

6.66 The results of key sensitivity analyses are summarised in Table 22 and Table 23. From the sensitivity analyses, it can be inferred that the models are highly sensitive to the

time horizon, the utility weights applied and to the choice of parametric extrapolations (particularly in NSCLC). Further, given that the extrapolations are based on highly uncertain data, the modelled incremental outcomes accrued over the model time horizon are also highly uncertain.

Table 22: Key results of the sensitivity analyses (NSCLC) (using the price proposed in the resubmission)

	Incremental cost	Incremental QALYs	ICER	% change from revised base case
NSCLC				
Revised base case	[redacted]	**1.88**	[redacted][1]	**-**
Time horizon (base case: 10 years)				
5 years	[redacted]	1.32	[redacted][2]	[redacted]
15 years	[redacted]	2.04	[redacted][1]	[redacted]
Discount rate (base case: 5% for costs and outcomes)				
0%	[redacted]	2.23	[redacted][1]	[redacted]
3.5%	[redacted]	1.97	[redacted][1]	[redacted]
Utility weights (base case: PF: 0.713, PD: 0.688)				
PF = 0.891; PD = 0.688 (unchanged)	[redacted]	2.18	[redacted][3]	[redacted]
PF = 0.713 (unchanged); PD = 0.516	[redacted]	1.71	[redacted][2]	[redacted]
PF = 0.81; PD = 0.72 (para 6.48, atezolizumab PSD, July 2022 PBAC meeting)	[redacted]	2.07	[redacted][3]	[redacted]
PF = 0.80, PD =0.73 (sourced from previous submission)	[redacted]	2.07	[redacted][3]	[redacted]
Including disutility due to AEs (0.024)	[redacted]	1.85	[redacted][1]	[redacted]
Larotrectinib KM truncation time point (base case: PFS: 12 months, OS: 24 months)				
Using only modelled data	[redacted]	1.84	[redacted][1]	[redacted]
Parametric model extrapolation (base case: larotrectinib PFS and OS: exponential; docetaxel PFS and OS: lognormal)				
Most conservative extrapolations for PFS (Gompertz and Log-logistic) and OS (Weibull and Log-logistic) for larotrectinib and docetaxel, respectively	[redacted]	1.59	[redacted][2]	[redacted]

Source: tabulated during evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.

ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression-free survival; PSD = public summary document; STS = soft tissue sarcoma; TOT = time on treatment

[a] The duration of scripts refers to the number of days one script (pack) provides treatment coverage for.

The redacted values correspond to the following ranges:

[1] $135,000 to < $155,000

[2] $155,000 to < $255,000

[3] $115,000 to < $135,000

Table 23: Key results of the sensitivity analyses (STS) (using the price proposed in the resubmission)

	Incremental cost ($)	Incremental QALYs	ICER ($)	% change from revised base case
STS				
Revised base case	[redacted]	**1.95**	[redacted][1]	**-**
Time horizon (base case: 10 years)				
5 years	[redacted]	1.23	[redacted][2]	[redacted]
15 years		2.24	[redacted][3]	[redacted]
Discount rate (base case: 5% for costs and outcomes)				
0%	[redacted]	2.37	[redacted][3]	[redacted]
3.5%		2.07	[redacted][1]	[redacted]
Utility weights (base case: 0.674, 0.568)				
PF = 0.843; PD = 0.568 (unchanged)	[redacted]	2.31	[redacted][3]	[redacted]
PF = 0.674 (unchanged); PD = 0.426		1.82	[redacted][1]	[redacted]
PF = 0.80, PD =0.73 (sourced from previous submission)		2.37	[redacted][3]	[redacted]
PF = 0.73, PD =0.67 (Table 10, eribulin PSD, November 2016 PBAC meeting)		2.17	[redacted][3]	[redacted]
Including disutility due to AEs (0.024)		1.93	[redacted][1]	[redacted]
Larotrectinib KM truncation time point (base case: PFS: 12 months, OS: 24 months)				
Using only modelled data	[redacted]	1.99	[redacted][1]	[redacted]
Parametric model extrapolation (base case: larotrectinib PFS and OS: exponential; pazopanib PFS and OS: lognormal)				
Most conservative extrapolations for PFS (Exponential and Weibull) and OS (Gompertz and Log-logistic) for larotrectinib and pazopanib, respectively	[redacted]	1.94	[redacted][1]	[redacted]

***** denotes the most conservative model as identified in the evaluation

Source: tabulated during evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook provided in the submission.

ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; OS = overall survival; PD = progressive disease; PF = progression free; PFS = progression-free survival; PSD = public summary document; STS = soft tissue sarcoma; TOT = time on treatment

[a] The duration of scripts refers to the number of days one script (pack) provides treatment coverage for.

The redacted values correspond to the following ranges:

[1] *$115,000 to < $135,000*

[2] *$155,000 to < $255,000*

[3] *$95,000 to < $115,000*

Drug cost/patient/course

Table 24: Drug cost per patient for proposed and comparator drugs (using prices proposed in the resubmission)

	Larotrectinib Model	Larotrectinib Financial estimates	SoC Model	SoC Financial estimates
NSCLC				
Mean dose	200 mg	200 mg	133.5 mg	250 mg
Mean duration (months)	30	20	6	3
Cost/patient/month	Initial: $[redacted] Continuing: $[redacted]	Initial: $[redacted] Continuing: $[redacted]	$203	$203
Cost/patient/course	$[redacted]	$[redacted]	$1,002	$608
STS				
Mean dose	200 mg	200 mg	800 mg	800 mg
Mean duration (months)	30	16	7	4
Cost/patient/month	Initial: $[redacted] Continuing: $[redacted]	Initial: $[redacted] Continuing: $[redacted]	$4,248.01	$4,248.01
Cost/patient/course	$[redacted]	$[redacted]	$30,070	$16,992

Source: constructed during the evaluation from the "Attachment 3.1 – Section 3 Workbook – cost effectiveness model" workbook and the "Attachment 4.1 – Section 4 utilisation and cost model" workbook provided in the submission

NSCLC = non-small cell lung cancer; STS = soft tissue sarcoma

Note: revised during the evaluation based on DPMQs of larotrectinib, correct treatment costs of larotrectinib in the STS model and cost of an average dose of docetaxel used in the financial estimations.

6.67 The resubmission based the financial estimations for larotrectinib on the median treatment durations for the specific subgroups from the larotrectinib studies. Treatment durations of 20 months and 16 months were applied to the NSCLC and STS subgroups. It may have been more appropriate to use the mean treatment duration from the economic model (which is 30 months for both NSCLC and STS). The PSCR presented revised financial estimates using a 30 month treatment duration.

6.68 For docetaxel, the modelled treatment duration was estimated to be 6 months while a treatment duration of 3 months was applied in the financial estimations. Since eviQ guidelines recommend a maximum of 4 cycles of docetaxel treatment, a treatment duration of 3 months is more appropriate. For pazopanib, the treatment duration of 4 months in the financial estimations is significantly lower than the modelled treatment duration (7 months) but similar to that used previously in the July 2012 pazopanib PBAC submission (4.5 months).

6.69 The PBAC noted the modelled cost per patient for larotrectinib using the price proposed in the pre-PBAC response was $[redacted] for patients with NSCLC and $[redacted] for patients with STS.

Estimated PBS & financial implications

6.70 This resubmission was not considered by DUSC. The resubmission presented an updated epidemiological approach to estimate the extent of use and financial implications of listing larotrectinib on the PBS. The approach and inputs were generally unchanged from the previous submission. The key inputs utilised in the financial analysis are summarised in Table 25.

Table 25: Key inputs for financial estimates

Data	Value applied and source	Comment
Estimated number of eligible patients – NSCLC		
NSCLC Yearly incidence	56.2/100,000; based on AIHW, Cancer data in Australia 2023	The source for this estimate remains unchanged, noting that incidence projections were updated (from 51.2/100,000 used previously). This is reasonable.
NTRK fusion frequency	0.23% based on *NTRK* frequency epidemiology; Soloman et al 2019 [13]; O'Haire et al., 2023 [14]	This is unchanged from the previous submission.
% advanced at diagnosis	53.4%; sourced from AIHW (Stage 3 + Stage 4)	This is unchanged from the previous submission noting this includes patients with resectable tumours who are not eligible to receive larotrectinib.
% progressed after prior therapy	59.6% (Velcheti et al., 2019) [15]	This is unchanged from the previous submission and uses 12-month PFS data from the KN024 study.
Estimated number of eligible patients – STS		
STS Yearly incidence	8.5/100,000; based on AIHW, Cancer data in Australia 2023	The source for this estimate remains unchanged, noting that incidence projections were updated (from 7.1/100,000 used previously).
NTRK fusion frequency	1.4%; based on *NTRK* frequency epidemiology (Attachment 4.2); Soloman et al 2019; O'Haire et al., 2023	This is unchanged from the previous submission. However, O'Haire et al., 2023 estimated a prevalence of 0.69%.
% advanced at diagnosis	47.3%; sourced from Gadgeel [16]	This appears to be erroneous as the source remains unchanged from the previous submission (42.3% used previously). The PSCR updated the estimate to 42.2%.
% progressed after prior systemic therapy	73.5%; sourced from In et al., 2017 [17]	This remains unchanged from the previous submission.
Use and cost in eligible patients		
Uptake rate	Yr 1-6: [redacted]% Assumption	This assumption implicitly assumes that uptake of testing would be [redacted]%, which may be reasonable for NSCLC, but not for STS. Previously, uptake was assumed to increase from [redacted]% to [redacted]%, which the ESC considered an overestimate (para 6.75, larotrectinib PSD, November 2021 PBAC meeting). The PSCR revised the uptake rates for STS to [redacted]% in Year 1 and [redacted]% in Years 2 to 6.
Daily dose of larotrectinib	192.5 mg; assuming that 95% of the population will use 100 mg while the remaining 5% will use 25 mg.	This has changed from the previous submission in which the financial estimations were based on an average dose of 188.6 mg from the larotrectinib studies.

[13] NTRK fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls - PubMed (nih.gov)
[14] Systematic review of NTRK 1/2/3 fusion prevalence pan-cancer and across solid tumours | Scientific Reports (nature.com)
[15] Outcomes of first-line pembrolizumab monotherapy for PD-L1-positive (TPS ≥50%) metastatic NSCLC at US oncology practices - PubMed (nih.gov)
[16] Patterns of care in a population-based sample of soft tissue sarcoma patients in the United States - PubMed (nih.gov)
[17] Treatment of advanced, metastatic soft tissue sarcoma: latest evidence and clinical considerations - PubMed (nih.gov)

Data	Value applied and source	Comment
Duration of larotrectinib treatment	NSCLC: 20 months STS: 16 months. Based on Median duration of treatment in Lung and STS subgroups of ePAS7 dataset	This is inconsistent with the average duration of treatment modelled (30 months). The financial estimations are highly sensitive to a longer treatment duration. The PSCR updated the treatment duration to 30 months.
Duration of docetaxel use	3 months (equivalent to 4 treatment cycles). In line with eviQ guidelines.	
Duration of pazopanib use	4 months; based on extrapolated TOT curves	This is reasonable and consistent with the treatment duration used in the previous submission (Section 12, pazopanib PSD, July 2012 PBAC meeting). However, the modelled treatment duration for pazopanib is significantly longer (7 months).
Larotrectinib (per script)	Initial: $[redacted] Continuing: $[redacted] Proposed effective AEMPs	The PSCR updated the financials to reflect DPMQs.
Docetaxel (per script)	$182.26 Weighted DPMA for PBS items 10148D and 10158P	It would be more appropriate to use the cost for the average dose dispensed ($151.90).
Pazopanib (per script)	$4,248.01 DPMQ for PBS items 10041L, 10043N	
IV administration	$118.30 MBS item 13950	the fee for this item increased to $118.90 from 1 November 2023

Source: tabulated during evaluation from Table4-2 of the submission.
BID = bis in die (twice a day) ; IV = intravenous; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tyrosine receptor kinase; PFS = progression-free survival; STS, soft tissue sarcoma.
Blue shading represents information previously considered by the PBAC.

6.71 NSCLC and STS cancer incidence estimates were updated from the AIHW and applied to the ABS Australian population projections (2017−2066) for ages 18 and above. Estimates for the frequency of *NTRK* fusions in the population were unchanged from the previous submission. However, a recent study identified lower estimates for *NTRK* fusions prevalence (0.19% vs 0.23% in submission for NSCLC and 0.69% vs 1.4% in submission for STS). [18] The PSCR provided updated financials with revised prevalence estimates. For each tumour type, the proportion of patients with advanced disease at diagnosis and proportion of patients whose disease progressed after first-line therapy were identified and used to estimate the number of eligible patients. The resubmission assumed that [redacted]% of all eligible patients would elect treatment with larotrectinib. The evaluation considered this may not be reasonable as some patients may not proceed with further treatment. The PSCR revised the uptake rates for STS to [redacted]% in Year 1 and [redacted]% in Years 2 to 6

6.72 The resubmission noted that < 500 grandfathered patients from the sponsor's compassionate access program would be included in Year 1 only. While grandfathered patients were included in the estimated number of initiating patients, these were not included in the derivation of larotrectinib use.

[18] Systematic review of NTRK 1/2/3 fusion prevalence pan-cancer and across solid tumours | Scientific Reports (nature.com)

6.73 The resubmission applied treatment durations of 20 months and 16 months for NSCLC and STS respectively. These durations were based on the median treatment duration from the trials. This was inconsistent with the average duration of treatment modelled (30 months, equivalent to 32.2 scripts per patient in NSCLC, and 32.1 scripts in STS). The resubmission assumed 1 script of larotrectinib per month (equivalent to 12 per year) on treatment, with all initial scripts assumed within the year of treatment initiation and continuing scripts in the year following. This is not reasonable and due to an error in the number of continuing treatment scripts estimated, the total number of larotrectinib scripts applied per patient was 14.3 in NSCLC and 7.3 in STS. The PSCR provided revised financials with this error corrected. This error was corrected in the PSCR (see paragraph 6.79).

6.74 The estimated number of patients eligible for larotrectinib and the resulting number of prescriptions are presented in Table 26.

6.75 The resubmission assumed that the listing of larotrectinib would result in a reduction in use of docetaxel and pazopanib. This may not be reasonable as larotrectinib is likely to displace, rather than replace, existing treatments.

6.76 A reduction in the costs associated with MBS item 13950 ($94.64, 80% rebate) was included in the resubmission (due to a reduction in the use of docetaxel). However, the reduction in MBS cost was calculated based on the number patients initiating and continuing treatment with larotrectinib which is incorrect. Rather, it should have been calculated based on the number of patients initiating treatment with larotrectinib only (as patients only receive 4 cycles of docetaxel).

6.77 The net financial implications of listing larotrectinib are presented in Table 26.

Table 26: Estimated use and financial implications (revised by evaluators as per description in footnotes, using price proposed in resubmission)

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
NSCLC						
Number of initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total scripts, [a]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
STS						
Number of initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total scripts [b]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total						
Total scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of larotrectinib						
Cost to PBS less copayments [c]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications for affected medicines						
Impact to PBS less copayments	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net financial implications						
Net impact to PBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Net impact to MBS	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net impact to Government	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: compiled during evaluation from the "Attachment 4.1 – Section 4 utilisation and cost model" workbook provided in the submission. Revised estimated were based on correct DPMQs and scripts of larotrectinib, average dose cost of docetaxel; correct weighted copayment costs and MBS cost offsets associated with a reduction in the use of docetaxel.

[a] In NSCLC, 3 initial scripts were applied per patient in the year of treatment initiation. All continuing scripts were assumed to be incurred in the year following initiation. For a treatment duration of 20 months, assuming one script per month, the remaining scripts (17) were incurred in the year following treatment initiation. Estimates were revised to assume 13.04 scripts each year, the remaining scripts within the year of treatment initiation were assumed to be continuing scripts (i.e., 10.04). For a treatment duration of 20 months, 21.74 scripts are assumed per patient. Therefore, the remaining scripts (8.70) were incurred in the year following treatment initiation.

[b] In STS, 3 initial scripts were applied per patient in the year of treatment initiation. All continuing scripts were assumed to be incurred in the year following initiation. For a treatment duration of 16 months, assuming one script per month, the remaining scripts (13) were incurred in the year following treatment initiation. Estimates were revised to assume 13.04 scripts each year, the remaining scripts within the year of treatment initiation were assumed to be continuing scripts (i.e., 10.04). For a treatment duration of 16 months, 17.39 scripts are assumed per patient. Therefore, the remaining scripts (4.35) were incurred in the year following treatment initiation.

[c] Assuming average cost of initial scripts of $[redacted] and cost of continuing script of $[redacted] (calculated as 0.95 multiplied by cost of 100 mg script + 0.05 multiplied by cost of 25 mg script).

The redacted values correspond to the following ranges:

[1] *< 500*

[2] *$0 to < $10 million*

[3] *net cost saving*

6.78 The total cost to the PBS of listing larotrectinib was estimated to be $0 to < $10 million in Year 6, and a total of $10 million to < $20 million in the first 6 years of listing.

6.79 The PSCR provided revised financial estimates that incorporated the following changes:

- The DPMQs were updated to include the appropriate mark-ups and estimate the net cost to the health budget.
- The number of larotrectinib prescriptions were estimated by correcting for the number of scripts per year (13.04 scripts/year) and correcting for the number of continuing scripts across the first 6 years of listing.
- The proportion of patients advanced at diagnosis for STS was updated to utilise the value used in the previous submission (42.3% instead of 47.3%).

- The modelled treatment duration of 30 months was applied to all incident patients likely to receive larotrectinib.
- The prevalence of *NTRK* fusions were updated to utilise alternate estimates identified during the evaluation (0.19% in NSCLC and 0.69% in STS).
- The uptake rates for STS patients were revised to [redacted]% in year 1 and [redacted]% from years 2 onwards.

6.80 The pre-PBAC response provided revised financial estimates using the model provided with the PSCR and the revised price (see Table 27).

Table 27: Estimated use and financial implications, using the revised model provided in PSCR and the price proposed in the pre-PBAC response

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
NSCLC						
Number of initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
STS						
Number of initiating patients	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Total						
Total scripts	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]
Estimated financial implications of larotrectinib						
Cost to PBS less copayments	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]
Estimated financial implications for affected medicines						
Impact to PBS less copayments	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]	[redacted][3]
Net financial implications						
Net cost to PBS	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]	[redacted][2]

Source: Section 4 spreadsheet provided with pre-PBAC response.
The redacted values correspond to the following ranges:
[1] *< 500*
[2] *$0 to < $10 million*
[3] *net cost saving*

6.81 The revised financial estimates provided with the pre-PBAC response resulted in a cost to the PBS of $0 to < $10 million over 6 years.

Financial Management – Risk Sharing Arrangements

6.82 The resubmission noted that a risk sharing arrangement (RSA) is currently in place for the existing listing of larotrectinib. The resubmission suggested that the existing RSA be amended to include the new proposed listing.

6.83 The subsidisation cap and Commonwealth payment for the existing larotrectinib listing is provided in Table 28. The rebate above the subsidisation cap is [redacted]%.

Table 28: Subsidisation cap and Commonwealth payment for current larotrectinib PBS listings

Year	Subsidisation Cap ($)	Commonwealth Payment
Year 1 (Jul 22 – Jun 23)	[redacted]	$[redacted]*
Year 2 (Jul 23 – Jun 24)	[redacted]	$[redacted]*#
Year 3 (Jul 24 – Jun 25)	[redacted]	-
Year 4 (Jul 24 – Jun 26)	[redacted]	-
Year 5 (Jul 26 – Jun 27)	[redacted]	-

*based on unadjusted data
part year – 6 months

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required listing of larotrectinib for the treatment of adults with locally advanced or metastatic non-small cell lung cancer (NSCLC) or soft tissue sarcoma (STS) harbouring neurotrophic tropomyosin receptor kinase (*NTRK*) gene fusions. The PBAC noted patients with NSCLC and STS have access to gene panel testing that includes *NTRK* fusions on the Medicare Benefits Schedule (MBS). The PBAC noted that patients with glioma, glioneuronal tumour or glioblastoma also have access to testing on the MBS and advised it would be reasonable for larotrectinib to be listed on the PBS for these patients harbouring *NTRK* gene fusions. The PBAC considered the incremental cost-effectiveness ratio (ICER) was high but acceptable at the price proposed in the pre-PBAC response. The PBAC noted the very small number of patients that would be eligible for treatment and considered the utilisation estimates provided in the pre-PBAC response were reasonable.

7.2 The PBAC noted the input from health care professionals and organisations which highlighted the need for additional treatment options for rare cancers.

7.3 The PBAC was satisfied that larotrectinib provides, for some patients, an improvement in efficacy over the nominated comparators.

7.4 The PBAC noted the initial restriction criteria proposed in the resubmission would allow patients to be treated with larotrectinib in the first-line treatment setting. The resubmission stated that this was to allow patients who were 'inappropriate' for immunotherapy and/ or chemotherapy to be treated with larotrectinib. The PBAC considered the suggested addition to the criteria proposed in the PSCR (see paragraph 3.6) was appropriate and consistent with the TGA indication that specifies that the tumours should be metastatic or where surgical resection is likely to result in severe morbidity and has either progressed following treatment or who has no satisfactory alternative therapy. The PBAC considered it was also reasonable to allow access for patients with locally advanced disease where surgical resection is likely to result in severe morbidity.

7.5 The PBAC noted the nominated comparator for NSCLC was docetaxel and for STS was pazopanib. The PBAC acknowledged the nominated comparators were relevant in the later-line treatment setting and may not be appropriate if larotrectinib was used in an earlier treatment setting (as discussed in paragraph 6.49). However, on balance, the PBAC considered a majority of larotrectinib use would likely be in the later-line treatment setting and the nominated comparators were reasonable.

7.6 The PBAC noted the resubmission presented updated pooled efficacy data (the ePAS7 analysis with July 2022 data cut-off) from the same single-arm larotrectinib studies as previously presented (Study 20288, NAVIGATE, and SCOUT). The PBAC noted ePAS7 included 25 patients with NSCLC and 30 patients with STS. The resubmission presented a descriptive non-matched (unadjusted) indirect comparison versus i) single arm docetaxel data from CheckMate 057 for NSCLC, and ii) single arm pazopanib data from

PALETTE for STS.

7.7 For NSCLC, the PBAC noted the overall response rate (ORR) for larotrectinib as assessed by the independent review committee (IRC) was 76%, the median progression free survival (PFS) was 33 months and overall survival (OS) was 39.3 months. The PBAC noted the investigator assessed ORR for docetaxel was 12%, the median PFS was 4.2 months and median OS was 9.4 months. The PBAC noted that there was likely to be a very high risk of bias and confounding associated with a comparison of outcomes from ePAS7 and CheckMate 057 because of the single arm nature of the comparison, small patient numbers and differences in baseline patient demographics. Additionally, the PBAC noted CheckMate 057 was not conducted in patients with *NTRK* gene fusions.

7.8 For STS, the PBAC noted the ORR for larotrectinib as assessed by IRC was 50%, the median PFS was 24.8 months and OS was 60.2 months. The PBAC noted the investigator assessed ORR for docetaxel was 12%, the median PFS was 4.2 months and median OS was 9.4 months. Similar to its consideration in NSCLC, PBAC noted that there was likely to be a very high risk of bias and confounding associated with a comparison of outcomes from ePAS7 and PALETTE. Additionally, the PBAC noted PALETTE was not conducted in patients with *NTRK* gene fusions.

7.9 The resubmission described larotrectinib as superior in terms of effectiveness compared with the nominated comparators for NSCLC and STS. The PBAC considered the claim of superior effectiveness was reasonable but the magnitude of the benefit was highly uncertain.

7.10 The resubmission described larotrectinib as having comparable safety compared to the nominated comparators for NSCLC and STS. The PBAC considered that, based on the available data, larotrectinib has a manageable safety profile and that the safety profile of larotrectinib is different to that of docetaxel or pazopanib.

7.11 The PBAC noted data for 13 adult patients with glioma-like CNS tumours, including glioma (n=5), glioblastoma (n=7) and astrocytoma (n=1), was provided in the resubmission. The PBAC noted outcomes were presented for adult and paediatric patients combined (n=41), rather than for adult patients. The ORR for larotrectinib as assessed by IRC was 22%, the median PFS was 11.1 months and the OS rates at 36 months and 48 months were 57% and 52%, respectively (median OS not reached, with 38 months of follow-up). The PBAC noted the limited clinical data but considered that, on balance, larotrectinib was likely to be of similar clinical benefit as in NSCLC and STS. The PBAC noted the high clinical need in this condition and that patients with glioma, glioneuronal tumour or glioblastoma currently have access to *NTRK* gene fusion testing on the MBS. The PBAC considered it would be reasonable for larotrectinib to be listed on the PBS for these patients harbouring *NTRK* gene fusions.

7.12 The PBAC noted the base case incremental cost effectiveness ratio (ICER) using the price proposed in the pre-PBAC response was $95,000 to < $115,000 per quality adjusted life year (QALY) gained for NSCLC and $75,000 to < $95,000 per QALY gained

for STS. The PBAC noted the ICER for STS using the effective price of pazopanib. The PBAC recalled it had previously advised the economic model for the low frequency *NTRK* population should use more conservative extrapolations for PFS and OS and a shorter time horizon. The PBAC noted a shorter time horizon was adopted in the model (10 years instead of 15 years) but considered this remained longer than what had previously been accepted in the later-line treatment setting for NSCLC and STS. The PBAC noted the economic model was sensitive to the time horizon with a 27% increase in the ICER for NSCLC and 37% increase for STS using a 5 year time horizon. The PBAC noted the resubmission maintained the previous extrapolation functions for PFS and OS and the model was sensitive to this, in particular the NSCLC model, with the ICER increasing by 17% if the most conservative extrapolation functions were applied. The PBAC considered the ICERs were high and likely underestimated but, on balance, noting the very small patient population, considered larotrectinib would be cost-effective at the price proposed in the pre-PBAC response. The PBAC considered it was also likely larotrectinib was similarly cost-effective for patients with glioma, glioneuronal tumour or glioblastoma.

7.13 The PBAC considered the assumptions informing the estimated use and financial implications provided with the PSCR were reasonable. The PBAC noted no financial estimates were provided for the population of patients with glioma, glioneuronal tumour or glioblastoma and *NTRK* gene fusions. The PBAC considered it could be assumed that three additional patients per year would be treated with larotrectinib with a cost per patient no higher than for NSCLC or STS.

7.14 The PBAC noted the financial estimates would need to be recalculated to include utilisation estimates for the < 500 grandfathered patients (see paragraph 6.72) (assuming a treatment duration of 15 months), the additional patients with glioma, glioneuronal tumour or glioblastoma (see paragraph 7.13), and the price proposed in the pre-PBAC response.

7.15 The PBAC advised that the new listing could be included in the existing Risk Sharing Arrangement for larotrectinib with the net cost of listing (as revised in paragraph 7.14) added to the expenditure caps currently in place.

7.16 The PBAC considered the following amendments to the restriction criteria in Section 3 would be appropriate:

- Include the population criterion “Patient must be at least 18 years of age” in the restriction criteria for initial treatment (noting that all patients under 18 years of age with *NTRK* gene fusions can access larotrectinib under the current PBS listing);
- Include the clinical criterion “OR The condition must be confirmed through a pathology report from an Approved Pathology Authority (of any date) as at least one of: (i) glioma, (ii) glioneuronal tumour, (iii) glioblastoma” in the restriction criteria for initial treatment;
- Amend the clinical criterion in the restriction for initial treatment “The condition

must be metastatic disease; OR The condition must be both: (i) locally advanced, (ii) unresectable; *OR The condition must be locally advanced where surgical resection is likely to result in severe morbidity*" as indicated by italics (see paragraph 7.4);

- Include the clinical criterion "*Patient must have received prior systemic treatment for this disease; or Patient must have a condition that predisposes them to an unacceptable risk of intolerance to other systemic therapies*" in the restriction criteria for initial treatment (see paragraph 7.4);
- Include the clinical criterion "*The condition must be at least one of: (i) non-small cell lung cancer, (ii) soft tissue sarcoma, (iii) glioma, (iv), glioneuronal tumour, (v) glioblastoma*" in the restriction criteria for continuing treatment;

7.17 The PBAC noted patients with NSCLC, STS, glioma, glioneuronal tumour and glioblastoma currently have access to gene panel testing that includes *NTRK* gene fusions. However, the PBAC recommended that advice be sought from the Department to ensure that the current MBS items are clinically appropriate and cover all relevant *NTRK* gene fusions.

7.18 The PBAC noted larotrectinib was effective in other tumours with a low frequency of *NTRK* gene fusions, including colorectal cancer and thyroid cancers, but that gene panel testing is not available on the MBS for these patients. The PBAC noted that, without gene panel testing, the cost of identifying patients with *NTRK* gene fusion would need to be accounted for in the economic evaluation, and it was unclear if larotrectinib would be cost-effective in these patients. The PBAC considered that for other tumours with a low frequency of *NTRK* gene fusions, it would be expected that the cost of identifying patients with *NTRK* gene fusions would be significantly reduced if such testing was limited to tumours that were positive for *NTRK* immunohistochemistry (the latter of which is currently available on the MBS).

7.19 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for larotrectinib:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, over alternative therapies, given the magnitude of the benefit is highly uncertain;

b) The treatment is not expected to address a high and urgent unmet clinical need due to the availability of other therapies for NSCLC and STS;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed

7.20 The PBAC noted that this resubmission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
LAROTRECTINIB					
larotrectinib 25 mg capsule, 56	NEW	1	56	2	Vitrakvi
larotrectinib 100 mg capsule, 56	NEW	1	56	2	Vitrakvi
larotrectinib 20 mg/mL oral liquid, 2 x 50 mL	NEW	1	1	2	Vitrakvi

Restriction Summary / Treatment of Concept	
	Category / Program: GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners
	Restriction type: ☒Authority Required (in writing-legacy) Postal/HPOS upload or Online PBS Authorities immediate assessment
	Administrative Advice: For a patient who has received non-PBS-subsidised supply of this drug, apply under an 'Initial treatment' phase listing provided that they meet all stated PBS eligibility criteria.
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
	Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001
	Indication: Solid tumours (of certain specified types) with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
	Treatment Phase: Initial treatment
	Clinical criteria:

	The condition must be confirmed to be positive for a neurotrophic tropomyosin receptor kinase (NTRK) gene fusion prior to treatment initiation with this drug through a pathology report from an Approved Pathology Authority – provide the following evidence: (i) the date of the pathology report substantiating the positive NTRK gene fusion, (ii) the name of the pathology service provider, (iii) the unique identifying number/code linking the pathology test result to the patient; the recency of the pathology report may be of any date,
	AND
	Clinical criteria:
	The condition must be non-small cell lung cancer confirmed through a pathology report from an Approved Pathology Authority (of any date); or
	The condition must be soft tissue sarcoma confirmed through a pathology report from an Approved Pathology Authority (of any date); or
	The condition must be confirmed through a pathology report from an Approved Pathology Authority (of any date) as either (i) glioma, (ii) glioneuronal tumour, (iii) glioblastoma
	AND
	Clinical criteria:
	The condition must be metastatic disease; OR
	The condition must be both: (i) locally advanced, (ii) unresectable; OR
	The condition must be locally advanced where surgical resection is likely to result in severe morbidity
	AND
	Clinical criteria:
	Patient must have received prior systemic treatment for this disease; or
	Patient must have a condition that predisposes them to an unacceptable risk of intolerance to other systemic therapies
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised anti-cancer therapy for this condition.
	Treatment criteria:
	Patient must not be undergoing treatment through this Initial treatment phase listing where the patient has developed disease progression while receiving this drug for this condition,
	AND
	Treatment criteria:
	Patient must not receive more than 3 months of treatment under this restriction
	Population criteria:
	Patient must be at least 18 years of age.
	Prescribing Instructions: The authority application must be made via the Online PBS Authorities System (real time assessment), or in writing via HPOS form upload or mail, and must include: (a) details of the pathology report substantiating the positive NTRK gene fusion. The recency of the pathology report may be of any date. (b) details of the pathology report establishing the carcinoma type (non-small cell lung cancer, soft tissue sarcoma or either glioma/ glioneuronal tumour/ glioblastoma) being treated, if different to the pathology report provided to substantiate the NTRK gene fusion. (c) details of prior systemic treatment for this disease or details of the condition that predisposes the patient to an unacceptable risk of intolerance to other systemic therapies. All reports must be documented in the patient's medical records.

	Prescribing Instructions: If the application is submitted through HPOS upload or mail, it must include: (i) a completed authority prescription form; and (ii) a completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№.of Rpts**	**Available brands**
LAROTRECTINIB					
larotrectinib 25 mg capsule, 56	NEW	1	56	5	Vitrakvi
larotrectinib 100 mg capsule, 56	NEW	1	56	5	Vitrakvi
larotrectinib 20 mg/mL oral liquid, 2 x 50 mL	NEW	1	1	5	Vitrakvi
Restriction Summary / Treatment of Concept					

		Category / Program: GENERAL – General Schedule (Code GE)
		Prescriber type: ☒Medical Practitioners
		Restriction type: ☒Authority Required (Telephone/Electronic)
		Administrative Advice: For a patient who has received non-PBS-subsidised supply of this drug, apply under an 'Initial treatment' phase listing provided that they meet all stated PBS eligibility criteria.
		Administrative Advice: No increase in the maximum number of repeats may be authorised.
		Administrative Advice: Special Pricing Arrangements apply.
		Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).
		Indication: Solid tumours with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
		Treatment Phase: Continuing treatment
		Treatment criteria:
		Patient must have previously received PBS-subsidised treatment with this drug for this condition.
		Clinical criteria:
		The condition must be either: (i) non-small cell lung cancer, (ii) soft tissue sarcoma, (iii) glioma, (iv), glioneuronal tumour, (v) glioblastoma
		AND
		Clinical criteria:
		The treatment must cease to be a PBS benefit upon radiographic progression
		AND
		Clinical criteria:
		The treatment must be the sole PBS-subsidised systemic anti-cancer therapy for this condition
		Population criteria:
		Patient must be at least 18 years of age.
		Prescribing Instructions: Where radiographic progression is observed, mark any remaining repeat prescriptions with the word 'cancelled'.

This restriction may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Bayer welcomes the PBAC's decision to recommend larotrectinib (Vitrakvi®) for PBS listing for the treatment of adult patients with positive *NTRK*-gene fusions in NSCLC, STS and glioma, glioneuronal tumour or glioblastoma tumours. Bayer will continue to work with the Department of Health and Aged Care to ensure a timely PBS listing.