

7.07 LAROTRECTINIB

Capsule 25 mg, Capsule 100 mg

Oral solution 20 mg per mL, 100 mL

Vitrakvi[®],

Bayer Australia Ltd

1 Purpose of submission

- 1.1 The integrated codependent resubmission requested 1) Medicare Benefits Schedule (MBS) listing of neurotrophic tropomyosin receptor kinase (*NTRK*) fusion testing using immunohistochemistry (IHC), fluorescence *in situ* hybridisation (FISH) or next generation sequencing (NGS), and 2) a Pharmaceutical Benefits Scheme (PBS) Schedule listing of larotrectinib for the targeted treatment of *NTRK* fusion solid tumours that are unresectable locally advanced, metastatic, or locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection.
- 1.2 A key change from the previous submission was that the resubmission specified specific solid tumour types for the adult population: two tumour types for the adult high fusion frequency subgroup (salivary gland and secretory breast carcinoma (SBC) tumours), and four tumour types for the adult low fusion frequency subgroup (soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC), thyroid cancer and colorectal cancer (CRC)).
- 1.3 As was the case for the previous submission, the requested basis for listing was cost-effectiveness relative to standard of care (SoC).
- 1.4 Larotrectinib is an orally bioavailable, adenosine triphosphate (ATP)-competitive and highly selective TRK inhibitor, rationally designed to avoid activity with off-target kinase.
- 1.5 The recommended larotrectinib dosage regimen, as per the approved product information (PI), remains the same (adults: 100 mg twice daily until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity; paediatric: based on body surface area (BSA): 100 mg/m² twice daily with a maximum of 100 mg per dose). These dosing regimens are consistent with those in the larotrectinib studies.

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

Component	Description
Population	<p>Test: Locally advanced or metastatic solid tumour patient subpopulations:</p> <ol style="list-style-type: none"> Paediatric patients newly diagnosed with solid tumours with high-frequency <i>NTRK</i> gene fusions that are metastatic or locally advanced (where surgical resection is likely to result in severe morbidity); Adult patients newly diagnosed with solid tumours with high-frequency <i>NTRK</i> gene fusion cancer types: salivary gland cancer/MASC^a or <u>SBC</u> that are metastatic or locally advanced (where surgical resection is likely to result in severe morbidity); Paediatric patients newly diagnosed solid tumours with low-frequency <i>NTRK</i> gene fusions that are metastatic or locally advanced (where surgical resection is likely to result in severe morbidity); Adult patients with solid tumours with low-frequency <i>NTRK</i> gene fusion cancer types: <u>CRC</u>, <u>STS</u>, <u>NSCLC</u>^b or <u>thyroid cancer</u> that are metastatic or locally advanced (where surgical resection is likely to result in severe morbidity) and have R/R disease with <u>no suitable alternate therapy</u>. <p>Treatment: Patients with locally advanced or metastatic solid tumours with confirmed <i>NTRK</i> fusion (first-line for the first three populations above and second- or later-line for the last population above)</p>
Intervention	<p>Test: FISH or RNA-NGS (with pan-Trk IHC used as a triage test for the last population above)</p> <p>Treatment: Larotrectinib 100 mg BID for adults or 100 mg/m² BID with a maximum of 100 mg BID administered for paediatric patients</p>
Comparator	No test + SoC
Outcomes	<p>Test: Sensitivity, specificity, PPV, NPV, NNT</p> <p>Treatment: Overall response rate, duration of response, overall survival, progression free survival, safety</p>
Clinical claim	In patients with a locally advanced or metastatic solid tumour with confirmed <i>NTRK</i> fusion, larotrectinib + <i>NTRK</i> gene fusion testing (FISH or NGS +/- IHC) is superior in terms of efficacy and safety when compared to no <i>NTRK</i> gene fusion testing + SoC

Source: Source: Table 1.2, p27 and Sections 1.1.2 and 1.4 of the resubmission

Changes from the original submission have been underlined

^aSalivary gland is broader than the subtype of MASC specified in the MBS item descriptor. MASC was the most represented high frequency *NTRK* cancer occurring in adults in the larotrectinib trials (n=23) and is approximately only 4.5 % of salivary gland tumours.^bThe resubmission specified lung cancer in the MBS descriptor whereas NSCLC was specified in the PBS restriction. The clinical evidence for larotrectinib was limited to NSCLC, as is the PBS restriction. The MBS item descriptor has been amended during the evaluation to NSCLC.

BID = "bis in die" or twice a day; CRC = colorectal cancer; FISH = Fluorescence in situ hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; NNT = number needed to treat; NPV = negative predictive value; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic receptor tyrosine kinase; MASC = mammary analogue secretory carcinoma; PPV = positive predictive value; RNA = ribonucleic acid; R/R = refractory/relapsed; SBC = secretory breast cancer; SoC = standard of care; STS = soft tissue sarcoma

1.6 Proposed place in the clinical management algorithm: For adult high fusion frequency cancers and paediatric cancers, a first-line treatment was proposed. For adults with low fusion frequency cancers, the clinical management algorithms proposed in the resubmission was that patients need to have progressed on first-line SoC, second-line SoC, and subsequent lines of therapy until patients have no other suitable therapies available.

1.7 Larotrectinib is expected to displace the SoC therapies available for the proposed treatment lines (as described above). The proposed first-line use for the adult high fusion frequency tumours and paediatric fusion tumours appears broader than the provisionally approved TGA indication which is for patients who have either progressed following treatment or who do not have any satisfactory alternative therapy. For some paediatric patients however, such as those who would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection, this may represent a scenario where larotrectinib may be used in an earlier treatment line for locally advanced resectable paediatric cancer (paragraph 2.7, larotrectinib Public Summary Document (PSD), November 2020).

2 Requested listing

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

Name, restriction, manner of administration, form	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Larotrectinib, 100 mg, oral capsules	56	2	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	VITRAKVI®, Bayer Australia Ltd
Larotrectinib, 25 mg, oral capsules	56	2	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	
Larotrectinib, 20 mg/ml, 1 × 100 ml bottle solution, oral administration	100	2	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	

Source: Table 1.20, p85 of the resubmission

Essential elements of the requested listing (continuing pack)

Name, restriction, manner of administration, form	Maximum amount (packs)	Maximum amount (units)	No. of repeats	Dispensed price for maximum amount	Proprietary name and manufacturer
Larotrectinib, 100 mg, oral capsules	1	56	5	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	VITRAKVI®, Bayer Australia Ltd
Larotrectinib, 25 mg, oral capsules	1	56	5	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	
Larotrectinib, 20 mg/ml, 1 × 100 ml bottle solution, oral administration	1	100	5	Public Published \$ ██████ Effective \$ ██████ Private Published \$ ██████ Effective \$ ██████	

Source: Table 1.21, p86 of the resubmission

Proposed PBS listing for paediatric patients – initial treatment

Category / Program	Section 100 – HSD
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Condition	Locally advanced or metastatic solid tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Initial treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The condition must be positive for a neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) gene fusion confirmed by next-generation sequencing or fluorescence in-situ hybridisation</p> <p>AND</p> <p>Patients must be diagnosed with a solid tumour</p> <p>AND</p> <p>Disease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection</p> <p>AND</p> <p>Patient must not have received prior treatment with a <i>NTRK</i> inhibitor</p> <p>AND</p> <p><u>Patient must not receive more than 3 months of treatment under this restriction</u></p>

Proposed PBS listing for paediatric patients – continuing treatment

Category / Program	Section 100 – HSD
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Condition	Locally advanced or metastatic solid tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Continuing treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The treatment must be the sole PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to treatment with this drug</p> <p>AND</p> <p>PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs</p>

*Public Summary Document – November 2021 PBAC Meeting with March 2022
Addendum*

Proposed PBS listing for adult patients with high frequency *NTRK* fusion tumour – initial treatment

Category / Program	Section 100 – HSD
Prescriber type	<input checked="" type="checkbox"/> Medical Practitioners
Condition	Locally advanced or metastatic salivary gland, secretory breast tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Initial treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The condition must be positive for a neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) gene fusion confirmed by next-generation sequencing or fluorescence in-situ hybridisation</p> <p>AND</p> <p>Patients must be diagnosed with a solid tumour</p> <p>AND</p> <p>Disease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection</p> <p>AND</p> <p>Patient must not have received prior treatment with a <i>NTRK</i> inhibitor</p> <p>AND</p> <p><u>Patient must not receive more than 3 months of treatment under this restriction</u></p>

Proposed PBS listing for adult patients with high frequency *NTRK* fusion tumour – continuing treatment

Category / Program	Section 100 – HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Locally advanced or metastatic salivary gland, secretory breast tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Continuing treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The treatment must be the sole PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to treatment with this drug</p> <p>AND</p> <p>PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs.</p>

Proposed PBS listing for adult patients with low frequency *NTRK* fusion tumour – initial treatment

Category / Program	Section 100 – HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Locally advanced or metastatic soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC), thyroid cancer and colorectal cancer (CRC) tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Initial treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The condition must be positive for a neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) gene fusion confirmed by next-generation sequencing or fluorescence in-situ hybridisation</p> <p>AND</p> <p>Disease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection</p> <p>AND</p> <p>The condition must have relapsed or be refractory to at least one prior therapy in the locally advanced or metastatic setting AND with no suitable alternate therapy available</p> <p>AND</p> <p>Patients must have a ECOG score of 2 or less</p> <p>AND</p> <p>Patient must not have received prior treatment with a <i>NTRK</i> inhibitor</p> <p>AND</p> <p><u>Patient must not receive more than 3 months of treatment under this restriction</u></p>

Proposed PBS listing for adult patients with low frequency *NTRK* fusion tumour – continuing treatment

Category / Program	Section 100 – HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Locally advanced or metastatic soft tissue sarcoma (STS), non-small cell lung cancer (NSCLC), thyroid cancer and colorectal cancer (CRC) tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Continuing treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	<p>The treatment must be the sole PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have previously received PBS-subsidised treatment with this drug for this condition</p> <p>AND</p> <p>Patient must have demonstrated an adequate response to treatment with this drug</p> <p>AND</p> <p>PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs</p>

Requested PBS Restriction – Grandfather treatment

Category / Program	Section 100 – HSD
Prescriber type	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Condition	Locally advanced or metastatic solid tumours harbouring <i>NTRK</i> gene fusion
Treatment phase	Grandfather treatment
Restriction	<input checked="" type="checkbox"/> Authority Required – In Writing
Treatment criteria	-
Clinical criteria	The condition must be positive for a neurotrophic tropomyosin receptor kinase (<i>NTRK</i>) gene fusion AND Disease must be metastatic OR unresectable locally advanced OR locally advanced and would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection. AND The patient must have previously received non-PBS subsidised treatment with this drug AND The treatment must be the sole PBS-subsidised therapy for this condition AND PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs

Source: Tables 120-128, pp84-90 of the resubmission

- 2.1 The submission requested an Authority Required (In Writing) listing under the Section 100 (Highly Specialised Drugs) program. The PBAC considered a General Schedule listing would be more appropriate given specialised administration is not required for an orally administered treatment and no additional immediate monitoring requirements are outlined in the Product Information. The PBAC considered that an Authority Required (In Writing) listing would be appropriate for initial treatment and an Authority Required (telephone/online PBS Authorities system) listing would be appropriate for continuing treatment.
- 2.2 The requested restriction specified specific solid tumour types for the adult population: two tumour types (salivary gland and SBC) for the high *NTRK* frequency subgroup, and four tumour types for the low *NTRK* frequency subgroup (STS, NSCLC, thyroid cancer and CRC). The PBAC previously advised that specifying the tumour types in the high and low frequency subgroups may reduce the risk of use beyond the intended populations, and that this may be particularly important for the adult populations if adult patients with low frequency *NTRK* fusion tumours remain ineligible for PBS subsidy (Paragraph 7.4, larotrectinib PSD, November 2020). The Pre-Sub-Committee Response (PSCR) indicated that tumour types were not specified for paediatric high and low frequency subgroups due to ethical considerations, as all paediatric patients have access to *NTRK* fusion testing through the Zero Childhood Cancer Initiative. The ESCs considered specifying tumour types for the adult population only was reasonable.
- 2.3 For the adult low frequency subgroup, the justification in the resubmission for the specified tumour types was based on i) the tumour types with the highest prevalence in the latest clinical data-cut (which together represented 74 patients from total 101

patients for this subgroup in the pooled analysis (ePAS5 + SAS3 New)), ii) demonstrated response rate, and iii) alignment with unmet clinical need in Australian patients with the respective tumour types (see Table 4).

- 2.4 How larotrectinib will be used in clinical practice in the adult low frequency subgroup remains uncertain given there are effective therapies available in the last line treatment setting. The PSCR indicated the Sponsor was willing to work with the Department to reduce ambiguity around last line usage in the restriction. The ESCs considered how larotrectinib would be used in the adult low *NTRK* frequency subgroup in clinical practice was particularly uncertain, given the availability of effective later line treatment options for low *NTRK* frequency tumours and given there is limited evidence to support a treatment benefit of larotrectinib compared to these existing treatments. The ESCs considered that the clinical need for larotrectinib in this adult low *NTRK* frequency population before last-line therapy was less justifiable.
- 2.5 The requested PBS restriction for adult high frequency salivary gland cancer was broader than the subtype of MASC specified in the MBS item descriptor. MASC was also the most represented high frequency *NTRK* cancer occurring in adults in the larotrectinib single-arm studies (n=23). MASC is approximately only 4.5 % of salivary gland tumours¹, and the frequency of *NTRK* fusions in non-MASC salivary gland tumours is low². The PSCR indicated the Sponsor was willing to amend the PBS restriction for the adult high frequency subgroup to specify MASC.
- 2.6 The restrictions need to specify the relevant age ranges at treatment initiation to distinguish between the paediatric and adult subgroups (<18 and ≥18 years of age, respectively).
- 2.7 The resubmission positioned larotrectinib as first line treatment for the paediatric population and adult high frequency subgroups. The PBAC had previously advised that a criterion restricting treatment to patients with prior treatment or patients who are not suitable for other treatments (regardless of tumour type), should be included in the PBS restriction (paragraph 7.3, larotrectinib PSD, November 2020). The criterion “would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection” has previously been considered reasonable by PBAC (paragraph 7.5, larotrectinib PSD, November 2020). This may represent a scenario where larotrectinib may be used in an earlier or first line of treatment for locally advanced resectable paediatric cancer. Use of larotrectinib first, second or subsequent treatment would likely depend on the intent of the treatment such as reducing tumour bulk in the first line setting (paragraph 4.7, larotrectinib PSD, November 2020).
- 2.8 The continuation criterion in the requested restriction, that treatment “will be provided until the patient is no longer clinically benefiting from therapy or until

¹ Damjanov et al (2016). Mammary Analogue Secretary Carcinoma (MASC) of the salivary gland: A new tumor entity. *Bosnian journal of basic medical sciences*, 16, 237-238.

² Solomon et al (2020). *NTRK* fusion detection across multiple assays and 33,997 cases: diagnostic implications and pitfalls. *Modern Pathology* 33(1):38-46; Westphalen et al. (2021). Genomic context of *NTRK1/2/3* fusion-positive tumours from a large real-world population. *npj Precision Oncology* 5(1):69.

unacceptable toxicity occurs”, could be better phrased to state that subsidy is to cease upon disease progression as there may be various interpretations of ‘clinical benefit’ in practice (paragraph 2.6, Larotrectinib PSD – November 2020 PBAC Meeting). The PBAC also previously noted there was insufficient data to determine whether there was a treatment benefit for patients receiving larotrectinib following disease progression and considered that larotrectinib is unlikely to be cost-effective beyond disease progression (paragraph 7.5, larotrectinib PSD, November 2020).

- 2.9 An Eastern Cooperative Oncology Group (ECOG) performance score of 2 or less was specified only in the restriction for the adult low frequency subgroup. As there was limited evidence for all patients with an ECOG performance score of ≥ 3 (2% in the pooled larotrectinib dataset), the evaluation considered an ECOG performance status score of ≤ 2 would be appropriate for all of the target subgroups. The PBAC considered limiting to performance status score of ≤ 2 for the adult low frequency subgroup only was reasonable.
- 2.10 Non-PBS subsidised to PBS-subsidised supply transitioning arrangements (i.e. a ‘Grandfather clause’) were requested for < 500 patients currently receiving compassionate supply of larotrectinib through the Sponsor. The PBAC considered that the treatment duration under the grandfather restriction should be limited to 3 months (i.e., 2 repeats only) consistent with the proposed initial treatment restriction.
- 2.11 The previous submission proposed an individual utilisation based program (UBP) approach, consisting of a duration based cap, and subsequent additional rebate. The PBAC considered that the individual patient based RSA proposed was not a feasible method of achieving cost-effectiveness, noting that it may not be possible to share confidential patient level data with the sponsor to validate RSA rebates and that the cost-effective price would not be realised until larotrectinib had been listed for at least two years (paragraph 7.17 of the Larotrectinib PSD, November 2020). The resubmission did not propose an RSA but rather proposed an SPA with a 33.7% price reduction compared to the previous effective price. A further ■% responder-based rebate is also proposed for the first ■ months of initial scripts (described below).
- 2.12 The additional responder-based rebate for the first ■ months of initial scripts was proposed to mitigate the risk of false positive test results and other non-responders and was based on the overall response and patients with stable disease in the updated pooled data set, ePAS5 (non-primary CNS tumours). A total of ■% of patients either had progressive disease or were not evaluable in ePAS5. This rebate is reflected in the effective prices for the initiation pack. The resubmission did not clarify how the proposed progressive disease/non-evaluable rates from ePAS5 would mitigate the risk of false positives.

Table 2: Comparison of proposed effective prices in the previous and current submission

	Proposed effective AEMP	
	November 2020 submission	November 2021 resubmission
100 mg, oral capsules	\$ [REDACTED]	Initial scripts: \$ [REDACTED] Subsequent scripts: \$ [REDACTED]
25 mg, oral capsules	\$ [REDACTED]	Initial scripts: \$ [REDACTED] Subsequent scripts: \$ [REDACTED]
20 mg/ml, 1 × 100 ml bottle solution, oral administration	\$ [REDACTED]	Initial scripts: \$ [REDACTED] Subsequent scripts: \$ [REDACTED]

For more detail on PBAC’s decision, see section 7 PBAC outcome.

3 Background

Registration status

3.1 Larotrectinib was granted provisional approval by the TGA on 7 September 2020 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 ORR and duration of response from single-arm clinical studies. The sponsor is required to submit further clinical data to confirm the clinical benefit of the medicine. The above TGA indication aligns with the FDA approved indication³.

3.2 Regarding the positioning of larotrectinib in the clinical management algorithm of patients with *NTRK* fusions, a published international expert consensus⁴ recommended TRK inhibitors for patients with *NTRK* fusions during the course of therapy when no other satisfactory treatment options exist.

³ Larotrectinib for the treatment for *NTRK* fusion solid tumours was granted FDA accelerated approval on 26 November 2018 and EMA approval on 19 September 2019 for the treatment of solid tumours that have a *NTRK* gene fusion in adult and paediatric patients that are either metastatic or where surgical resection is likely to result in severe morbidity, and who have no satisfactory alternative treatments or whose cancer has progressed following treatment.

⁴ Ypshino et al (2020). JSCO-ESMO-ASCO-JSMO- TOS: international expert consensus recommendations for tumour-agnostic treatments in patients with solid tumours with microsatellite instability or *NTRK* fusions. *Annals of Oncology*. Volume 31, Issue 7.

Previous PBAC consideration

- 3.3 This is the second submission to list larotrectinib on the PBS for the targeted treatment of *NTRK* fusion solid 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.

A summary of PBAC concerns raised in the November 2020 larotrectinib PSD and how they were addressed in the resubmission are summarised with comments in Table 3.

Table 3: Previous PBAC concerns and how these were addressed in the resubmission

PBAC issue from November 2020 PSD	How the resubmission addressed it Comments
<p>Paragraph 7.3 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.</p> <p>Paragraph 5.7 The requested restriction for this subpopulation [adult low frequency] requires patients to be refractory to a prior therapy however permits use of larotrectinib in earlier treatment lines such as second-line.</p>	<p>Given the availability of effective treatment options for patients in this population, the proposed PBS restriction for adult low frequency tumours has been amended to R/R disease with no suitable alternate therapy.</p>
<p>Paragraph 2.6 The continuation criterion 'PBS-subsidised treatment with this drug for this condition will be provided until the patient is no longer clinically benefiting from therapy or until unacceptable toxicity occurs' should be amended to specify that patients must only be treated until disease progression as there may be various interpretations of 'clinical benefit' in practice.</p>	<p>This continuation criterion remained in the resubmission but with the added criterion "Patient must have demonstrated an adequate response to treatment with this drug".</p>
<p>Paragraph 5.7 For adult low frequency (representative tumours STS and CRC), the SoC comparators nominated in the submission for STS and CRC were dacarbazine and BSC, represented by trifluridine/tipiracil. The choice of these comparators was not reasonable as they are likely to favour larotrectinib.</p>	<p>Given the availability of effective treatment options for patients in this subpopulation (e.g. immunotherapies in NSCLC, multiple therapies in CRC) and the rarity of <i>NTRK</i>-fusions, the choice of comparators have been amended to reflect the new proposed PBS restriction i.e. R/R disease with no suitable alternate therapy.</p> <p>How larotrectinib will be used in clinical practice remains uncertain.</p>
<p>Paragraph 7.4 The PBAC further advised that specifying the names of the tumour types in the high and low frequency subgroups may reduce the risk of use beyond the intended populations. This may be particularly important for the adult populations if adult patients with low frequency <i>NTRK</i> fusion tumours remain ineligible for PBS subsidy.</p>	<p>Updated restriction criteria to reflect PBAC advice by specifying the names of each tumour type in the high and low adult frequency subgroups.</p>

Public Summary Document – November 2021 PBAC Meeting with March 2022
Addendum

PBAC issue from November 2020 PSD	How the resubmission addressed it Comments
<p>Paragraph 7.11 The PBAC agreed with the ESCs that paediatric STS was misclassified in the submission as a representative tumour type in the paediatric high frequency <i>NTRK</i> fusion subpopulation noting that studies in the literature reported a prevalence of <i>NTRK</i> fusions of <5% for various paediatric STS.</p>	<p>The sponsor acknowledged that paediatric STS is a low-<i>NTRK</i> frequency tumour and noted the lack of comparator data for IFS, and maintained that its inclusion as a proxy in this population is appropriate. Implications of lower prevalence (0.68%) of <i>NTRK</i> in paediatric STS were considered in the economic evaluation. For the paediatric population overall, this analysis was considered informative.</p>
<p>Paragraph 7.12 The PBAC considered the claim of superior effectiveness compared to SoC was likely acceptable for the high frequency adult and paediatric populations, but the magnitude of the benefit was uncertain due to issues around the larotrectinib trial data and applicability of the data presented for SoC to current SoC, and the uncertainties around the naïve indirect comparisons. The PBAC considered that the efficacy results from the SoC data was unlikely to reflect that of current clinical practice given the inclusion of historic studies and studies which did not include the most effective therapy for the treatment setting.</p>	<p>While the uncertainties relating to the naïve indirect comparisons are acknowledged, the sponsor maintained this is the most appropriate methodology to compare the efficacy and safety of larotrectinib to SoC given the single-arm nature of the larotrectinib trials and the lack of data specific to <i>NTRK</i> fusions in the SoC arms. Nominated comparators in the original submission for high frequency adult and both paediatric populations reflect current SoC and the proposed line of therapy for larotrectinib and thus remain unchanged in the resubmission. These concerns remain outstanding.</p>
<p>Paragraph 7.12 The PBAC considered the claim of superior effectiveness compared to SoC for the low frequency adult and paediatric populations was not sufficiently supported.</p>	<p>Two additional comparators for thyroid and lung tumours were included for the adult low frequency population. The claim of superiority for the low frequency subgroups was not sufficiently supported. Noteworthy is that the clinical need is higher in the paediatric population as these paediatric cancers are rare and available therapies are limited. There is also a high clinical need in paediatric patients for therapies other than current SoC which primarily consists of cytotoxic chemotherapy.</p>
<p>Paragraph 7.20 The PBAC also requested the Department approach the Sponsor to seek a suitable price reduction for larotrectinib (para. 7.1 larotrectinib November 2020 PSD). The PBAC considered that the price reduction could be achieved through either a SPA or an alternative means such as an RSA which does not impose an unnecessary administrative burden or privacy issues.</p>	<p>The Sponsor proposed a revised SPA (33.7% reduction compared to previous effective price) with a further ■% price reduction proposed on initial scripts (estimated based on responders in the pooled analyses).</p>
<p>Paragraph 7.23 The PBAC advised that any further consideration of listing larotrectinib for adult patients with low <i>NTRK</i> fusion frequency tumours would need to be through a future major resubmission which includes the forthcoming data from NAVIGATE and MoST trials to address the uncertainty of the treatment effect of larotrectinib in this patient population with modified cost-effectiveness analyses incorporating more conservative assumptions and a price reduction.</p>	<p>Updated data across the larotrectinib trials (ePAS5+SAS3 – July 2020 data cut-off) are provided with two additional comparators for adult low frequency <i>NTRK</i> tumours (thyroid and lung). The uncertainty of the incremental benefit of larotrectinib remains outstanding particularly for the adult low frequency subgroup. The resubmission noted that updated data from MoST were not available. Conservative extrapolations were not chosen for the larotrectinib tumour type subgroup analyses.</p>

PBAC issue from November 2020 PSD	How the resubmission addressed it Comments
<p>Paragraph 7.20 The PBAC advised that a price reduction for adult patients with high frequency <i>NTRK</i> fusion tumours and all paediatric patients should be of a magnitude sufficient to achieve an ICER within the range of \$70,000/QALY to \$80,000/QALY. The PBAC advised that the adjustments to the economic analysis, as specified in paragraph 6.73 to account for the uncertainties of the larotrectinib data, should be used to determine the magnitude of price reduction required.</p> <p>Paragraph 6.73 The PBAC noted that the resulting ICER for the combined high <i>NTRK</i> fusion frequency population was \$155,000 to < \$255,000 /QALY when i) the most conservative OS and PFS extrapolations; ii) an <i>NTRK</i> fusion frequency of 0.68% for paediatric STS and; iii) exclusion of the RSA rebate was applied in the economic analysis.</p>	<p>The changes described in ii) and iii) of paragraph 6.73 have been adopted in the resubmission's base case. When the additional changes have been accounted for, the ICER for adult patients with high frequency <i>NTRK</i> fusion tumours and all paediatric patients is within the requested range of \$70,000/QALY to \$80,000/QALY requested. This was achieved in part through a price reduction, but also with the presentation of updated data. The updated data, however, lead to substantial differences in the long term modelled estimates.</p>
<p>Paragraph 7.17 The 20-year time horizon used in the economic analysis is substantially longer than the median duration of follow-up (16 months) in the pooled larotrectinib analysis.</p>	<p>To mitigate this uncertainty, the time horizon in the model base-case was amended to 15 years. The 15 year time horizon remains longer than the median duration of follow-up in the larotrectinib studies (2 years). In adult tumour types that have a low frequency of <i>NTRK</i> fusions a shorter time horizon (5 years) may be more appropriate.</p>

Source: Table ES 1 page 2 of the resubmission and the larotrectinib PSD November 2020 (Additional concerns to Table ES1 of the resubmission were incorporated from the PSD).

BSC = best supportive care; CRC = colorectal cancer; ECOG = Eastern Cooperative Oncology Group; ePAS = extended primary analysis set; ESCs = Economics and Evaluation Subcommittees; *NTRK* = neurotrophic tyrosine receptor kinase; NSCLC = non-small cell lung cancer; OS = overall survival; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; P_fP = pay for performance; PFS = progression-free survival; PSD = public summary document; R/R = relapsed/refractory; RSA = risk-share arrangement; SAS = supplemental analysis set; SoC = standard of care; SPA = special pricing arrangement; STS = soft tissue sarcoma; ToT = time on treatment; WHO = World Health Organization

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

4 Population and disease

- 4.1 *NTRK* gene fusions occur in <5% of most solid tumour types, both common (such as lung cancer, breast cancer, melanoma, prostate cancer and CRC) and less common (thyroid cancer, pancreatic cancer, bone carcinomas and hepatic cancer). CNS tumours (mainly brain tumours) account for the largest number of cancer deaths for children in Australia with the frequency of *NTRK* fusions in CNS/glioma tumours being estimated at 2.2%. However, in some rare solid tumour types, such as MASC, SBC, infantile fibrosarcoma (IFS) and congenital mesoblastic nephroma (CMN), *NTRK* gene fusions are found at frequencies above 75%⁵.

⁵ Hsiao SJ, Zehir A, Sireci AN, Aisner DL. Detection of Tumor *NTRK* Gene Fusions to Identify Patients Who May Benefit from Tyrosine Kinase (TRK) Inhibitor Therapy. *The Journal of Molecular Diagnostics*. 2019;21(4):553-71

- 4.2 Consistent with the previous submission and the PICO Advisory Sub-Committee (PASC) recommendations, four subpopulations based on age (adult and paediatric patients) and *NTRK* fusion frequency were proposed in the resubmission.
- 4.3 **Paediatric high-frequency *NTRK* fusions (no treatment line specified):** Based on the most recent data cut-off of July 2020, there were 62 IFS and STS patients (patient numbers were not provided separately for IFS and STS) included from the larotrectinib studies. As no SoC data were identified for IFS in both the previous and current submissions, for the indirect comparison, paediatric IFS and STS patients were combined in the larotrectinib arm and compared with historical SoC data for non-IFS STS tumours.
- 4.4 The resubmission recognised that the prevalence of the *NTRK* fusion oncogenic driver mutations in STS is likely to be low. The PBAC previously noted that i) it was not possible to exclude the paediatric STS data from the analysis of the paediatric high frequency *NTRK* fusion subpopulation based on the available data , and ii) excluding STS from the analysis of the high frequency paediatric population was not possible as the Kaplan-Meier data included in the submission combined both paediatric STS with the IFS patients, and so the individual patient level data would be required to generate the new Kaplan-Meier curves (which would then require extrapolation).
- 4.5 **Adult high-frequency *NTRK* fusions (no treatment line specified):** The representative tumour type for this subpopulation remains MASC (a type of salivary gland tumour) as in the previous submission. A total of 23 patients with MASC were used from the larotrectinib studies in the indirect comparison. Two tumour types were specified in the requested restriction of the resubmission: salivary gland (amended to MASC in the PSCR) and SBC tumours.
- 4.6 **Paediatric low frequency *NTRK* fusions (no treatment line specified):** As in the previous submission, the representative tumour type for this subpopulation is primary central nervous system (CNS) tumours/glioma. A total of 26 patients with a primary CNS tumour were used from the larotrectinib studies in the indirect comparison. Of these, the most commonly diagnosed tumour subtype was glioblastoma multiforme (GBM), which is a grade IV tumour.
- 4.7 **Adult low-frequency *NTRK* fusions (refractory line specified):** The resubmission specified four tumour types in the requested restriction: adult STS; CRC; thyroid cancer, and NSCLC. Indirect comparisons were conducted for each of these tumour types. The resubmission noted that *NTRK* fusions have been extensively characterised in CRC and it is likely that *NTRK* fusion testing may be more prevalent in this cancer type. Table 4 reports the proportion of patients with diverse solid tumours that were treated with larotrectinib and had a response. The response rate varied from 37.5-86.7% in the four tumour types proposed for PBS listing.

Table 4: Summary of larotrectinib efficacy, based on tumour types by primary diagnosis, in the adult low NTRK fusion frequency subgroup

Adult low <i>NTRK</i> frequency tumour assessed in the larotrectinib studies	<i>NTRK</i> frequency (epidemiology)	Number of patients within adult low frequency subpopulation in pooled trial analysis set (ePAS5+SAS3 New, N) Most recent data cut-off July 2020	Overall response rate (ORR) ^a n (%)
Adult STS	1.40%	23	12 (52.2)
Lung	0.23%	15	13 (86.7)
Colorectal	0.30%	8	3 (37.5)
Thyroid	3.65%	28	18 (64.2)
Melanoma	0.34%	7	3 (42.9)
GIST	2.20%	4	4 (100)
Pancreas	0.75%	2	0
Adult bone sarcoma	1.24%	2	1 (50)
Cholangiocarcinoma	0.26%	2	0
Appendix	0.58%	1	0
Hepatic	1.24%	1	0
Prostate	0.24%	1	0
Adult CNS	2.20%	7	0

Source: Table 1.4, p37 of the resubmission.

^a Overall response rate (%): the proportion of patients with best overall response in the adult low frequency subpopulation based on IRC assessments.

CR, complete response; CRC, colorectal cancer; CNS, central nervous system; GIST, gastrointestinal stromal tumours; IRC, institute review committee; NE, not evaluable; *NTRK*, Neurotrophic tropomyosin receptor kinase; STS, soft tissue sarcoma; ePAS, extended primary analysis set; SAS, supplementary analysis set

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

5 Comparator

- 5.1 The nominated representative comparators in the resubmission were unchanged from the original submission for the paediatric population (both high and low frequency tumour subgroups) and the adult high frequency subgroup.
- 5.2 For the adult low frequency subgroup, new comparators were added for the specified NSCLC (docetaxel and placebo) and thyroid cancer (lenvatinib) tumours. The nominated comparator for CRC in the resubmission is now the trifluridine/tipiracil (TT) arm, rather than the placebo arm in the previous submission, from the same historical study. The comparators for adult STS (dacarbazine or BSC) remain the same. The ESCs considered these comparators represented current SoC in the last treatment line setting where larotrectinib is intended to be used for adult low frequency tumours. Lenvatinib is a reasonable second line comparator for progressed thyroid cancer, with subsequent treatment options limited.
- 5.3 Table 5 summarises the SoC comparators nominated in the resubmission, by subgroup, representative tumour type, SoC study population and line of therapy.

Table 5: SoC comparators by subgroup, representative tumour type, SoC study population and line of therapy

Population sub-group	Representative/ specified tumour type	SoC (single-arm)	Study	Line of therapy/population	Outstanding/new limitations
Paediatric high <i>NTRK</i> fusion frequency	Infantile fibrosarcoma	VAC	None identified in the submission	-	
	Soft tissue sarcoma	Ifosfamide + doxorubicin	Sandler 2001	First line Metastatic (Stage 4) rhabdomyosarcoma patients (aged <21 years)	The treatment of sarcoma is complex with combined modality therapy. Sandler study is >2 decades old. Survival with old SoC may not reflect survival with current SoC.
		Irinotecan + Vincristine ^a	Mascarenhas 2010	Later line Progressed rhabdomyosarcoma	
Adults high <i>NTRK</i> fusion frequency	Salivary gland	Cisplatin + vinorelbine	Airoldi 2001	First line Between April 1993 and February 1997, 36 patients (aged >20 years) were entered into the study ^b .	Old study (> two decades old) may not reflect survival with current SoC. MASC was the salivary gland subtype included in the larotrectinib studies whereas for this study, MASC was not recognised as a distinct form of salivary gland carcinoma ^e . MASC represents 4.5 % of salivary gland tumours.
Paediatric low <i>NTRK</i> fusion frequency	CNS/glioma	TMZ ^c	Grill 2018	First line Patients aged between 3 and 18 with localised, centrally neuropathology-confirmed, non-brainstem high grade glioma (HGG) ^c .	
		Lomustine	Wick 2017	Later line Between November 2011 through to December 2014, adult ^d patients aged >21 years with progressed glioblastoma received lomustine alone or lomustine + bevacizumab over a period of 37 months	Applicability issue. This study was in adults (used in the resubmission as a proxy for paediatric patients).

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Population sub-group	Representative/ specified tumour type	SoC (single-arm)	Study	Line of therapy/population	Outstanding/new limitations
Adults low <i>NTRK</i> fusion frequency	Soft tissue sarcoma	Dacarbazine	Schöffski 2016	Later line (not specified as last line). Patients aged ≥18 years with locally recurrent, advanced, or metastatic liposarcoma (de-differentiated, myxoid or round-cell, or pleomorphic liposarcoma) or leiomyosarcoma. For eligibility, patients were required to have disease that was not amenable to curative surgery or radiotherapy	Eribulin (available on the PBS for liposarcoma ^f), was determined by the PBAC to provide, for some patients, a significant improvement in efficacy over dacarbazine (paragraph 7.2, eribulin PSD, November 2016).
		Placebo/ BSC	van der Graaf 2012 (PALETTE)	Later/last line. Patients with metastatic non-adipocytic soft-tissue sarcoma after failure of standard chemotherapy. Patients were randomly assigned to receive pazopanib (n=246) or placebo (n=123).	56% had received ≥2 lines of therapy, and 21% had received ≥3 lines of therapy. Should earlier use of larotrectinib occur, placebo would not be an appropriate comparator.
	Colorectal carcinoma	BSC represented by TT	Mayer 2015	Last line. Patients >27 years with refractory metastatic colorectal cancer or who had had clinically significant adverse events that precluded the re-administration of prior therapies	Comparators appear to be reasonable for the last line/BSC for heavily pre-treated patients.
	Non-small cell lung cancer	Docetaxel	Borghaei 2015 (CheckMate 057)	Second line Patients with non-squamous NSCLC that had progressed during or after platinum-based doublet chemotherapy Randomised to receive nivolumab (N=292) or docetaxel (N=290)	
		BSC (placebo)	Shepherd et al (2005)	Last line NSCLC Patients ≥18 years of age, ECOG PS between 0 and 3, and	

Population sub-group	Representative/ specified tumour type	SoC (single-arm)	Study	Line of therapy/population	Outstanding/new limitations
				had to have received one or two regimens of combination chemotherapy and not be eligible for further chemotherapy.	
	Thyroid	Placebo/ BSC Lenvatinib	Schlumberger 2015 (SELECT)	Second/last line. Patients with progressive thyroid cancer that was refractory to iodine-131 randomised to lenvatinib (N=261) or placebo (N=131).	Appears reasonable for this tumour type. Those with differentiated thyroid cancer who develop relapsed/refractory disease can be treated with PBS-subsidised lenvatinib or chemotherapy where lenvatinib is contraindicated

Sources: Individual CSRs for the larotrectinib studies, publications for SoC comparator studies and Section 2D.4 of the submission.

Shaded: SoC studies previously considered by PBAC (Larotrectinib PSD, November 2020 PBAC Meeting).

^aTwo treatment schedules of I+V: regimen 1A included irinotecan 20 mg/m²/day IV for 5 days at weeks 1, 2, 4, and 5 with vincristine 1.5 mg/m² administered IV on day 1 of weeks 1, 2, 4, and 5; regimen 1B included irinotecan 50 mg/m²/day intravenously for 5 days at weeks 1 and 4 with vincristine as in regimen 1A. Disease response was assessed at week 6. Those with responsive disease continued to receive 44 weeks of multi-agent chemotherapy that incorporated the assigned I+V regimen. Only Regimen 1B was considered in the indirect comparison.

^bRecurrent malignancy of major (parotid, submandibular, sublingual) or minor (hard palate, buccal mucosa, base of tongue, floor of mouth, paranasal sinus, nasopharynx, retromolar trigone, or other) salivary gland origin and one of the following histologies: adenoid cystic carcinoma, malignant mixed carcinoma, adenocarcinoma, or poorly differentiated mucoepidermoid carcinoma.

^cStudy aimed to evaluate the efficacy and safety of adding bevacizumab to postoperative radiotherapy + temozolomide (RT+TMZ+BEV) in in these patients.

^dStudy conducted in adult patients – used as a proxy as paediatric studies were not identified

^eSkálová A, Vanecek T, Majewska H, Laco J, Grossmann P, Simpson RH, et al. Mammary analogue secretory carcinoma of salivary glands with high-grade transformation: report of 3 cases with the ETV6-NTRK3 gene fusion and analysis of TP53, β-catenin, EGFR, and CCND1 genes. *The American journal of surgical pathology*. 2014;38(1):23-33.

^fThe Surveillance, Epidemiology, and End Results (SEER) Program indicated the most common sarcomas were liposarcomas (17.1%), leiomyosarcomas (13.6%), and malignant fibrous histiocytoma (8.2%). – Refer to Paragraph 4.1, eribulin PSD, November 2016.

BSC = best supportive care (TT=Trifluridine with tipiracil also known as TAS-102); CNS = central nervous system; NTRK = tropomyosin receptor kinase; PSD = public summary document; TMZ = temozolomide; VAC = vincristine, actinomycin D, and cyclophosphamide; I+V = irinotecan + vincristine

5.4 There were no comparator data by tumour type, or by the proposed subgroups for listing, in *NTRK* fusion patients. Some additional SoC therapies used in the later-line setting were selected for some tumour types to match the refractory population in the larotrectinib studies.

5.5 Concerns relating to the SoC comparators, nominated for the proposed four subgroups for listing, largely remain the same as those raised for the previous submission. These concerns 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 (paragraphs 5.2-5.8, larotrectinib PSD, November 2020). A summary is provided below.

5.6 **For paediatric high fusion frequency**, the key issues were that 1) there were no SoC data identified for IFS and thus a comparison with paediatric STS (generally consisting

of low frequency tumour types) had to be conducted, and 2) the SoC data for STS were sourced from a study more than two decades old⁶ which was unlikely to represent current SoC treatment outcomes. With the exclusion of paediatric STS, there are no available SoC data for paediatric high fusion frequency tumours (paragraph 5.4, larotrectinib PSD, November 2020).

- 5.7 **For paediatric low frequency** (representative tumour CNS/glioma), a SoC study conducted specifically in adults with progressive glioblastoma⁷, was included as a proxy for SoC in paediatric CNS in a later-line setting, as other studies were not identified. This may not be conservative and the comparator study has limited applicability.
- 5.8 **For adult high frequency** (specified tumour types MASC and SBC, representative tumour type MASC), there are applicability concerns with the SoC study which was conducted more than two decades ago (Airoldi 2001), and therefore may not represent survival outcomes associated with current SoC. Furthermore, MASC was also not recognised as a distinct form of salivary gland carcinoma. MASC makes up approximately 4.5 % of salivary gland tumours⁸⁹.
- 5.9 **For adult low frequency**, 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.

These comparators and their corresponding studies in the resubmission 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. In addition, both the previous and current submissions did not fully address the possible implications of the co-occurrence of other predictive biomarkers in *NTRK* fusion positive tumours for other targeted treatment options.

As for the previous submission, for STS, the SoC study compared dacarbazine with eribulin in patients with advanced STS¹⁰. However, eribulin was determined to be superior to dacarbazine in terms of OS benefit, which formed the clinical basis for

⁶ Sandler E *et al.* Efficacy of ifosfamide and doxorubicin given as a phase II “window” in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group. *Medical and Pediatric Oncology: The Official Journal of SIOP—International Society of Pediatric Oncology (Société Internationale d’Oncologie Pédiatrique)*. 2001;37(5):442-8.

⁷ Wick W *et al.* Lomustine and bevacizumab in progressive glioblastoma. *New England Journal of Medicine*. 2017;377(20):1954-63.

⁸ Luk PP, Selinger CI, Eviston TJ, Lum T, Yu B, O’Toole SA, *et al.* Mammary analogue secretory carcinoma: an evaluation of its clinicopathological and genetic characteristics. *Pathology*. 2015;47(7):659-66.

⁹ Majewska H, Skalova A, Stodulski D, Klimkova A, Steiner P, Stankiewicz C, *et al.* Mammary analogue secretory carcinoma of salivary glands: a new entity associated with ETV6 gene rearrangement. *Virchows Arch*. 2015;466(3):245-54.

¹⁰ Schöffski P *et al.* Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial. *The Lancet*. 2016;387(10028):1629-37

listing eribulin on the PBS for liposarcoma, a common STS subtype¹¹. Therefore, at least for liposarcoma, eribulin may be a more reasonable comparator.

- 5.10 Aside from concerns relating to the age and applicability of the SoC studies, the ESCs noted there remained high heterogeneity in efficacy outcomes within and between specific tumour types, treatment lines, and types of SoC therapy. This is reflective of clinical heterogeneity by disease site/histology, tumour type, other clinical patient characteristics, and different treatment options and corresponding efficacy by treatment line. The SoC data included in the resubmission may not reliably inform any incremental benefit of larotrectinib.

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

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item and provided a written statement from a clinician which was specific to use of larotrectinib in sarcomas harbouring *NTRK* fusions. The clinician noted that *NTRK* fusions are characteristic in certain subtypes of sarcomas such as infantile fibrosarcoma. The clinician described results from Demetri et al., 2019 of patients with *NTRK* fusion sarcomas treated with larotrectinib from the three larotrectinib trials LOXO-001, NAVIGATE, and SCOUT. The clinician noted that the objective response rate and median overall survival in Demetri et al., 2019 of 88% (95% CI:77, 94) and 44.4 months respectively, was higher than that previously observed for doxorubicin (18% - 23%, approximately 24 months median overall survival) in patients with metastatic soft-tissue sarcoma. The clinician considered it would be appropriate to position larotrectinib as first-line therapy for soft-tissue sarcoma on the basis of the benefit observed. The clinician indicated that first-line combination chemotherapy with doxorubicin and ifosfamide would likely have a substantially smaller benefit compared with larotrectinib for soft-tissue sarcoma and would be associated with costs due to inpatient management of ifosfamide and greater toxicities compared to larotrectinib.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from health care professionals (3) and organisations (2) via the Consumer Comments facility on the PBS website. The comments noted that most treatment with larotrectinib in Australia to date has been in paediatric patients with unresectable tumours. The comments highlighted the high response rates and tolerability of larotrectinib and that treatment with larotrectinib

¹¹ Soft tissue sarcomas are rare malignancies. There are more than 50 histological subtypes of sarcoma, with US data from the Surveillance, Epidemiology, and End Results (SEER) Program indicating the most common sarcomas were liposarcomas (17.1%), leiomyosarcomas (13.6%), and malignant fibrous histiocytoma (8.2%). Source: Paragraph 4.1, Eribulin Public Summary Document –November 2016 PBAC Meeting.

has resulted in several paediatric patients avoiding disfiguring surgery and ongoing cytotoxic chemotherapy.

- 6.3 One of the comments from a clinician involved in the ongoing MoST study, indicated that the MoST study may only identify a small number of additional individuals with *NTRK* fusion tumours. The clinician indicated that based on experience to date, there would likely be tumour types identified which are not included in those proposed for PBS listing. The clinician considered that patients with tumour types outside of those proposed for listing would still benefit from treatment with larotrectinib and that the total number of this population would likely be similar to that of the population proposed for listing.
- 6.4 The Spark of Gold alliance and the Zero Childhood Cancer program supported listing larotrectinib on the PBS for the treatment of patients with *NTRK* fusion solid tumours. The Spark of Gold alliance emphasised that there are significant barriers and challenges for paediatric cancer patients in terms of accessing novel targeted therapies as it is often difficult to obtain evidence of efficacy through randomised trials due to the rarity of certain paediatric cancers. The Spark of Gold alliance noted that subsidy of larotrectinib through the PBS would allow further evidence of its efficacy and safety to be collected in the clinical setting. The Zero Childhood Cancer program noted that current standard of care chemotherapy is associated with acute and long term effects which reduce patients' quality of life. The Zero Childhood Cancer program described benefits of treatment with larotrectinib for paediatric and adolescent patients including stabilising disease and increasing survival, minimal toxicity, improved quality of life and reduced hospitalisation as a result of fewer side-effects. The Zero Childhood Cancer program referred to unpublished results from the program noting that of the < 500 patients with *NTRK* fusion cancers identified from approximately 500 to < 5,000 patients screened, < 500 have had a clinical response to larotrectinib.
- 6.5 The Medical Oncology Group of Australia (MOGA) also 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 pooled analysis of the single-arm LOXO-001, NAVIGATE, and SCOUT 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)¹².

Overview of the evidence base

- 6.6 The approach taken in the resubmission is to present evidence that *NTRK* fusion testing (FISH or NGS ± IHC) plus larotrectinib is superior to no *NTRK*-testing plus SoC in terms of efficacy and safety, in the proposed testing and treatment population.

¹² Cherny NI, Dafni U, Bogaerts J, et al: ESMO-Magnitude of Clinical Benefit Scale version 1.1. *Annals of Oncology* 28:2340-2366, 2017

Table 6: Summary of the linked evidence approach

	Type of evidence supplied	Extent of evidence supplied
Accuracy and performance of the test (analytical validity)	DNA- vs RNA-NGS: 4 comparative studies FISH vs RNA-NGS: 1 comparative study IHC vs FISH: 2 comparative studies IHC vs RNA-NGS: 3 comparative studies 2 case-control studies IHC vs DNA-NGS: 1 case-control study IHC positive vs RNA-NGS or FISH: 6 cohort studies	<input checked="" type="checkbox"/> k=4; n=34,807 <input checked="" type="checkbox"/> k=1; n=44 <input checked="" type="checkbox"/> k=2; n=75 <input checked="" type="checkbox"/> k=5; n=4,982 <input checked="" type="checkbox"/> k=1; n=78 <input checked="" type="checkbox"/> k=6; n=13,470
Prognostic evidence	<i>NTRK</i> fusion positive cancers: 2 prospective case-control studies, 2 retrospective cohort studies and 1 retrospective case-control study Trk IHC positive cancers: 3 retrospective cohort studies and 1 retrospective case-control study	<input checked="" type="checkbox"/> k=5 n=5,345 <input checked="" type="checkbox"/> k=4 n=858
Change in patient management	No evidence provided	<input type="checkbox"/> k=0
Treatment effectiveness		
Predictive effect (treatment effect variation)	[Comparison of outcomes in patients with and without the biomarker who receive the medicine or its comparator]	<input type="checkbox"/> k=0 n=0
Treatment effect (enriched)	[Single randomised controlled trial of medicine vs usual care in patients that are test positive in both arms]	<input type="checkbox"/> k=0 n=0
Naïve indirect comparison	[<i>NTRK</i> fusion positive patients from 3 single-arm larotrectinib studies and SoC patients, regardless of <i>NTRK</i> fusion status, from single arms of 11 historical studies] Naïve indirect comparison was between updated pooled data from three single-arm larotrectinib studies (ePAS5 and SAS3 New) and single-arm SoC data	<input checked="" type="checkbox"/> k=3 n=225 <input checked="" type="checkbox"/> k=11 n=2,356 Population 1: n= 62 vs 199 Population 2: n= 23 vs 20 Population 3: n= 26 vs 208 Population 4: n= 74 vs 1,929

Source: Sections 2B and 2D of the previous submission and the resubmission, as well as additional data identified during evaluation. New data sources in the resubmission and the commentary have been underlined.

k = number of studies, n = number of patients; Population 1=Paediatric high frequency; Population 2=Adult high frequency; Population 3=Paediatric low frequency; Population 4=Adult low frequency.

ePAS5 includes paediatric and adult tumour types other than primary CNS with documented *NTRK* fusion (N=192, median follow-up for overall survival 24 months compared to 15.8 months for the ePAS4 (N=164) in the previous submission; SAS3 New includes paediatric and adult primary CNS patients with documented *NTRK* fusion tumours (N=33; median follow-up for overall survival 16.5 months compared to 6 months for the SAS3 (N=24) in the previous submission)

ePAS, extended primary analysis set; k, number of studies, n, number of patients; SAS, supplementary analysis set.

6.7 The resubmission presented evidence as outlined in Table 7.

6.8 The PBAC previously considered that additional data from the ongoing NAVIGATE and MoST trials would be useful for assessing the overall efficacy of larotrectinib in the adult low frequency *NTRK* fusion subpopulation (paragraph 7.13, larotrectinib PSD, November 2020). Additional data were provided for NAVIGATE. However, no

published data was identified in the resubmission for the MoST study and there was insufficient information in the public domain on the status of the MoST substudy¹³.

- 6.9 As in the previous submission, the evidence to support the comparative clinical benefit of larotrectinib was based on a naïve indirect comparison between updated pooled data from the same single-arm larotrectinib studies in the previous submission (LOXO-001, NAVIGATE, and SCOUT) and SoC data from historical single-arm studies. The justification provided in the resubmission for using pooled larotrectinib data was because of “the small patient numbers in each individual trial and to increase statistical validity of the results”. The updated pooled data included in the resubmission was based on a more recent data cut-off, July 2020 (July 2019 cut-off in the previous submission).
- 6.10 There were an additional 23 and 29 patients from NAVIGATE (n=139) and SCOUT (n=108), respectively, in the July 2020 cut-off compared to the July 2019 cut-off. No additional patients were included from the previous data cut-off for LOXO-001.
- 6.11 Pooled analysis across LOXO-001, NAVIGATE, and SCOUT – An updated extended primary analysis set (ePAS5, N=192; median follow-up for OS 24 months compared to 15.8 months for the ePAS4 dataset) and an updated supplementary analysis set (SAS3) (henceforth referred to as “SAS3 New”, N=33; median follow-up for OS 16.5 months compared to 6 months for the previous SAS3 dataset) were presented in the resubmission based on the most recent data cut-off (July 2020). The presentation of separate pooled analyses of efficacy by CNS status (ePAS5 included all tumour types except for primary CNS and SAS3 New which only included primary CNS tumours) appears inconsistent with the site agnostic listing proposal for larotrectinib.

The tumour types included in the updated pooled larotrectinib analysis sets are summarised in Table 8. The pooled datasets in the previous submission (July 2019 data cut-off) have been included for comparative purposes.

- 6.12 For the paediatric and the adult high frequency subgroups, the SoC studies remain the same as in the previous submission. For the adult low frequency subgroup, the resubmission specified four tumour types (CRC, NSCLC, STS, and thyroid tumours) in the requested restriction. Thus, additional SoC studies for this subgroup have been included in the resubmission.

¹³ Cancer Molecular Screening and Therapeutics (MoST) Program
<https://www.australianclinicaltrials.gov.au/anzctr/trial/ACTRN12619001147178>; Addendum 6 substudy 14-15:
Larotrectinib

Table 7: Data availability to inform comparisons

Proposed test vs alternate test	DNA-NGS vs RNA-NGS: 3 (<u>plus 1 new</u>) comparative studies FISH vs RNA-NGS: 1 comparative study IHC vs FISH: <u>2 comparative studies</u> IHC vs RNA-NGS: 1 (<u>plus 2 new</u>) comparative studies, 2 case-control studies IHC vs DNA-NGS: 1 case-control study IHC positive vs RNA-NGS or FISH: <u>6 cohort studies</u>	
	Proposed medicine	Comparator medicine
Biomarker test positive	LOXO-001, NAVIGATE, SCOUT single-arm studies (<u>updated data from NAVIGATE and SCOUT; July 2020 data cut-off</u>) Updated pooled data across the LOXO-001, NAVIGATE, and SCOUT studies bases on new July 2020 cut-off (<u>ePAS5 and "SAS New"</u>)	<u>Exploratory analysis in NTRK fusion patients (N=29) from a genomic database (VOYAGER) were presented but did not inform the economic evaluation</u>
Biomarker test negative	LOXO-001 and SCOUT single-arm studies (updated data from NAVIGATE and SCOUT; July 2020 data cut-off)	No evidence presented
Biomarker untested	No evidence presented	Sandler et al. (2001), Mascarenhas et al. (2010), Airoidi et al. (2001), Grill et al. (2018), Wick et al. (2017), Schöffski et al. (2016), <u>van der Graaf et al. (2012)</u> , Mayer et al. (2015), <u>Borghaei et al. (2015)</u> , <u>Shepherd et al. (2005)</u> , <u>Schlumberger et al. (2015)</u>

Source: Sections 2B and 2D of the previous submission and the resubmission, as well as additional data identified during evaluation. New data sources in the resubmission and the commentary have been underlined.

ePAS5 includes paediatric and adult tumour types other than primary CNS with documented *NTRK* fusion (N=192, median follow-up for overall survival 24 months compared to 15.8 months for the ePAS4 (N=164) in the previous submission; SAS New includes paediatric and adult primary CNS patients with documented *NTRK* fusion tumours (N=33; median follow-up for overall survival 16.5 months compared to 6 months for the SAS3 (N=24) in the previous submission)

ePAS = extended primary analysis set; k=number of studies, n=number of patients; SAS = supplementary analysis set.

Table 8: Primary diagnosis of patients (*NTRK* fusion positive tumours types) included in the pooled analyses from the larotrectinib studies (previous July 2019 and updated July 2020 data cut-offs)

Proposed subgroups	July 2019 data cut-off (Previous submission)		July 2020 data cut-off (Resubmission)	
	ePAS4 N = 164 n, (% of N)	SAS3 N = 24 n, (% of N)	ePAS5 N = 192 n, (% of N)	SAS3 New ^a N = 33 n, (% of N)
Adult high frequency <i>NTRK</i> tumours				
Salivary gland (MASC)	21 (13)	0	22 (10) ^a	0
Breast	5 (3)	0	7 (3)	0
Adult low frequency <i>NTRK</i> tumours				
Thyroid	27 (16)	0	28 (12)	0
Adult soft tissue sarcoma	17 (10)	0	23 (10)	0
Lung (NSCLC)	13 (8)	0	15 (7)	0
Colorectal	8 (5)	0	8 (4)	0
Melanoma	7 (4)	0	7 (3)	0
GIST	4 (2)	0	4 (2)	0
Adult bone sarcoma	2 (1)	0	2 (1)	0
Pancreas	2 (1)	0	2 (1)	0
Cholangiocarcinoma	2 (1)	0	2 (1)	0
Appendix	1 (1)	0	1 (0)	0
Hepatic	1 (1)	0	1 (0)	0
Cervix	0	0	1 (0)	0
Prostate	1 (1)	0	1 (0)	0
Adult CNS ^b	0	3 (12)	0	7 (21)
Paediatric high frequency <i>NTRK</i> tumours				
Infantile fibrosarcoma	32 (20)	0	40 (18)	0
Congenital mesoblastic nephroma	1 (1)	0	2 (1)	0
Paediatric soft tissue sarcoma (proxy) ^c	19 (12)	0	25 (11)	0
Paediatric low frequency <i>NTRK</i> tumours				
Paediatric bone sarcoma	0	0	0 (0)	0
Paediatric CNS ^b	0	21 (88)	0 (0)	26 (76)
Other				
Cancer of unknown primary	1 (1)	0	1 (0)	0

Source: Table 2.75, p225 of the resubmission.

^aThere were some inconsistencies in the number of patients with salivary gland tumours from the data in the resubmission: 22 in this table for ePAS5 (source Table 2.75, p225 of the resubmission), 25 (5 from LOXO-001 and 20 from NAVIGATE) in Table 129 of the Commentary (sources interim CSRs for LOXO-001 (Table 14.1.5.1, p17 of CSR "Cancer History by Dose Level", July 2020 cut-off) and NAVIGATE (Cohort 5, Table 14.1.2.1, July 2020 data cut-off) and 23 in the indirect comparison (Table 2.143, p348 of the resubmission).

^bGlioblastoma was the most prevalent subtype in patients with primary CNS tumour (n=7). This informed the comparator choice for CNS tumours in the resubmission

^cProxy as these tumours are actually low frequency tumours. As there were no comparator data for IFS, and only 2 patients with congenital mesoblastic nephroma, STS was included in this group as a proxy.

Notes: High frequency *NTRK* refer to cancer histologies where *NTRK* fusion occurs in $\geq 75\%$ of cancers of that histology. All other tumours, where *NTRK* frequency occur at frequencies below 75% are described as low frequency.

CNS = central nervous system; GIST = gastrointestinal stromal tumour; MASC = Mammary analogue secretory carcinoma; N/a = not

applicable; SAS = supplementary analysis set; ePAS = extended primary analysis set; STS = soft tissue sarcoma; CNS = central nervous system; GIST = Gastrointestinal Stromal Tumour; MASC = Mammary analogue secretory carcinoma; *NTRK* = Neurotrophic Tropomyosin-Related Kinase

6.13 The three larotrectinib studies had different designs/objectives, patient/disease characteristics. There was an indication of heterogeneity of treatment effects by tumour type (within and between the studies), although the small patient numbers hampered this assessment. The ESCs maintained the pooled results should be interpreted with caution. These issues, taken together with the limitations of the SoC data discussed previously, contributed to high uncertainty associated with the incremental benefit of larotrectinib.

Comparative effectiveness (based on linked evidence)

6.14 Details of the included studies in the submission for the naïve indirect comparisons are provided in the table below.

Table 9: Listing of the relevant studies included for the naïve indirect comparisons

Trial ID/First Author	Protocol title/ Publication title	Publication citation
LOXO-TRK-14001 (LOXO-001)	LOXO-TRK-14001 CSR: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumours Interim CSR. LOXO-TRK-14001 CSR: A Phase 1 Study of the Oral TRK Inhibitor LOXO-101 in Adult Patients with Solid Tumors Interim CSR. July 2020 Update. Hong D, Bauer T, Lee J, Dowlati A, Brose M, Farago A et al. Larotrectinib in adult patients with solid tumours: A multi-centre, open-label, phase I dose-escalation study.	February 2020. July 2020 Annals of Oncology. 2019;30(2):325-331
LOXO-TRK-14002 (LOXO-002 or NAVIGATE)	LOXO-TRK-15002 (NAVIGATE) CSR: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with <i>NTRK</i> Fusion-Positive Tumours Interim CSR LOXO-TRK-15002 (NAVIGATE) CSR: A Phase 2 Basket Study of the Oral TRK Inhibitor Larotrectinib in Subjects with <i>NTRK</i> Fusion-Positive Tumors. July 2020 update. Rosen E, Italiano A. et al.: Efficacy and safety of larotrectinib in patients with TRK fusion breast cancer. 2020 San Antonio Breast Cancer Virtual Symposium. Abstract PS11-06 Drilon A, Moreno V, et al. Efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion lung cancer.	February 2020 July 2020 February 2021. Annals of Oncology. 2020;31 (Supplement 4):S834.
LOXO-TRK-14003 (LOXO-003 or SCOUT)	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. Laetsch T, DuBois S, Mascarenhas L, Turpin B, Federman N, Albert C et al. Larotrectinib for paediatric solid tumours harbouring <i>NTRK</i> gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. DuBois S, Laetsch T, Federman N, Turpin B, Albert C, Nagasubramanian R et al. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas.	July 2020 The Lancet Oncology. 2018;19(5):705-714 Cancer. 2018;124(21):4241-4247
Pooled/combined	LOXO-TRK-14001, NAVIGATE and SCOUT pooled efficacy and safety analysis based on July 2019 interim data-cut	July 2019

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Trial ID/First Author	Protocol title/ Publication title	Publication citation
larotrectinib studies/exploratory analyses: LOXO-001, NAVIGATE, SCOUT	<p>LOXO-TRK-14001, NAVIGATE and SCOUT pooled efficacy and safety analysis based on July 2020 interim data-cut</p> <p>LOXO-TRK-14001, NAVIGATE and SCOUT pooled efficacy and safety analysis Statistical Analysis Plan.</p> <p>Bayer post-hoc analysis (data on file). Matching-Adjusted Indirect Comparison Applied to Treatment of <i>NTRK</i> Gene Fusion with Larotrectinib or Best Supportive Care from the Voyager-1 Study</p> <p>Drilon A, Laetsch T, Kummar S, DuBois S, Lassen U, Demetri G et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children.</p> <p>Hong D, DuBois S, Kummar S, Farago A, Albert C, Rohrberg K et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials</p> <p>Italiano A, Nanda S, Keating K, Childs B, Fellous M, Drillon A et al. Retrospective Analysis to evaluate the growth modulation index (GMI) as a measure of clinical activity of larotrectinib in adult and paediatric TRK fusion cancers.</p> <p>Drilon A et al. Activity and Safety of Larotrectinib in Adult Patients With TRK Fusion Cancer: An Expanded Data Set.</p> <p>Leyvraz S, Hyman D, Van Tilburg C, Albert C, Tan D, Georger B, et al. Durability of response with larotrectinib in adult and pediatric patients with TRK fusion cancer.</p>	<p>July 2020</p> <p>July 2020</p> <p>April 2021</p> <p>New England Journal of Medicine. 2018;378(8):731-739</p> <p>The Lancet Oncology. 2020; 21(4): 531-540</p> <p>Annals of Oncology (2019) 30 (suppl_5): v159-v193.</p> <p>American Society of Clinical Oncology (ASCO) Virtual Scientific Program, May 29–31, 2020</p> <p>Oncology Research and Treatment. 2020;43 (Supplement 1):204.</p>
Single-arm studies of SoC^a by the four subgroups proposed in the resubmission		
Subgroup 1: Paediatric tumour type with high <i>NTRK</i> fusion frequency		
<u>Representative tumour type - Soft tissue sarcoma</u>		
<p><u>SoC</u> Ifosfamide+doxorubicin Sandler (2001)</p> <p><u>SoC</u> Irinotecan + Vincristine Mascarenhas (2010)</p>	<p>Sandler E, Lyden E, Ruymann F, Maurer H, Wharam M, Parham D, Link M, Crist W. Efficacy of ifosfamide and doxorubicin given as a phase II “window” in children with newly diagnosed metastatic rhabdomyosarcoma: a report from the Intergroup Rhabdomyosarcoma Study Group.</p> <p>Mascarenhas L, Lyden ER, Breitfeld PP, Walterhouse DO, Donaldson SS, Paidas CN, Parham DM, Anderson JR, Meyer WH, Hawkins DS. Randomized phase II window trial of two schedules of irinotecan with vincristine in patients with first relapse or progression of rhabdomyosarcoma: a report from the Children's Oncology Group.</p>	<p>Medical and Paediatric Oncology. 2001 Nov;37(5):442-8.</p> <p>Journal of clinical oncology. 2010 Oct 20;28(30):4658</p>
<u>Representative tumour type - Infantile Fibrosarcoma</u>		
<p><u>SoC</u> VAC^b No study identified</p>	-	-
Subgroup 2 – Adult tumour type with high <i>NTRK</i> fusion frequency		
<u>Representative tumour type - Salivary gland</u>		
<p><u>SoC</u> Cisplatin + vinorelbine Airoldi (2001)</p>	<p>Airoldi M, Pedani F, Succo G, Gabriele AM, Ragona R, Marchionatti S, Bumma C. Phase II randomized trial comparing vinorelbine versus vinorelbine plus cisplatin in patients with recurrent salivary gland malignancies.</p>	<p>Cancer. 2001 Feb 1; 91(3):541-7.</p>
Subgroup 3: “Paediatric” tumour type with low <i>NTRK</i> fusion frequency		
<u>Representative tumour type - CNS/glioma</u>		

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Trial ID/First Author	Protocol title/ Publication title	Publication citation
SoC Temozolomide (> 3 years age) Grill (2018):	Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, Saran F, Le Deley MC, Varlet P, Morgan PS, Jaspan T. Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in paediatric patients with newly diagnosed high-grade glioma.	Journal of Clinical Oncology. 2018 Apr 1; 36(10):951-8.
SoC Lomustine Wick (2017): Adults ^c	Wick W, Gorlia T, Bendszus M, Taphoorn M, Sahm F, Harting I, Brandes AA, Taal W, Domont J, Idbaih A, Campone M. Lomustine and bevacizumab in progressive glioblastoma.	New England Journal of Medicine. 2017 Nov 16; 377(20):1954-63.
Subgroup 4 – Adult tumour type with low <i>NTRK</i> fusion frequency		
<u>Specified tumour type – Soft tissue sarcoma</u>		
SoC Dacarbazine Schöffski 2016	Schöffski P, Chawla S, Maki RG, Italiano A, Gelderblom H, Choy E, Grignani G, Camargo V, Bauer S, Rha SY, Blay JY. Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial.	Lancet. 2016. Apr 16;387(10028):1629-37.
SoC Placebo/BSC Van der Graaf 2012	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. May 16; 379: 1879–86
<u>Specified tumour type – Colorectal carcinoma</u>		
SoC Trifluridine/tipiracil Mayer 2015	Mayer RJ, Van Cutsem E, et al. A. Randomized trial of TAS-102 for refractory metastatic colorectal cancer.	New England Journal of Medicine 2015. May 14;372(20):1909-19
<u>Specified tumour type – NSCLC</u>		
SoC Docetaxel Borghaei 2015	Borghaei H, Paz-Ares L, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non–Small-Cell Lung Cancer.	New England Journal of Medicine. 2015. September 27;373:1627-39
SoC Placebo/BSC Sheperd 2005	Shepherd F, Rodrigues Pereira J, et al. Erlotinib in Previously Treated Non–Small-Cell Lung Cancer.	New England Journal of Medicine. 2005. July 14;353:123-32
<u>Specified tumour type – Thyroid</u>		
SoC Placebo/BSC Lenvatinib Schlumberger 2015	Schlumberger M, Tahara M, et al. Lenvatinib versus Placebo in Radioiodine Refractory Thyroid Cancer.	New England Journal of Medicine. 2015. February 12; 372:621-30

Source: Table 2.44, pp179-180 of the resubmission.

SoC = standard of care; BSC = best supportive care; CNS = central nervous system; NSCLC = non-small cell lung cancer; *NTRK* = tropomyosin receptor kinase; TMZ = temozolomide; VAC = vincristine, actinomycin D, and cyclophosphamide

Note: Tumour type representatives or exemplars were nominated for the subgroups and SoC studies provided for the exemplars to inform the comparative efficacy and safety for the subgroup of tumours they represent. For the adult high frequency subgroup, salivary gland was the exemplar for the salivary gland + secretory breast tumours. For the adult low frequency subgroup, four tumour types were specified and SoC evidence provided for each tumour type to inform the comparative effectiveness and safety of larotrectinib compared with SoC.

^aRegardless of whether the included studies were randomised, SOC data from these studies were essentially single arm in nature.

^bNo studies examining VAC in advanced unresectable population were identified in the submission

^cStudy conducted in adult patients – used as a proxy in the submission as paediatric studies were not identified

6.15 A naïve indirect comparison was presented between pooled larotrectinib data and SoC data from 11 single-arm studies in “representative tumour types” for the paediatric and adult high frequency subgroups (IFS/paediatric STS, CNS/glioma, salivary gland (MASC)), and in the four specific tumour types for the adult low frequency subgroup (STS, CRC, NSCLC, and thyroid cancer). The risk of bias was high across the body of the evidence.

6.16 The ESCs considered that for the larotrectinib evidence, the following specific concerns, raised in the November 2020 PBAC Meeting, remain:

- Pooling was conducted in the resubmission to address the limited reliability – however, interpreting the pooled results from the three different studies remained problematic.
- Unreliability of the data due to small patient numbers (despite the additional data provided in the resubmission), and apparent differences within and between the studies in terms of design, patient characteristics, and treatment outcomes. This limited reliability also hampered the assessment of whether the treatment effect was consistent across different tumour types.
- Subsequent therapies that were received by patients in the larotrectinib studies, post-progression, – to treat resistance mutations to larotrectinib –, may have contributed to gains in OS. Early clinical data suggest that target resistance mechanisms might be overcome by next generation TRK inhibitors, such as selitrectinib and repotrectinib (p27, Australian Public Assessment Report (AusPAR) for larotrectinib - PM-2019-03170-1-4, December 2020). Based on the July 2019 data cut-off (no data were provided for the July 2020 data cut-off with respect to subsequent therapies), there were 41% (15/36) of patients in NAVIGATE who were administered either selitrectinib or entrectinib post progression. This proportion in SCOUT was 9%. Second generation TRK inhibitors are not currently PBS-subsidised and thus any observed OS benefit in these studies may not be realised in Australian clinical practice. The PSCR contended that the impact of post-progression treatments in the larotrectinib trials is not expected to be significantly different to Australian practice. The PSCR noted that in the updated ePAS5+SAS3 data, only 1.8% (4/225), 11.6% (26/225) and 0.9% (2/225) of patients were treated post-progression, with entrectinib, selitrectinib and repotrectinib, respectively.
- NAVIGATE and SCOUT are ongoing open label studies. An applicability issue would arise if there is selective enrolment of patients over time, with highly responding tumour types, which may result in the distribution of tumour types which are not representative of Australian clinical practice.

6.17 OS and PFS outcomes by tumour type, were presented only for NAVIGATE. For LOXO-001, the number of participants by tumour type appears to be the same as for the previous data cut-off and remains too small to be informative (lung: 1; STS: 2; salivary: 3; thyroid: 4; GIST: 2; cancer of unknown origin: 1). Table 10 summarises the PFS results, by *NTRK* fusion status, from LOXO-001. OS results were not available in the resubmission. Table 11 and Table 12 summarise OS results from NAVIGATE and SCOUT, respectively.

Table 10: LOXO-001 - Progression-free survival in patients with and without *NTRK* fusion cancer

Status	<i>NTRK</i> fusion N = 13	Non- <i>NTRK</i> fusion N = 62	<i>NTRK</i> fusion N = 13	Non- <i>NTRK</i> fusion N = 62
	Previous submission (July 2019 data cut-off)		Resubmission (July 2020 data cut-off)	
Progression status ^{a,b}				
Progressed	4 (31%)	54 (87%)	6 (46%)	54 (87%)
Censored	9 (69%)	8 (13%)	7 (54%)	8 (13%)
Duration of PFS (months) ^{c,d}				
Median	NE	1.8	51.1	1.8
95% CI for median	9.9, NE	1.4, 1.9	10.9, NE	1.4, 1.9
Minimum, maximum	0.0+, 51.6+	0.0+, 25.2+	0.0+, 60.4+	0.0+, 25.2+
Duration of follow-up (months) ^{c,d}				
Median	38.9	25.2	51.5	25.2
Rate (%) of PFS (months) ^{c,d}				
6 months or more	100%	10%	100%	10%
95% CI	100%, 100%	2%, 19%	100%, 100%	2%, 19%
12 months or more	80%	5%	82%	10%
95% CI	55%, 100%	0, 12%	59%, 100%	0%, 12%

Source: Modified from Table 2.98, p161 of the resubmission.

Note: Based on Investigator assessment of response and on the subgroup of the Full Analysis Set with *NTRK* fusions. + denotes censored observation.

^a Based on investigator assessments using RECIST v1.1.

^b Status as of cut-off visit.

^c Estimate based on Kaplan-Meier method.

^d 95% CI was calculated using Greenwood's formula

CI = confidence interval; NE = Not estimable; *NTRK* = neurotrophic tropomyosin receptor kinase

Table 11: NAVIGATE July 2020 data cut-off: Summary of overall survival (all *NTRK* fusion cancers)

	NSCLC N = 18	Thyroid N = 23	Sarcoma N = 25	CRC N = 10	Salivary N = 20	Biliary N = 3	Primary CNS N = 8	Other N = 26	Uncon- firmed N = 6	Total N = 139
OS (months) ^a										
Median	40.7	NE	NE	29.4	NE	2.00	16.9	NE	20.8	NE
95% CI	40.7, NE	23.4, NE	NE	2.8, 36.5	38.7, NE	1.8, 33.4	8.9, 23.7	14.13, NE	12.0, 21.0	36.5, NE
Rate of OS for at least										
12 months	84.6	86.4	85.6	75.0	95.0	33.3	80.0	76.8	100	83.9
95% CI	51.2, 95.9	63.4, 95.4	61.5, 95.1	31.5, 93.1	69.5, 99.3	0.9, 77.4	20.4, 96.9	52.3, 89.7	NE	75.9, 89.5
18 months	84.6	77.3	85.6	75.0	89.7	33.3	30.0	62.8	66.7	75.8
95% CI	51.2, 95.9	53.7, 89.8	61.5, 95.1	31.5, 93.1	64.8, 97.3	0.9, 77.4	1.2, 71.9	36.0, 80.9	5.4, 94.5	66.5, 82.8
Follow-up time for OS (months)^b										
Median	16.2	27.3	26.7	7.8	31.3	NE	16.2	17.7	14.4	24.0
95% CI	6.5, 24.0	22.2, 28.5	15.2, 37.0	1.7, NE	22.3, 29.3	NE	3.2, NE	9.3, 28.1	0.49, NE	20.0, 27.3
Min, max	0.0, 52.2	1.2, 43.3	0.0, 55.4	1.7, 36.5+	4.1+, 53.4	1.8+, 33.4+	3.2, 23.7+	0.5+, 37.5	0.5, 20.8+	0.0, 55.4

Source: Table 2.103, p273 of the resubmission

^a Median, Q1, and Q3 are Kaplan-Meier estimate. CI (2-sided) for median was computed using the Greenwood's formula. Minimum and maximum included the censored observations where using "+" after value indicates censoring.

^b Median, Q1, and Q3 are Kaplan-Meier estimate of potential follow-up using the method by Schemper and Smith (9). CI (2-sided) for median was computed using the Greenwood's formula. Minimum and maximum included the censored observations where using "+" after value indicates censoring.

Notes: Percentage was calculated using the number of patients in the column heading as the denominator. The table is based on the Full Analysis Set, N = 139

CRC, colorectal cancer; CI = confidence interval; CNS = central nervous system; NE = not estimable; NSCLC = non-small cell lung cancer; OS = overall survival

Table 12: SCOUT - Summary of overall survival

	Previous submission July 2019 data cut-off		Resubmission July 2020 data cut-off	
	<i>NTRK</i> fusion N = 79	Non- <i>NTRK</i> fusion N = 9	<i>NTRK</i> fusion N = 108	Non- <i>NTRK</i> fusion N = 9
Patients who died, n (%)	3 (4)	7 (78)	5 (5)	7 (78)
OS (months), Kaplan-Meier estimate ^a				
Median	NE	4.3	NE	4.3
95% CI	NE	0.4, 12.5	NE	0.4, 12.5
Minimum, maximum	1.8+, 38.6+	0.4, 30.7+	0.3+, 50.6+	0.4, 44.3+
Rate (%) of being alive for at least				
12 Months	94	26	94	26
95% CI	87, 100	0, 57	89, 99	0, 57
Follow-up time for OS (months), Kaplan-Meier estimate ^a				
Median	12.9	30.7	19.2	44.3

Source: Table 2.109, p288 of the resubmission

^a Medians are Kaplan-Meier estimate. CI (2-sided) for median was computed using Greenwood's formula. Minimum and maximum included the censored observations where using "+" after value indicates censoring. Median, Q1, and Q3 are Kaplan-Meier estimate of potential follow-up using the method by Schemper and Smith.

CI = confidence interval; NE = not estimable; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival

- 6.18 LOXO-OO1: For *NTRK* fusion patients, median durations of follow-up for PFS was 38.9 months and 51.5 months for the July 2019 and July 2020 data cut-offs respectively. The median PFS durations were not reached, and 51.1 months, for the July 2019 and July 2020 data cut-offs respectively. PFS rates at ≥ 12 months did not change between data cut-offs (approximately 80%). For non-*NTRK* fusion patients, median PFS did not change between data cut-offs, and was substantially lower (1.8 months) than observed for *NTRK* fusion patients. These results were unreliable as the data was based on a small number of patients.
- 6.19 NAVIGATE: The median follow-up, across all tumour types, was approximately 24 months. OS results were presented by tumour type in specific cohorts, although the data remain unreliable due to the small number of patients. As for the previous submission, the results were indicative of heterogeneity in outcomes across the different tumour type cohorts. For the 2019 and 2020 data cut-offs, median OS durations for all cohorts combined, remained immature (not reached). Based on the 2020 data cut-off for specific tumour types, the point estimates for the median duration of OS was not reached for thyroid, sarcoma, and salivary gland tumour types, but ranged from 40.7 months for NSCLC to 2.0 months for biliary tumours. The OS rate at 18 months was highest for the high *NTRK* frequency salivary gland tumour type (89.7%; 95% CI: 47.8, 88.2), and lowest for the low *NTRK* frequency primary CNS tumour type (30.0%; 95% CI: 1.2, 71.9). ORR point estimates at the July 2020 data cut-off (tabulated data not presented here) varied from approximately 90.0% for salivary gland MASC to 12.5% for primary CNS tumours.

6.20 SCOUT: For the 2020 versus 2019 data cut-offs:

The median follow-up durations in the *NTRK* fusion subgroup were 19.2 months versus 12.9 months. The OS remained immature for both data cut-offs (median OS duration not reached).

The Kaplan-Meier estimate of OS of at least 12 months remained unchanged (94%) (95% CI: 87, 100).

The estimated median overall survival duration in the non-*NTRK* fusion subgroup remained unchanged (4.3 months (95% CI: 0.4, 12.5)) with a Kaplan-Meier estimate of OS rate for at least 12 months of 26% for both data cut-offs.

6.21 Pooled larotrectinib OS results are summarised in Table 13. Kaplan Meier curves, by the proposed subgroups, are presented for the previous and most recent data cut-offs in Figure 1 and Figure 2.

Table 13: Pooled overall survival estimates

	Previous submission July 2019 data cut-off		Resubmission July 2020 data cut-off	
	ePAS4 N = 164	SAS3 N = 24	ePAS5 N = 192	SAS3 New N = 33
Vital status^a				
Dead	25 (15%)	1 (4%)	36 (19%)	7 (21%)
Alive	139 (85%)	23 (96%)	156 (81%)	26 (79%)
Duration of OS (months)^{b, c}				
Median	NE	NE	NE	NE
95% CI for median	44.4, NE	9.4, NE	NE, NE	16.9, NE
Minimum, maximum	0.5+, 51.6+	1.9+, 21.4+	0.5+, 62.0+	3.0+, 31.8+
Duration of follow-up (months)^b				
Median	15.8	6.0	24.0	16.5
25 th , 75 th percentiles	9.3, 28.8	4.6, 11.0	16.8, 36.7	11.1, 19.1
Rate (%) of OS^{b, c}				
12 months or more (95% CI)	90% (85%, 95%)	88% (65%, 100%)	89% (85%, 94%)	85% (71%, 99%)
24 months or more (95% CI)	82% (75%, 90%)	NE (NE, NE)	82% (76%, 88%)	58% (28%, 88%)

Source: Table 2.133, p330 of the submission

July 2019 data-cut

^a Status as of the last contact on or before visit cut-off.

^b Estimate based on Kaplan-Meier method.

^c 95% confidence interval was calculated using Greenwood's formula.

+ = censored observation; NE = not estimable; CI = confidence interval; OS = overall survival; PR = partial response; ePAS = extended primary analysis set; SAS = supplemental analysis set

6.22 The OS data remain immature for the July 2020 data cut-off. With a median follow-up period of 24 months for patients in the ePAS5 dataset, median OS was not reached (95% CIs not reached). The proportion of non-CNS tumour larotrectinib patients alive at 24 months remained unchanged from that observed for the July 2019 data cut-off in the previous submission at 82% (95% CI: 76%, 88%).

- 6.23 With a median follow-up period of 16.5 months for SAS3 New patients, median OS was not estimable (95% CI: 16.9, not estimable). At 24 months, the probability of being alive was 58% (95% CI: 28%, 88%) compared to not reached for the July 2019 data cut-off in the previous submission.
- 6.24 Table 14 summarises pooled PFS and OS by representative/specified tumour types, for the most recent data cut-off. Figure 1 and Figure 2 compare the Kaplan Meier curves, by representative tumour type for the proposed subgroups for listing, between the previous and most recent data cut-offs.

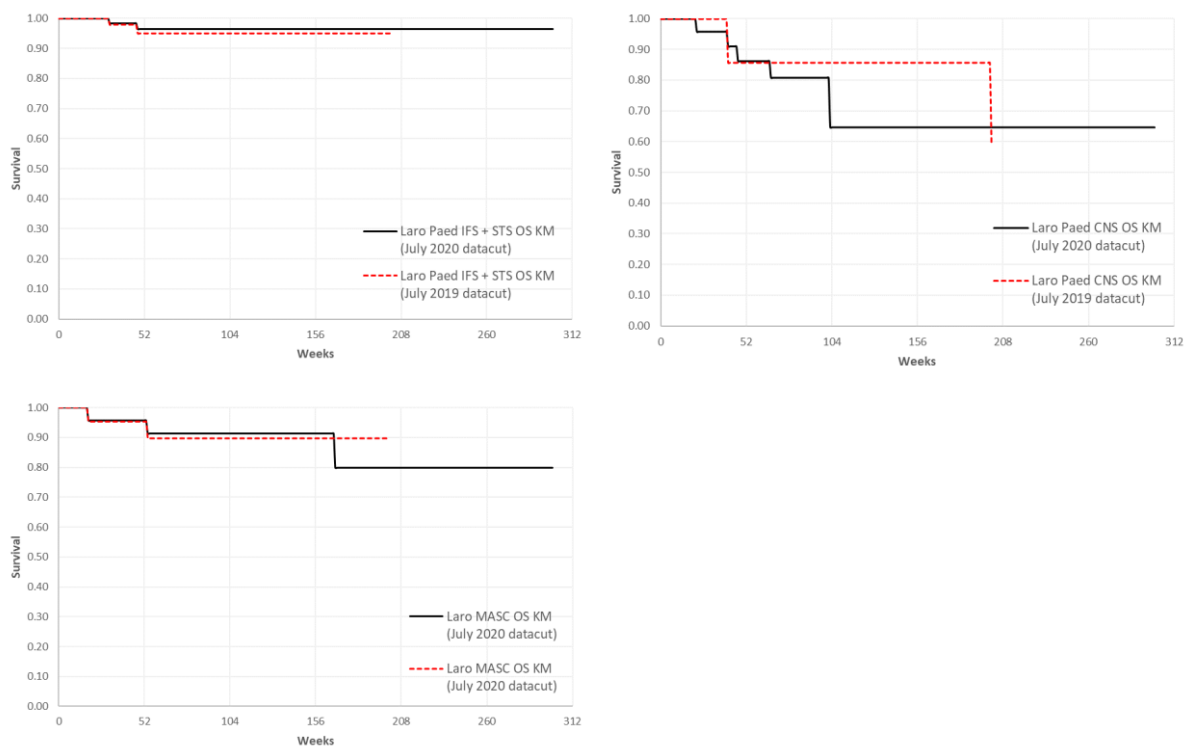
Table 14: Summary of pooled PFS and OS results, by tumour type/subgroup based on frequency of *NTRK* fusion and adult/paediatric status (July 2020 data cut-off)

	Subgroups							Overall
	Adult <i>NTRK</i> fusion high frequency (salivary)	Adult <i>NTRK</i> fusion low frequency (CRC)	Adult <i>NTRK</i> fusion low frequency (STS)	Adult <i>NTRK</i> fusion low frequency (NSCLC)	Adult <i>NTRK</i> fusion low frequency (thyroid)	Paediatric <i>NTRK</i> fusion high frequency (IFS/STS)	Paediatric <i>NTRK</i> fusion low frequency (CNS)	
Median PFS (months)	55.7	5.5	29.2	32.9	34.3	34.7	NE	32.9
PFS at 12 months	83%	33%	52%	62%	75%	78%	65%	66%
PFS at 24 months	78%	33%	52%	62%	62%	56%	52%	55%
Median OS (months)	NE	29.2	NE	40.5	NE	NE	NE	NE
OS at 12 months	96%	71%	85%	86%	88%	96%	86%	89%
OS at 24 months	91%	71%	70%	75%	73%	96%	65%	80%

Source: Table 2.142, p346 of the resubmission.

1L = first-line; CRC = colorectal cancer; CNS = central nervous system; IFS = infantile febrile sarcoma; *NTRK* = Neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; STS = soft tissue sarcoma

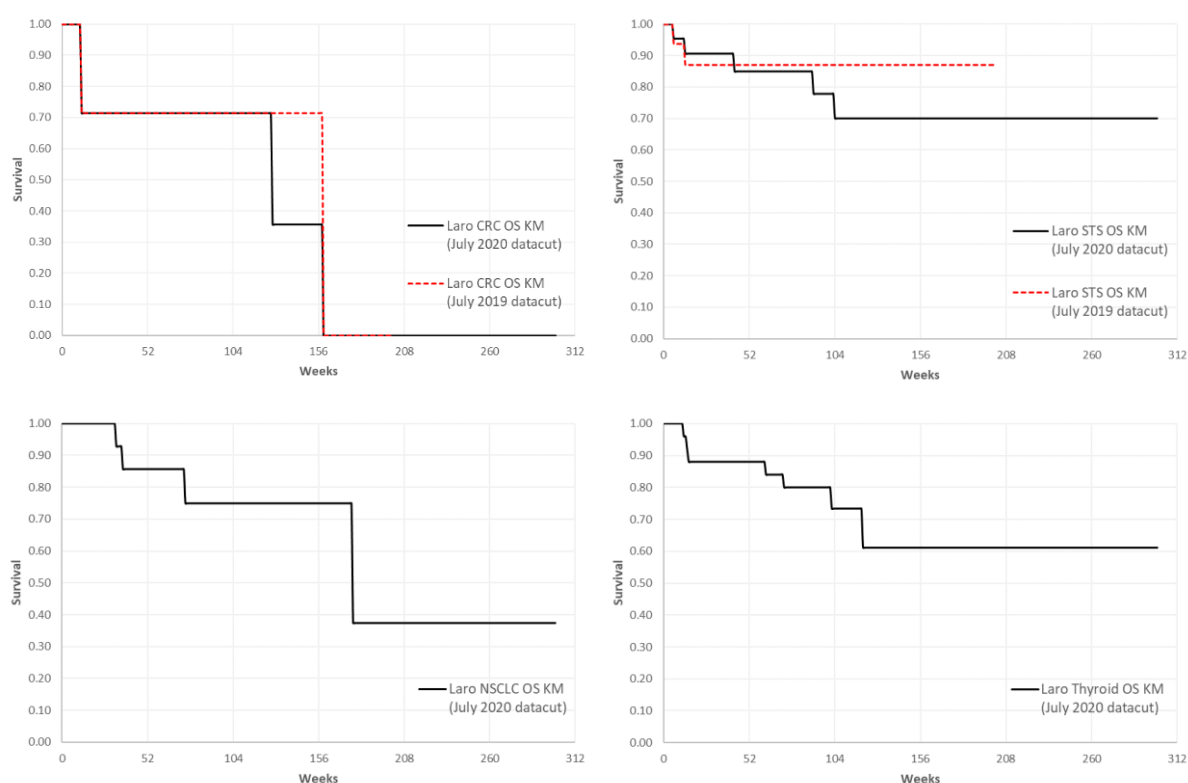
Figure 1: Pooled Kaplan-Meier overall survival curves, by proposed subgroups for listing (previous submission November 2020 (July 2019 data cut-off) and resubmission (July 2020 data cut-off): Paediatric “high” frequency (IFS+STS), paediatric low frequency (primary CNS), adult high frequency (MASC salivary gland)



Source: Constructed during the evaluation from the 'A2.6_Larotrectinib subgroup OS and PFS KM MAY20.xlsx' and 'A2.6_Larotrectinib subgroups ToT OS PFS KM Para 12APR21.xlsx' workbooks included in the resubmission.

KM = Kaplan-Meier; IFS = infantile fibrosarcoma; MASC = mammary analogue secretory carcinoma; CNS = central nervous system; OS = overall survival.

Figure 2: Pooled Kaplan-Meier overall survival curves, by proposed subgroups for listing (previous submission November 2020 (July 2019 data cut-off) and resubmission (July 2020 data cut-off): proposed adult low frequency tumour types



Source: Constructed during the evaluation from the 'A2.6_Larotrectinib subgroup OS and PFS KM MAY20.xlsx' and 'A2.6_Larotrectinib subgroups ToT OS PFS KM Para 12APR21.xlsx' workbooks included in the resubmission.

Kaplan-Meier data for patients with thyroid and lung (NSCLC) tumours were not presented for the July 2019 data cut-off.

KM = Kaplan-Meier; NSCLC = non-small cell lung cancer; STS = soft tissue sarcoma; OS = overall survival

- 6.25 The Kaplan Meier curves in Figure 1 and Figure 2 were based on small patient numbers and should be interpreted cautiously. The curves for low *NTRK* frequency tumour types appear to have a sharper decline for the more recent July 2020 data cut-off. The OS curves for STS+IFS combined (paediatric “high” frequency) appear similar between the July 2019 and July 2020 data cut-offs. The curves clearly reflect immaturity of the data (median OS duration not reached) with a high proportion of paediatric patients still alive at the July 2020 data cut-off. The OS data remain immature for MASC (adult high frequency), CNS (paediatric low frequency), and thyroid (adult low frequency) with more events having occurred for CNS at the July 2020 data cut-off compared to the previous data cut-off. For the adult low frequency CRC and NSCLC tumours, the median OS durations were approximately 29 months and 40 months, respectively.
- 6.26 The ESCs noted that the clinical data remained limited and immature across the tumour subgroups despite the latest data cut. Overall, the ESCs considered that the updated data did not provide additional certainty around the interpretation of the larotrectinib results compared to the previous submission.
- 6.27 Naïve indirect comparisons between larotrectinib and SoC, for the paediatric high frequency (Table 15), adult high frequency (Table 16), paediatric low frequency (Table 17), and adult low frequency (Table 18 and Table 19) tumours, based on the July 2020

data cut, are presented below. There is high uncertainty with the naïve indirect comparisons given issues with the SoC data and transitivity. The larotrectinib point estimates were relatively unreliable as the number of patients across the studies remained small.

Table 15: PFS and OS - larotrectinib and SoC in paediatric high frequency *NTRK* tumours (STS/IFS)

	Larotrectinib (STS/IFS) N=62	I+D (Sandler 2001) – 1L N=152	I+V (Mascarenhas 2010) – 2L N=47
Median PFS (months)	34.7	15.6	8.0
PFS at 12 months	78%	61%	38%
PFS at 24 months	56%	35%	15%
Median OS (months)	Not reached	22.1	15.9
OS at 12 months	96%	76%	62%
OS at 24 months	96%	49%	30%

Source: Table 2.146, p350 of the resubmission
July 2020 data cut-off for larotrectinib

1L = first-line; 2L = second-line; I+D, ifosfamide and doxorubicin; I+V = irinotecan and vincristine; IFS = infantile fibrosarcoma; STS = soft tissue sarcoma, PFS = progression-free survival; OS = overall survival

Table 16: PFS and OS - larotrectinib and SoC in adult high frequency *NTRK* tumours (salivary gland tumours)

	Larotrectinib (salivary gland: MASC) N=23	Cisplatin + VNB salivary gland (Airoldi 2001) N=20
Median PFS (months)	55.7	6.9
PFS at 12 months	83%	31%
PFS at 24 months	78%	10%
Median OS (months)	NR	10.8
OS at 12 months	96%	33%
OS at 24 months	91%	19%

Source: Table 2.143, p348 of the resubmission
July 2020 data cut-off for larotrectinib

MASC = mammary analogue secretory carcinoma; PFS = progression-free survival; OS = overall survival; VNB = vinorelbine

Table 17: PFS and OS - larotrectinib and SoC in paediatric low frequency *NTRK* tumours (CNS/glioma)

	Larotrectinib N=26	RT+TMZ (Grill 2019) – 1L N=59	Lomustine (Wick 2017) – 2L N=149
Median PFS (months)	Not reached	12.2	1.6
PFS at 12 months	65%	51%	3%
PFS at 24 months	52%	34%	1%
Median OS (months)	Not reached	17.7	8.0
OS at 12 months	86%	69%	30%
OS at 24 months	65%	50%	9%

Source: Table 2.147, p350 of the resubmission
July 2020 data cut-off for larotrectinib

RT+TMZ = radiotherapy plus temozolomide; PFS = progression-free survival; OS = overall survival; CNC = central nervous system

Table 18: PFS and OS - larotrectinib and SoC in adult low frequency *NTRK* tumours (colorectal tumours and STS)

	Larotrectinib (CRC) N=8	Trifluridine/tipiracil ^a (CRC)(Mayer 2015) N=534	Larotrectinib (STS) N=23	Dacarbazine (Schoffski 2016) (STS, liposarcoma or leiomyosarcoma) N=224	BSC (van der Graaf 2012) (STS) N=246
Median PFS (months)	5.5	2.0	29.2	2.3	1.6
PFS at 12 months	33%	3%	52%	5%	1%
PFS at 24 months	33%	2% ^b	52%	0%	1%
Median OS (months)	29.2	7.1	Not reached	11.3	10.6
OS at 12 months	71%	27%	85%	47%	46%
OS at 24 months	71%	12% ^b	70%	20%	23%

Source: Table 2.144, p349 of the submission
July 2020 data cut-off for larotrectinib

^aIn the previous submission (November 020 PBAC Meeting), the SoC arm was the placebo/BSC arm of Mayer 2015, whereas in the resubmission, the trifluridine/tipiracil arm was the nominated SoC arm.

^b24 month rates could not be identified from the publication

Table 19: PFS and OS - larotrectinib and SoC in adult low frequency *NTRK* NSCLC and thyroid tumour types

	Larotrectinib (NSCLC) N=15	Docetaxel (Borghaei 2015) (NSCLC) N=290	BSC (Shepherd 2005) (NSCLC) N=243	Larotrectinib (thyroid) N=28	BSC (Schlumberger 2015) (thyroid) N=131	Lenvatinib (Schlumberger 2015) (thyroid) N=261
Median PFS (months)	32.9	4.4	1.6	34.3	3.7	18.4
PFS at 12 months	62%	8%	2%	75%	10%	63%
PFS at 24 months	62%	3%	2%	62%	4%	45%
Median OS (months)	40.5	9.4	4.6	Not reached	Not reached	Not reached
OS at 12 months	86%	40%	21%	88%	76%	82%
OS at 24 months	75%	13%	2%	73%	55%	58%

Source: Table 2.145, p349 of the submission
July 2020 data cut-off for larotrectinib

NSCLC = non-small cell lung cancer; BSC = best supportive care; PFS = progression-free survival; OS = overall survival

6.28 Paediatric high frequency: For STS/IFS, the median PFS duration was 34.7 months and the median OS was not reached. These were much higher than those observed for STS SoC: Median PFS and OS values for first line SoC in STS were 15.6 and 22.1 months, respectively, and for second line SoC in STS, 8.0 and 15.9 months, respectively. The

STS comparator studies, Sandler et al. (2001) and Mascarenhas et al. (2010), only enrolled patients with the histological STS subtype of rhabdomyosarcoma. The larotrectinib data included both IFS (a non-rhabdomyosarcoma subtype of STS that accounts for approximately 1-2% of all paediatric STS cases) and other STS tumour types, though IFS was the predominant subtype of the larotrectinib cohort (61% of the larotrectinib NTRK fusion positive STS cohort). For the paediatric population overall, this analysis is informative.

- 6.29 Adult high frequency (salivary gland, MASC): The median PFS duration was 55.7 months for larotrectinib compared with 6.9 months in the SoC arm. The PFS rate at 24 months was much higher for larotrectinib (78%) compared to SoC (10%). The median duration of OS was not reached for larotrectinib compared with 10.8 months in the SoC arm. The OS rate at 24 months was 91% in patients treated with larotrectinib compared to 19% in the SoC arm.
- 6.30 Paediatric low frequency (CNS/glioma): The median PFS and OS durations were not reached for larotrectinib treated patients in the later line setting. Median PFS and OS values for first line SoC in CNS tumours at 12.2 and 17.1 months respectively, were longer than for second line SoC, at 1.6 months and 8.0 months, respectively. OS rates at 12 and 24 months for CNS patients treated with larotrectinib were 86% and 65% respectively, compared to those for first line SoC (69% and 50%, respectively) or second line SoC (30% and 9%, respectively). The SoC Wick 2017 study, which was conducted in adults with progressive glioblastoma, was used as a proxy for this paediatric population. The impact of any important differences in disease severity and prognosis, by age, on the incremental benefit of larotrectinib is difficult to determine from the available data.
- 6.31 Adult low frequency: For CRC, median PFS was 5.5 months for larotrectinib compared to 2 months for SoC (trifluridine/tipiracil). Median OS was 29.2 months for larotrectinib compared to 7.1 months for SoC.

For STS, median PFS was 29.2 months for larotrectinib compared to 1.6 to 2.3 months for SoC (dacarbazine or BSC). Median OS was not reached for larotrectinib compared to approximately 11 months for SoC.

For NSCLC, median PFS was 32.9 months for larotrectinib compared to 4.4 months for SoC (docetaxel). Median OS was 40.5 months for larotrectinib compared to 9.4 months for SoC. The median PFS and OS durations for BSC from the other Shepherd 2005 trial were 1.6 months and 4.6 months, respectively. The Shepherd 2005 study is more than a decade and a half old which may underestimate survival in current SoC for NSCLC.

For thyroid, median PFS was 34.3 months for larotrectinib compared to 3.7 months and 18.4 months for BSC and lenvatinib, respectively. Median OS was not reached for the larotrectinib, BSC, and lenvatinib treatment groups.

- 6.32 The indirect comparisons should be interpreted cautiously given their naïve nature and i) the limited reliability and potential heterogeneity associated with the

larotrectinib and SoC data, and ii) the applicability of the corresponding SoC data to current SoC.

- 6.33 The ESCs noted that as per the previous submission, the updated data indicated a potential treatment effect with larotrectinib, particularly for high frequency NTRK fusion tumours. The ESCs noted it remained difficult to draw conclusions regarding the clinical evidence due to the issues noted above in paragraph 6.16.

Comparative harms (Naïve indirect comparison)

- 6.34 The summary of overall AEs, pooled from the larotrectinib studies (regardless of NTRK fusion status), is presented in the table below.

Table 20: Summary of overall adverse events (Safety Analysis Set: regardless of the presence of NTRK fusions)

TEAE	Previous submission July 2019 data cut-off	Resubmission July 2020 data cut-off
	Overall safety set n=279	Overall safety set n=331
Patients with TEAE	275 (99%)	320 (97%)
Patients with TEAE related to larotrectinib	216 (77%)	260 (79%)
Patients with TEAE Grade 3 or 4	148 (53%)	176 (53%)
Patients with TEAE Grade 3 or 4 and related to larotrectinib	43 (15%)	59 (18%)
Patients with TEAE and action taken of larotrectinib permanently discontinued	26 (9%)	33 (10%)
Patients with TEAE and action taken of larotrectinib permanently discontinued and related to larotrectinib	6 (2%)	8 (2%)
Patients with serious TEAE	96 (34%)	129 (39%)
Patients with serious TEAE and related to larotrectinib	15 (5%)	20 (6%)
Patients with fatal TEAE ^a	16 (6%)	21 (6%)

Source: Table 2.136, p242 of the resubmission

^aRefers to TEAEs both related and unrelated to larotrectinib treatment

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.

TEAE = treatment emergent adverse event; CTCAE = Common Terminology Criteria for Adverse Events

- 6.35 Approximately half of the patients (53%) 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 18%. There were 33 patients (10%) who had TEAEs that led to permanent treatment discontinuation.

- 6.36 The resubmission presented pooled safety data for three paediatric subgroups treated with larotrectinib: Infants/toddlers (28 days to 23 months of age, n=39), children (2 to 3 years of age, n=53), and adolescents (12 to <18 years of age, n=25). TEAEs in paediatric patients were assessed to be serious by the investigator for 15 (38%) infants/toddlers, 19 (36%) children and 11 (33%) adolescents.

The risk of “neurodevelopment impairment in paediatric patients” was evaluated in the context of important potential risk “severe neurologic reactions”. In 117 paediatric

patients, approximately 8% experienced dizziness, 5% insomnia, 3% each for gait disturbance and somnolence, 2% each for paraesthesia and dysgeusia, and 1% each for somnolence and memory impairment. The risk of neurodevelopment impairment for paediatric patients may increase the longer patients remain on treatment.

Overall, the available data indicated a manageable safety profile for larotrectinib, although there were insufficient data to assess the long-term safety of larotrectinib.

- 6.37 A naïve indirect comparison of safety was presented. The indirect comparison is difficult to interpret as SoC data were not reported for many of these events. Furthermore, some of the Grade ≥ 3 AEs observed across the SoC studies of different tumour types may have been disease related rather than drug related.
- 6.38 AEs were considered in the economic evaluation. However, the SoC AEs for the paediatric population were sourced exclusively from Sandler (2001). This does not appear to be a reasonable approach. Management of chemotherapy-related AEs in current SoC has improved over time with more frequent monitoring and earlier recognition of these events, with more effective prophylaxis and treatment compared to that employed in a study conducted more than 20 years ago. The toxicity profile also differs between larotrectinib (neurological) and chemotherapy (haematological). Neurological AEs are reflective of larotrectinib's mechanism of action and are relevant in the assessment of benefit/risk, particularly in the paediatric population.

Benefits and harms

- 6.39 The basis of the evidence in the submission was a naïve indirect comparison. Therefore, the magnitude of the incremental benefit of larotrectinib could not be quantified. Accordingly, a benefits/harms table has not been presented.

Interpretation of clinical evidence

- 6.40 The therapeutic conclusion presented in the submission was that *NTRK* fusion testing plus larotrectinib is superior to no *NTRK* testing plus SoC in terms of efficacy and safety, in the proposed testing and treatment population.
- 6.41 The ESCs recognised the effort made in the resubmission to address several uncertainties raised during the previous PBAC consideration in November 2020, within the confines of the limited available data. This included presentation of additional data from an extended follow-up, and several exploratory analyses. However, the clinical evidence at this stage still remains limited, to varying degrees, across all four proposed populations. Due to the rarity of *NTRK* fusion cancers, comparative randomised trial data is unlikely to be forthcoming.
- 6.42 Collectively, the single-arm design of the larotrectinib studies, small patient numbers, potential heterogeneity in disease characteristics and treatment outcomes by tumour type, the impact of confounding of OS from subsequent treatments received post-progression in the larotrectinib studies, and variability of the SoC data and their applicability to current Australian SoC, engender a high degree of uncertainty regarding the magnitude of incremental benefit of larotrectinib.

The entirety of the evidence was indicative of a larger treatment effect in patients with high *NTRK* fusion frequency tumours compared to patients with low *NTRK* fusion frequency tumours. The evidence for the effectiveness of larotrectinib for some of the paediatric low *NTRK* fusion frequency tumours was less convincing than that observed for the paediatric high frequency tumours. However, there is a high clinical need for alternate therapies in paediatric patients, particularly for whom current SoC primarily consists of cytotoxic chemotherapy, which may have a lifelong detriment (among others, reduced fertility and cognitive impairment) on the patient's quality of life. Taken together, the benefit/risk of larotrectinib may be positive for some rare paediatric cancers with a low *NTRK* fusion frequency. Noting the limitations of the clinical data discussed above, the ESCs considered the claim of superior effectiveness of larotrectinib, compared to SoC, appears acceptable for adult and paediatric patients with high *NTRK* fusion frequency solid tumours.

- 6.43 The ESCs considered the claim of superior effectiveness in the adult low *NTRK* fusion frequency tumours was not sufficiently supported as observed for adult high frequency tumours.
- 6.44 The pooled larotrectinib safety data have not changed substantially since the previous submission. The updated safety results indicated a manageable safety profile associated with larotrectinib. Neurological AEs reflective of larotrectinib mechanism of action are relevant in the assessment of benefit/risk, particularly in the paediatric population. Thus, longer term safety data from a larger patient cohort are required to assess any rare neurological/other relevant TEAEs.
- 6.45 The assessment of comparative safety was not feasible. It was difficult to interpret the indirect comparison as many AEs were not reported in the SoC studies. Furthermore, some of the Grade ≥ 3 AEs observed across the SoC studies of different tumour types may likely have been disease related rather than drug related. The toxicity profile differs between larotrectinib (neurological) and chemotherapy (haematological).

For the economic evaluation, the SoC AEs for the paediatric population were sourced exclusively from Sandler (2001) which was more than two decades old. Management of chemotherapy-related AEs has improved significantly over time, with more frequent monitoring and earlier recognition of these events, and more effective prophylaxis or treatment in current SoC.

Claim of codependence

- 6.46 The therapeutic conclusion presented in the submission was that *NTRK* fusion testing (FISH or NGS \pm IHC) plus larotrectinib was superior to no *NTRK* fusion testing plus SoC in terms of efficacy and safety, in the proposed testing and treatment population. There were several uncertainties associated with the evidence which did not allow a definitive conclusion regarding this claim.
- 6.47 Given the several key uncertainties identified, the claim of superiority of testing plus treatment over no testing plus SoC, in a site agnostic context, was not sufficiently demonstrated.

Economic analysis

- 6.48 The resubmission presented an updated modelled economic evaluation, based on a naïve indirect comparison of single-arm studies. This compared *NTRK* testing and larotrectinib treatment in patients identified with *NTRK* fusions and SoC treatment in those without, to no testing, where all patients were treated with SoC. This differed to the previous submission which modelled only *NTRK*-positive patients and compared larotrectinib treatment to SoC. The ESCs considered this change was reasonable and is consistent with the preferred approach in the PBAC and MSAC Guidelines for codependent technologies. The types of economic evaluation presented were a cost-effectiveness analysis and a cost-utility analysis, measuring outcomes in terms of life-years (LYs) gained and quality-adjusted life years (QALYs) gained, respectively. This is unchanged since the previous submission. The key components of the economic evaluation are summarised in Table 21.

Table 21: Summary of model structure and rationale

Component	Summary
Cohorts modelled	<ul style="list-style-type: none"> • Patients treated with larotrectinib: overall cohort of patients from the pooled larotrectinib analysis (i.e. mix of adult and paediatric patients and a mix of high and low frequency <i>NTRK</i> fusion tumour types – including tumour types that have been excluded from the resubmission’s proposed population) • Patients treated with SoC: seven weighted cohorts: <ul style="list-style-type: none"> ○ Paediatric STS (representative of paediatric high frequency <i>NTRK</i> fusion tumour types), weight: 29.8% ○ Paediatric glioma (representative of paediatric low frequency <i>NTRK</i> fusion tumour types), weight: 11.6% ○ Salivary gland (representative of adult high frequency <i>NTRK</i> fusion tumour types), weight: 12.9% ○ Colorectal cancer, weight: 5.1% ○ Adult STS, weight: 14.6% ○ NSCLC, weight: 9.5% ○ Thyroid cancer, weight: 16.5% <p>Tumour type subgroup analyses of the pooled larotrectinib studies were also presented to allow within-tumour comparisons.</p> <p>The approach used, which compares larotrectinib use (in a broad range of tumour types, including those not specified in the proposed restrictions) to SoC therapies across a select number of representative tumour types is unchanged from the previous submission. A weighted analysis based on the tumour type subgroup analyses may be more appropriate (as per Table 15, 5.08 larotrectinib PSD, November 2020). Further, the tumour types in the SoC arm were weighted according to the distribution of <i>NTRK</i> fusion-positive patients in the pooled larotrectinib analysis (i.e. weighted according to the <u>treated</u> population). This is not appropriate, weighting should instead reflect the distribution of tumour types in the <u>tested</u> population of eligible tumour types expected in Australian clinical practice.</p>
Type of analysis	Cost-utility analysis and cost-effectiveness analysis. This is appropriate.
Outcomes	Quality-adjusted life years gained, life-years gained. This is appropriate.
Time horizon	<p>Base case: 15 years (compared to a median follow-up for OS of 24 months)</p> <p>While the time horizon was reduced from 20 years in the previous submission, this remains inadequately justified and is substantially longer than the median follow-up in the pooled larotrectinib analysis (2 years). A time horizon of 5 years may be more appropriate in the adult populations with low <i>NTRK</i> fusion frequency tumour types. Identifying a singular appropriate time horizon across diverse populations (both adults and children) with diverse prognoses is challenging. Where the model structure does not easily allow for the application of different time horizons for different populations, there is increased onus on ensuring plausible extrapolations.</p>
Methods used to generate results	Partitioned survival analysis. This is reasonable.
Health states	Progression-free, Progressed, Dead. This is reasonable.
Utilities	Baseline health state utility weights were mapped from HRQoL assessments from the NAVIGATE and SCOUT studies. The baseline health state utility applied in the progression-free health state was adjusted for response to therapy and for AEs. The approach is unchanged from the previous submission. As the relationship between HRQoL and adverse events is clear, adjustment for adverse events is appropriate. However, the relationship between HRQoL and response is less clear and it may not be reasonable to adjust for this.
Cycle length	Weekly. This is reasonable.

Component	Summary
Transition probabilities	Health state allocation over time was determined by extrapolated progression free and overall survival curves from the larotrectinib pooled analysis and comparator trials. The approach is unchanged from the previous submission. While this is reasonable, the use of the PFS and OS data from the overall pooled larotrectinib analysis may not be appropriate. For all of the tumour type subgroups – except the high frequency <i>NTRK</i> fusion paediatric subgroup – extrapolations were based on small patient numbers (<30), with small numbers of events experienced (<10). For colorectal cancer, which is the tumour type/tumour type group expected to have the highest use in practice, only eight patients were enrolled across the larotrectinib studies, with only four OS and five PFS events experienced at the time of the latest data cut. These data are inadequate for extrapolation.
Test parameters	NGS or FISH: assumed to perform as per the evidentiary standard (i.e. 100% sensitivity and 100% specificity). Where IHC is proposed as a triage test, the accuracy of IHC relative to the reference standard was used. This is unchanged from the previous submission and may not be reasonable, as performance of NGS varies depending on the type and the performance of FISH remains uncertain. Further, the IHC scoring algorithm used in practice is unclear, and so the applicability of the IHC performance modelled to the proposed setting is uncertain.
False positives/negatives	<p>The model structure has been revised to allow the implications of false positive and false negative results to be explored. This is appropriate. However, only false negative results are modelled in the base case analysis arising from IHC testing in adults with low <i>NTRK</i>-fusion frequency tumour types. These patients are assumed to receive the cost of <i>NTRK</i> testing, but do not receive larotrectinib treatment – and so costs and outcomes modelled are based on receiving SoC treatment. This is reasonable.</p> <p>False positives are modelled in sensitivity analyses only. These patients are generally modelled as true negative patients where only the cost of pre-progression treatment (and associated administration) varied. Thus, the cost and disutility related to AEs was based SoC treatment, rather than larotrectinib, which is not appropriate. While it is assumed that these patients would receive an initial script of larotrectinib lasting 13 weeks, the cost of larotrectinib treatment for these patients is modelled through an adjustment in the first 13 cycles of <u>true positives</u>. This is not appropriate given the test-treat structure of the model. The additional cost of larotrectinib treatment in false positives is subsequently weighted by the proportion in the model that are true positive, which is not appropriate.</p>

Source: Table 3.2, p388 of the resubmission.

Note: shaded text denotes no change from the previous submission.

AE = adverse event; CNS = central nervous system; FISH = fluorescence *in situ* hybridisation; HRQoL = health-related quality-of-life; IFS = infantile fibrosarcoma; IHC = immunohistochemistry; KM = Kaplan-Meier; *NTRK* = neurotrophic tropomyosin receptor kinase; NGS = next generation sequencing; NSCLC = non-small cell lung cancer; OS = overall survival; PFS = progression-free survival; STS = soft tissue sarcoma; SoC = standard of care; ToT = time-on-treatment.

6.49 The PBAC previously noted that the incremental cost-effectiveness ratio (ICER) was \$155,000 to < \$255,000/QALY for the high *NTRK* fusion frequency and low *NTRK* fusion frequency paediatric populations combined when i) the most conservative OS and PFS extrapolations; ii) an *NTRK* fusion frequency of 0.68% for paediatric STS and; iii) exclusion of the RSA rebate was applied in the economic analysis (paragraph 6.73, 5.08 larotrectinib November 2020 PBAC PSD). The changes described in ii) and iii) have been adopted in the resubmission's base case, noting that the base case was not restricted to the high *NTRK* fusion frequency and low *NTRK* fusion frequency paediatric populations combined, and the most conservative OS and PFS extrapolations were not chosen for each of the larotrectinib subgroup analyses or the comparator. Further, the ICER previously noted by the PBAC was based on the Australian distribution of tumour types, whereas the resubmission maintained the use of the distribution in the pooled larotrectinib analysis. In addition to the changes described in ii) and iii), the main additional changes applied in the resubmission were a decrease in the time horizon

from 20 to 15 years, updated larotrectinib and *NTRK*-fusion testing costs, and updated larotrectinib data.

- 6.50 The revised structure contains two main components – a (new) testing component, which allows treatment allocation to be guided by the results of *NTRK* fusion testing; and a treatment component, which captures the costs and outcomes of alternative treatment options. The testing component of the model is structured to allocate patients by test result (e.g. true negative, false positive, etc.). As such, tumour type cohort costs and outcomes are weighted within each of these test outcome points. Regardless of the testing outcome, tumour types were weighted by the distribution of *NTRK*-positive patients. This is not appropriate. Costs and outcomes should have been weighted according to the distribution of tumour types in those that are found to have that test result. For example, as perfect test performance has been assumed for some tumour type groups, no false results are expected in these tumour types and so their costs and outcomes should not be included in the false negative and false positive outcome points.
- 6.51 Consistent with the previous submission, different test strategies are proposed based on patient age and the frequency of *NTRK* fusions within that tumour type, however the restrictions list specific adult tumour types:
- NGS or FISH: all paediatric patients, and adults with specified high *NTRK* fusion frequency tumour types (secretory breast and MASC); and
 - IHC, followed by NGS or FISH in those that are IHC-positive: adults with specified low *NTRK* fusion frequency tumour types (CRC, STS, NSCLC and thyroid only).
- 6.52 As the model structure has changed from entry at the point of treatment to entry at the point of testing, the average cost of testing across the tested population is applied, rather than the average cost to identify one *NTRK*-positive patient. However, the test parameters (i.e. prevalence of *NTRK* fusions and test performance) in the resubmission are generally unchanged from the previous submission. While the lower prevalence estimate, 0.68%, was applied in paediatric STS, the modelled prevalence within the paediatric high subgroup was subsequently weighted by the distribution of tumour types in the treated population (i.e. *NTRK*-positives) rather than the distribution of tumour types in the population eligible for testing, which is not appropriate.
- 6.53 The structure of the treatment component of the model is unchanged from the previous submission, where modelled costs and outcomes from larotrectinib or SoC treatment were generated through a partitioned survival analysis. This was used to estimate the proportion of patients in one of three health states: progression-free, progressed and dead. This is reasonable. In patients treated with larotrectinib, PFS and OS curves were derived from the pooled analysis of the larotrectinib studies (July 2020 combined ePAS5 + SAS3 New data set). The ESCs considered that the pooled data have limited applicability to the proposed clinical setting, due to the tumour types included and their distribution. Subgroup analyses were presented for each of the seven tumour types (or tumour type groups), noting that these remain associated with small patient numbers and are associated with substantial uncertainty. Despite these

limitations, when exploring combinations of tumour types, it is more appropriate to use the weighted subgroup data rather than the pooled analysis, and to weight tumour types according to the distribution that is expected in Australian clinical practice.

- 6.54 Differences were noted between the overall proportion of *NTRK* fusion-positive tumour types between the larotrectinib studies and the Australian population. In particular, it appears that the paediatric populations may be substantially over-represented in the overall larotrectinib pooled group compared to Australian clinical practice, whereas adult low frequency tumours are under-represented and likely to be more commonly observed in Australian clinical practice. Using the weighting based on *NTRK*-positivity further reduces the applicability of the distribution of *NTRK*-positives to practice.
- 6.55 In patients treated with SoC, modelled costs and outcomes were generated from published PFS and OS curves for each of the tumour types from the studies used in the naïve indirect comparisons. The studies included and approach to including costs and outcomes for patients treated with SoC is generally unchanged from the previous submission however, the analyses include two additional tumour types (NSCLC and thyroid). These were included so that each of the adult low *NTRK* fusion frequency tumour types specified in the MBS and PBS listings could have their cost-effectiveness assessed. This is reasonable.
- 6.56 The modelled incremental benefits need to be interpreted with caution, given the inherent caveats with naïve indirect comparisons on which these are generated. Furthermore, extrapolations of immature data based on small patient numbers are associated with a high degree of uncertainty and in some of the subgroups, the OS benefit estimated over the model time horizon may not be plausible. The ESCs noted that the uncertainties around the clinical benefit of larotrectinib were further magnified by extrapolation in the economic analyses.
- 6.57 The key drivers are summarised in Table 22 below.

Table 22: Key drivers of the model

Description	Method/Value	Impact
Time horizon	While this was reduced since the previous submission to 15 years, it remains inadequately justified and is substantially longer than the median follow-up in the pooled larotrectinib analysis (2 years). A time horizon of 5 years may be more appropriate in the adult populations with low <i>NTRK</i> fusion frequency tumour types, as this is more consistent with previous submissions for later-line treatments to the PBAC (PBAC 7.13 crizotinib PSD, July 2018 and PBAC 6.06 pembrolizumab PSD, March 2019)	High – favours larotrectinib. Decreases in the time horizon lead to substantial increases in the ICER.
Larotrectinib treatment duration	Derived from the extrapolated ToT curve, where patients could continue treatment beyond disease progression. This assumption was unchanged from the previous submission. The PBAC had previously advised that treatment should be until disease progression (para 7.5, larotrectinib PSD, November 2020).	High – favours SoC. As modelled ToT is substantially longer than modelled PFS in paediatric patients, stopping larotrectinib treatment at disease progression leads to a substantial reduction in the ICER.
Modelled comparator for adults with low <i>NTRK</i> frequency tumour types (STS, NSCLC, thyroid)	Active (last-line) treatment. While this is consistent with expected larotrectinib use in very late stage disease, there is uncertainty around how it would be used in clinical practice.	High – favours larotrectinib. When BSC is chosen as the modelled comparator, the ICER increases substantially. Comparisons to earlier treatments were not presented.
Duration of thyroid cancer SoC	Until disease progression (modelled 39.6 months). This is longer than the average duration of treatment previously presented to the PBAC (17.45 months, para 6.45, 5.08 lenvatinib PSD, November 2015)	High – favours larotrectinib. The ICER is sensitive to shorter durations of thyroid SoC treatment.
OS and PFS extrapolations	Parametric models for the tumour type subgroup analyses were selected based on AIC/BIC, in addition to an assessment of face-validity and plausibility. The PBAC had previously considered that the most conservative OS and PFS extrapolations should be used (para 6.74, larotrectinib PBAC PSD, November 2020).	Moderate – favours larotrectinib. A moderate increase was observed when the most conservative PFS and OS functions were applied.

Source: Compiled during the evaluation.

AIC/BIC = Akaike information criterion/Bayesian information criterion; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tropomyosin receptor kinase; PFS = progression-free survival; SoC = standard of care; STS = soft tissue sarcoma; ToT = time on treatment.

6.58 The results of the economic evaluation are presented for the following tumour type groups:

- Adult high *NTRK* frequency and all paediatric patients;
- Specified adult low frequency *NTRK* tumour types combined; and the
- Overall population proposed for larotrectinib treatment.

6.59 The results of the economic evaluation for the group of adult high *NTRK* frequency and all paediatric tumour types combined is presented in Table 23. The resubmission's base case analysis was based on the overall pooled larotrectinib data set, and so also included adults with low *NTRK* frequency tumour types. Analyses based on the tumour types subgroup analyses (i.e. only those tumour types that are relevant or representative of the proposed population), weighted firstly as per the larotrectinib studies, and then as expected in practice are also presented.

Table 23: Results of the economic evaluation, adult high *NTRK* frequency and all paediatric patients combined

	<i>NTRK</i> testing + larotrectinib in <i>NTRK</i> + and SoC in <i>NTRK</i> -	No testing + SoC	Increment
Resubmission base case (larotrectinib data based on the overall pooled analysis set)			
Cost (\$)	████████	\$71,686	████████
QALY gained	3.455	2.383	1.072
Incremental cost/extra QALY gained			████████ ¹
Relevant tumour type subgroup analyses, weighted as per the distribution in the larotrectinib studies[#]			
Cost (\$)	████████	\$71,686	████████
QALY gained	4.398	2.383	2.015
Incremental cost/extra QALY gained			████████ ¹
Relevant tumour type subgroup analyses, weighted as per the distribution in Australian clinical practice[#]			
Cost (\$)	████████	\$71,559	████████
QALY gained	5.072	2.058	3.014
Incremental cost/extra QALY gained			████████ ²
Relevant tumour type subgroup analyses, weighted as per the distribution in Australian clinical practice – revised^{1#}			
Cost (\$)	████████	\$64,593	████████
QALY gained	3.623	2.712	0.910
Incremental cost/extra QALY gained			████████ ¹

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission.

[#] additional or revised analyses conducted during the evaluation.

- Changes include revising the distribution of tumour types to reflect the distribution in the tested Australian population (rather than the treated population), applying the most conservative OS and PFS parametric models for the high *NTRK* fusion frequency tumour types and other minor revisions to treatment costs.

NTRK = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$55,000 to < \$75,000

- 6.60 The ICER presented in the resubmission for this tumour type group was lower than the PBAC had considered previously (\$155,000 to < \$255,000, para 6.74, 5.08 larotrectinib PBAC PSD, November 2020). Table 24 presents a stepped incorporation of the changes in the resubmission to the ICER presented previously.

Table 24: Stepped incorporation of changes relative to the previous submission, adult high *NTRK* frequency and all paediatric patients combined

	Inc. cost (\$)	Inc. QALYs	ICER
ICER cited in November 2020 PBAC PSD ^a	█	3.980	█ ¹
Cumulative changes applied in the resubmission			
New proposed effective price (33.7% reduction compared to previously proposed effective price, plus additional █% reduction on initial scripts)	█	3.980	█ ²
+ reduction in time horizon to 15 years	█	3.658	█ ²
+ updated larotrectinib data (including demographics, such as age and proportion of females)	█	4.260	█ ³
+ most conservative OS and PFS extrapolations (high frequency only) for the updated larotrectinib data	█	4.186	█ ³
+ updated <i>NTRK</i> testing costs	█	4.186	█ ³
+ updated Australian tumour type distributions in <i>NTRK</i> -positive patients	█	4.309	█ ³
+ updated cost of AEs	█	4.298	█ ³
+ updated costs and life tables	█	4.298	█ ³
+ updated model structure (patients enter at point of testing rather than treatment) ^b	█	0.910	█ ³

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission, and from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June2020.xlsm' workbook included in the previous submission.

^a This analysis was restricted to adult high *NTRK* fusion frequency and all paediatric tumour types; assumed a 0.68% prevalence in patients with paediatric STS; excluded the proposed utilisation-based rebate; and applied the Australian distribution of tumour types and the most conservative OS and PFS extrapolations for both the larotrectinib and SoC models arms, in high *NTRK* fusion frequency tumour types only.

^b The ICER is the same as the step previous as the assumption of perfect test performance has been retained.

ICER = incremental cost-effectiveness ratio; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care.

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$115,000 to < \$135,000

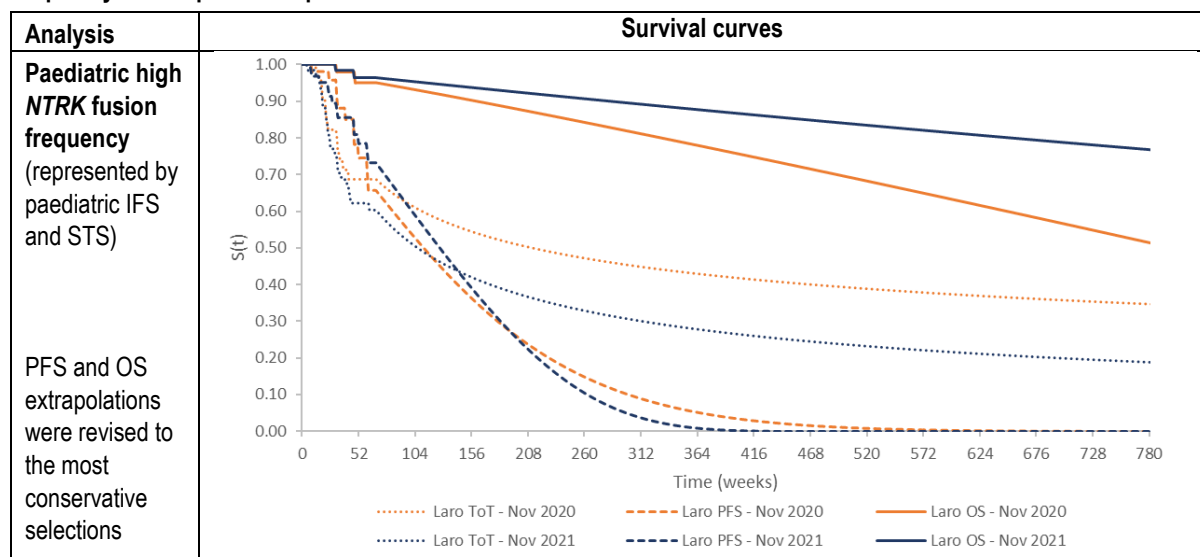
³ \$75,000 to < \$95,000

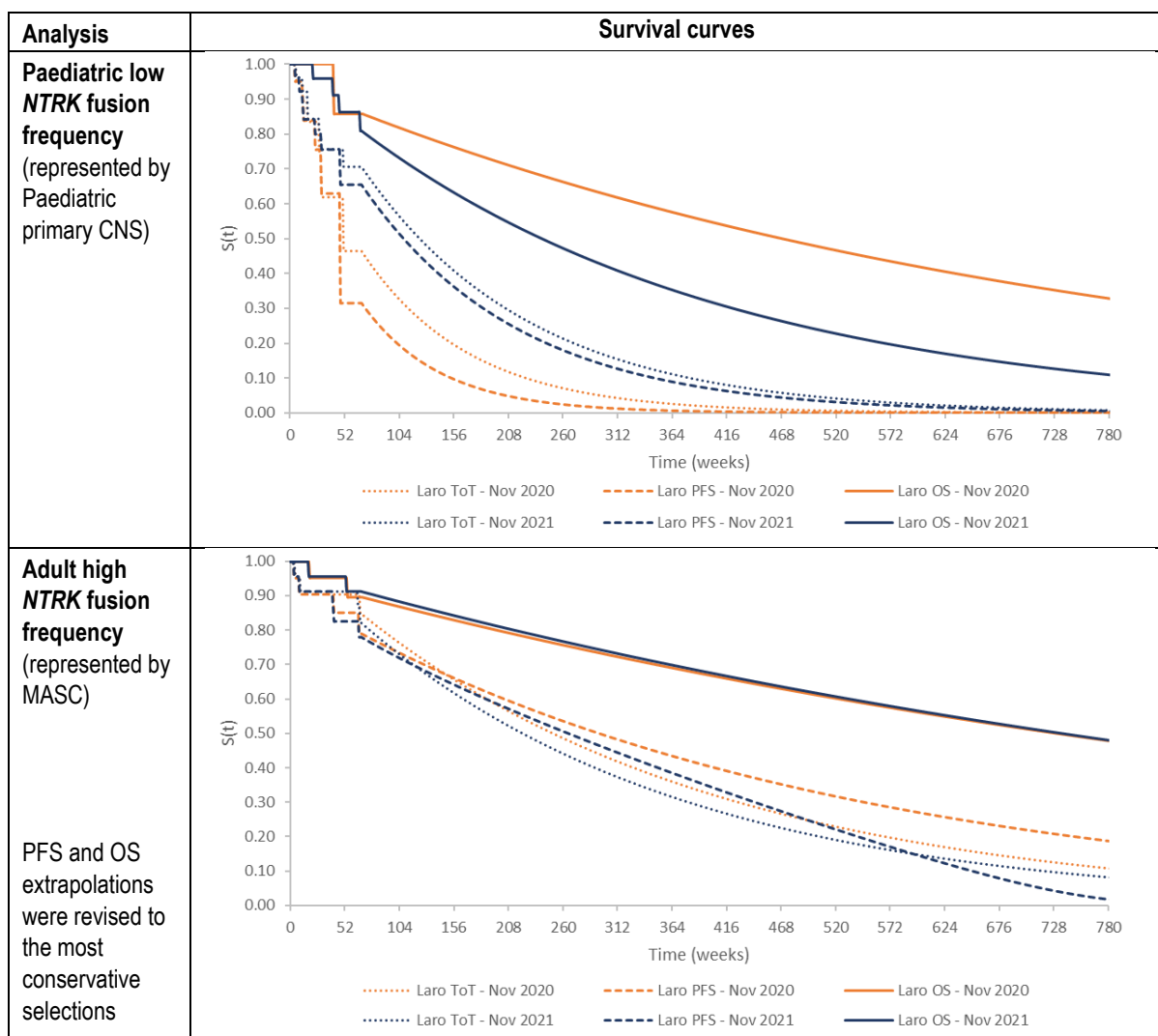
6.61 The changes that most contribute to the updated ICER are the newly proposed effective price of larotrectinib and the updated larotrectinib data. The updated data lead to substantial differences in the long term modelled estimates (Table 25), particularly in the paediatric population that have a high frequency of *NTRK* fusions. In this population, substantially longer OS is predicted, with shorter ToT compared to the previous submission. As the OS KM data between the two data cuts do not appear to be substantially different (Figure 1), the difference in the long term modelled estimates may not be reasonable. In the paediatric population that have a low frequency of *NTRK* fusions, substantially shorter OS is estimated, but with longer PFS and ToT assumed, whereas in the adult population with a high frequency of *NTRK* fusions, similar OS is projected, with shorter PFS and ToT. The ESCs noted that including the updated data reduced the ICER from \$115,000 to < \$135,000/QALY to \$75,000 to < \$95,000/QALY. The ESCs noted that the magnitude of increase in QALYs gained resulting from the inclusion of the updated larotrectinib data into the model, did not appear consistent with the lack of substantial differences between the previous and updated data. Further, the ESCs noted that the substantially longer OS modelled did not appear consistent with the shorter ToT modelled, compared to the

previous submission. Overall, the ESCs considered there was uncertainty around the internal validity of these model inputs. The pre-PBAC response noted it is common for paediatric patients who are treated with larotrectinib to show significant response, undergo curative surgery and then discontinue treatment. The pre-PBAC Response noted that 33 of the 78 paediatric patients with non-CNS tumours had discontinued larotrectinib at the July 2020 data cut and 16 (45.5.8%) of these patients had discontinued larotrectinib due to successful tumour resection.

6.62 The ESCs considered that while the ICER per QALY was now within the range \$70,000/QALY to \$80,000/QALY previously specified by the PBAC, it was potentially underestimated given the uncertainty around whether the additional QALYs gained from the updated data would be realised in practice. The pre-PBAC response stated that the results of the economic analysis should be considered highly conservative. The pre-PBAC response noted that Bokemeyer et al., 2021 found that patients with tumours harbouring *NTRK* fusions had rapid disease progression indicating that the presence of *NTRK* gene fusion events are not prognostic for favourable outcomes. Further, the pre-PBAC Response considered that the presence of *NTRK* fusions would have been negligible across the included SoC studies given the studies did not select from the presence of *NTRK* fusion and given the rarity of *NTRK* fusions.

Table 25: Comparison of modelled survival curves between the previous and current submission, adult high *NTRK* frequency and all paediatric patients





Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission, and from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June2020.xlsx' workbook included in the previous submission.

CNS = central nervous system; CRC = colorectal cancer; IFS = infantile fibrosarcoma; KM = Kaplan-Meier; MASC = mammary analogue secretory carcinoma; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; ToT = time on treatment.

6.63 The results of the economic evaluation for the group of adult low *NTRK* frequency tumour types combined is presented in Table 26. The ESCs considered the resubmission base case estimate for this tumour type group is not appropriate, as the larotrectinib data used in the analysis was not restricted to adult tumour types with low *NTRK* fusion frequency. As per the group of adult high *NTRK* frequency and all paediatric tumour types combined, analyses are also presented based on the tumour types subgroup analyses (i.e. only those tumour types that are relevant), weighted firstly as per the larotrectinib studies, and then as expected in practice. The ESCs considered that the base case for the adult low *NTRK* frequency tumour subgroup should be respecified to \$75,000 to < \$95,000 per QALY, to account for only low *NTRK* frequency tumours and weighting of tumour types according to their expected distribution in Australian clinical practice. The PBAC noted the ICER was higher using the effective prices for trifluride+tipiracil and lenvatinib (rather than the published price).

Table 26: Results of the economic evaluation, specified adult low NTRK frequency tumour types combined

	NTRK testing + larotrectinib in NTRK+ and SoC in NTRK-	No testing + SoC	Increment
Resubmission base case (larotrectinib data based on the overall pooled analysis set)			
Cost (\$)	████████	\$194,976	████████
QALY gained	1.607	1.564	0.043
Incremental cost/extra QALY gained			████████ ²
Relevant tumour type subgroup analyses, weighted as per the distribution in the larotrectinib studies			
Cost (\$)	████████	\$194,976	████████
QALY gained	1.599	1.564	0.034
Incremental cost/extra QALY gained			████████ ³
Relevant tumour type subgroup analyses, weighted as per the distribution in Australian clinical practice			
Cost (\$)	████████	\$176,167	████████
QALY gained	1.400	1.376	0.024
Incremental cost/extra QALY gained			████████ ³
Relevant tumour type subgroup analyses, weighted as per the distribution in Australian clinical practice – revised¹			
Cost (\$)	████████	\$78,294	████████
QALY gained	0.812	0.804	0.008
Incremental cost/extra QALY gained (ESCs respecified base case)[#]			████████ ³

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission.

Note: These are additional or revised analyses conducted during the evaluation.

1. Changes include revising the distribution of tumour types to reflect the distribution in the tested population (rather than the treated population) and other minor revisions to treatment costs modelled and SoC STS data.

NTRK = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care.

*costs for lenvatinib and trifluridine+tipiracil are based on published prices

Cost of lenvatinib per 28-day cycle is based on one 10 mg and two 4 mg capsule packs. A mean daily dose of 18 mg is assumed. This differs from the mean daily dose used in the resubmission (17.2 mg) which is based on the key lenvatinib trial.

The redacted values correspond to the following ranges:

² \$35,000 to < \$45,000

³ \$75,000 to < \$95,000

6.64 The PSCR noted that the cost offsets for lenvatinib had been overestimated due to an error in the calculation of the cost of lenvatinib per cycle, where 30 instead of 60 capsules were used to calculate the cost per mg. The PSCR noted that the ICER for the adult low frequency and overall population increases from \$35,000 to < \$45,000/QALY to \$55,000 to < \$75,000/QALY and from \$55,000 to < \$75,000/QALY to \$55,000 to < \$75,000/QALY respectively, when the cost of lenvatinib per cycle was revised using the cost for two 10 mg capsule packs. The ESCs noted that the cost of lenvatinib per cycle used in the ICER calculated by the evaluation was based on one 10 mg pack and two 4 mg packs of lenvatinib. The ESCs considered that the evaluation's method of determining the cost of lenvatinib, was appropriate as the 4 mg and 10 mg capsule packs have different prices and the method takes into account the price of both these strengths. The PSCR stated the time on treatment for lenvatinib presented in the economic evaluation was 18 months. However, the ESCs noted that while the median time on treatment was 18 months, the average modelled time on treatment (which informed the treatment cost for lenvatinib) was 3.3 years.

6.65 The results of the economic evaluation for the overall population proposed for larotrectinib treatment is presented in in Table 27.

Table 27: Results of the economic evaluation, overall population proposed for larotrectinib treatment

	NTRK testing + larotrectinib in NTRK+ and SoC in NTRK-	No testing +SoC	Increment
Resubmission base case (larotrectinib data based on the overall pooled analysis set)			
Cost (\$)	██████████	\$128,125	██████████
QALY gained	2.713	2.008	0.705
Incremental cost/extra QALY gained			██████████ ¹
Relevant tumour type subgroup analyses, weighted as per the distribution in Australian clinical practice – revised			
Cost (\$)	██████████	\$78,170	██████████
QALY gained	0.838	0.821	0.016
Incremental cost/extra QALY gained			██████████ ²

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission.

Note: These revisions were conducted during the evaluation. These included revising the distribution of tumour types to reflect the distribution in the tested population (rather than the treated population), applying the most conservative OS and PFS parametric models for the high NTRK fusion frequency tumour types and other minor revisions to treatment costs modelled and SoC STS data.

NTRK = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care.

*costs for lenvatinib and trifluridine+tipiracil are based on published prices

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$75,000 to < \$95,000

6.66 The ESCs noted that the modelled benefits associated with adult low NTRK frequency fusion tumour types (QALY gain 0.008) is considerably lower than that compared to the paediatric and high adult NTRK frequency tumour types subgroups (QALY gain 0.910). Given the adult low NTRK frequency tumours would likely make up the majority of NTRK fusion tumours observed in clinical practice, the cost-effectiveness in the overall population proposed for larotrectinib treatment is highly dependent on the treatment benefit of larotrectinib in this subpopulation.

6.67 Across all of the analyses, the main driver of costs is the cost of larotrectinib treatment, with the cost of disease management and NTRK testing being minor contributors. In the group of all paediatric patients and adults with high NTRK frequency tumour types, disaggregated health outcomes were predominantly driven by incremental gains in the progressive disease health state and in adults with low NTRK frequency tumour types, incremental outcomes were predominantly gained in the progression-free health state. The ESCs considered the modelled benefits are uncertain due to the high degree of uncertainty in the extrapolated estimates as these are based on immature data on subgroups with small patient numbers.

6.68 Results of the key sensitivity analyses presented by the resubmission and additional analyses conducted during the evaluation are summarised in Table 28 for the combined group of adults with high NTRK frequency tumour types and all paediatric patients and Table 29 for adults with the specified low NTRK frequency tumour types. Given the nature of the naïve indirect comparisons presented, and that the larotrectinib data are immature and rely on subgroup analyses based on small patient

numbers, a high degree of uncertainty remains in the underlying data, which extends to the extrapolated estimates and the modelled incremental benefit of larotrectinib. These uncertainties cannot be addressed through sensitivity analyses and cannot be resolved, as the confounding in the initial comparison is unmeasured.

Table 28: Key sensitivity analyses, adult high NTRK frequency and all paediatric patients combined

	Inc. cost (\$)	Inc. QALYs	ICER	%
Base case, adult high NTRK frequency and all paediatrics	██████	0.910	██████ ¹	
Time horizon, (base case: 15 years)				
10 years (#3)	██████	0.700	██████ ¹	13%
5 years for adults, 10 years for paediatrics (#4)	██████	0.539	██████ ²	21%
Paediatric high frequency NTRK prevalence, 55.6%	██████	1.195	██████ ³	-6%
Most conservative paediatric low OS and PFS parametric models (base case: best fit) (#2)	██████	0.889	██████ ¹	2%
Larotrectinib treatment costs (base case: best fit ToT)				
Cease larotrectinib treatment at disease progression (#1)	██████	0.910	██████ ³	-21%
Larotrectinib ToT, second best fit	██████	0.910	██████ ³	-17%
Use PFS curve for ToT	██████	0.910	██████ ³	-14%
Planned dose (base case: actual average dose)	██████	0.910	██████ ¹	11%
Multivariate analyses				
#1 AND #2	██████	0.889	██████ ³	-20%
#1, #2 AND #3	██████	0.684	██████ ¹	-3%
#1, #2 AND #4	██████	0.522	██████ ¹	0%

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission.

Note: These analyses were revised during the evaluation: the distribution of tumour types was revised to reflect the distribution in the tested population (rather than the treated population). The most conservative OS and PFS parametric models were also applied for the high NTRK fusion frequency tumour types. Other minor revisions to treatment costs modelled.

ICER = incremental cost-effectiveness ratio; NTRK = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; ToT = time on treatment.

The redacted values correspond to the following ranges:

¹ \$75,000 to < \$95,000

² \$95,000 to < \$115,000

³ \$55,000 to < \$75,000

6.69 In the population of adults with high NTRK tumour types combined with paediatric patients, the analyses were most sensitive to the time horizon and the approach used to estimate larotrectinib treatment duration. Multivariate analyses reducing both the time horizon and restricting larotrectinib use to before disease progression had the combined effect of no change in the base case estimate.

Table 29: Key sensitivity analyses, specified adult low *NTRK* frequency tumour types combined

	Inc. cost (\$)	Inc. QALYs	ICER	%
Base case, adult low frequency <i>NTRK</i> tumours combined	█	0.008	█ ¹	
Time horizon, 5 years (base case: 15 years) (#1)	█	0.005	█ ²	23%
BSC comparators for STS, NSCLC and thyroid (base case: active treatment comparators)	█	0.009	█ ³	37%
Most conservative OS and PFS extrapolation – all ^a (base case: best fit OS and PFS functions) (#2)	█	0.006	█ ³	29%
Use PFS curve for larotrectinib ToT (base case: best fit ToT)	█	0.008	█ ²	22%
Thyroid SoC treatment duration, 17.45 months (base case: disease progression) (#3)	█	0.008	█ ³	34%
Multivariate analyses				
#1 AND #2	█	0.004	█ ³	43%
#1, #2 AND #3	█	0.004	█ ⁴	82%

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' workbook included in the resubmission.

Note: Analyses in were revised during the evaluation: the distribution of tumour types was revised to reflect the distribution in the tested population (rather than the treated population). Other minor revisions to treatment costs modelled and STS SoC data.

^a The most conservative OS and PFS parametric models were chosen for both larotrectinib and SoC extrapolation for all tumour types, except SoC for thyroid cancer, where the base case extrapolations appeared to be more plausible than the most conservative extrapolations. BSC = best supportive care; ICER = incremental cost-effectiveness ratio; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tropomyosin receptor kinase; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; SoC = standard of care; STS = soft tissue sarcoma; ToT = time on treatment.

The redacted values correspond to the following ranges:

- ¹ \$75,000 to < \$95,000
- ² \$95,000 to < \$115,000
- ³ \$115,000 to < \$135,000
- ⁴ \$155,000 to < \$255,000

6.70 In adults with the specified low *NTRK* frequency tumour types, the analyses were most sensitive to assumptions regarding thyroid SoC (i.e. lenvatinib), and in particular, the duration of treatment. While the choice of lenvatinib as the modelled comparator is reasonable, the duration assumed in the base case (39.6 months) was higher than estimates the PBAC have previously considered (17.45 months, para 6.45, 5.08 lenvatinib PSD, November 2015). The analyses were also sensitive to the parametric models chosen for OS and PFS extrapolation and the time horizon. Multivariate analyses led to substantial increases in the ICER. The PSCR stated that the overestimation of the cost offsets for lenvatinib was due to the error in the calculation of the cost of lenvatinib per cycle (see paragraph above). The ESCs considered that correcting for this error did not fully address their concerns that the lenvatinib cost offsets were overestimated.

Drug cost/patient/course

6.71 The per patient cost of larotrectinib based on the overall analysis and tumour type subgroups used in the model, and as used in financial analysis are presented in Table 30. While the cost of larotrectinib applied in the financial analysis is consistent with the treatment course cost of larotrectinib applied in the resubmission's base case, these were based on overall pooled larotrectinib data set, where the tumour types included and their distribution are not likely to be applicable to the proposed setting.

6.72 The per patient cost of SoC is also presented in Table 30. Patients continued on SoC treatment until disease progression or until a maximum treatment number of cycles had been reached.

Table 30: Drug cost per patient for larotrectinib, overall and tumour type analyses, and SoC

	Economic analysis		Financial impact analysis	
	Modelled ToT (years)	Treatment course cost ^a (\$)	Duration (years)	Treatment course cost (\$)
Larotrectinib				
Overall pooled larotrectinib analysis ^b	2.49	████████	2.50	Paed: ██████████ Adults: ██████████
<u>Larotrectinib subgroup analyses ^c</u>				
Paediatric high <i>NTRK</i> fusion frequency	4.95	████████	2.50	████████
Paediatric low <i>NTRK</i> fusion frequency	3.20	████████		
Adult high <i>NTRK</i> fusion frequency	5.60	████████		
Adult low <i>NTRK</i> fusion frequency				
• Colorectal	0.78	████████	2.50	████████
• STS	2.08	████████		
• NSCLC	2.62	████████		
• Thyroid	5.83	████████		
<u>Tumour type subgroup combinations</u>				
Paediatric + adult high <i>NTRK</i> frequency	5.11 ^d	████████#	2.50	████████ - ██████████
Adult low <i>NTRK</i> frequency	2.93 ^e	████████#		████████ - ██████████
Overall proposed population	3.64 ^f	████████#		████████ - ██████████
SoC				
[duration of treatment in clinical study]				
Paediatric high <i>NTRK</i> fusion frequency [4 treatment cycles]	0.29 revised: 0.33	\$9,276 ^g revised: \$9,234 ^h	0.35 (IFS only)	\$2,810 revised: \$2,617
Paediatric low <i>NTRK</i> fusion frequency [Up to 54 weeks]	0.73	\$970 revised: \$1,354	CNS: 1.03 STS: 0.23	CNS: \$1,378 (89%) STS: \$8,415 (11%) revised: \$6,175
Adult high <i>NTRK</i> fusion frequency [median 5 treatment cycles]	0.24	\$1,847 revised: \$1,601	0.35	\$2,241 revised: \$1,942
Adult low <i>NTRK</i> fusion frequency				
• Colorectal [mean 12.7 weeks]	0.31 ⁱ	\$12,761 revised: \$13,128	0.17 ^j	\$6,897 revised: \$7,100
• STS [until progression] ^k	0.28 ⁱ revised: 0.30	\$629 revised: \$672	-	-
• NSCLC [median 4 treatment cycles]	0.19	\$607 revised: \$446	0.23	\$729 revised: \$536
• Thyroid [median 13.8 months]	3.30 ⁱ	\$447,662 revised: \$388,243	1.53 ^l	\$206,517 revised: \$156,919

Source: Constructed during the evaluation from the 'A3.1_Larotrectinib_PBACMSAC_CEA_June21_resub_6June21.xlsx' and the 'A4.2_larotrectinib_PBACMSAC_Section4_June21_3June21.xlsx' workbooks included in the resubmission.

Note: For the revised costs, Larotrectinib treatment costs in tumour type subgroup combinations were revised to reflect the distribution of tumour types eligible for testing on model entry. SoC treatment costs were revised to reflect the lowest cost combinations. The duration of SoC treatment in the paediatric high subgroup was revised to reflect the distribution of IFS and STS *NTRK*-positive patients expected in Australian clinical practice, and the SoC duration in patients with STS was revised to correct for an error where the Kaplan-Meier data had been offset by one row.

Calculated by the evaluation

^a Undiscounted

^b Truncated mean treatment duration: ePAS5: 18.6 months; SAS3 New: 11.8 months

^c Mean treatment in larotrectinib studies not reported for the subgroups

^d Reduces to 3.64 years assuming no use beyond progression.

^e Reduces to 2.90 years assuming no use beyond progression.

^f Reduces to 3.14 years assuming no use beyond progression.

^g Weighted 62% IFS treatment cost of \$9,423 and 38% STS treatment cost of \$8,009. IFS treatment cost includes actinomycin D, which is not PBS listed, and so was not included in the financial analysis.

^h Weighted 98.8% IFS treatment cost of \$9,240 and 1.2% STS treatment cost of \$5,877. IFS treatment cost includes actinomycin D, which is not PBS listed, and so was not included in the financial analysis.

ⁱ Based on extrapolated PFS curve

^j Based on median PFS of 2 months

^k Median PFS was 2.6 months

^l Based on median PFS of 18.3 months

CNS = central nervous system; IFS = infantile fibrosarcoma; NSCLC = non-small cell lung cancer; *NTRK* = neurotrophic tropomyosin receptor kinase; SoC = standard of care; STS = soft tissue sarcoma; ToT = time on treatment.

Estimated PBS & financial implications

- 6.73 The resubmission presented an updated epidemiological approach to estimate the use and financial impact of listing *NTRK* fusion testing and larotrectinib treatment. This was presented for each of the paediatric tumour types included in the pooled larotrectinib studies, and the adult tumour types specified in the proposed MBS and PBS listings.
- 6.74 The epidemiological approach taken was generally unchanged since the previous submission. Incidence estimates, from the AIHW or from the published literature, were applied to population estimates projected by the ABS. The incidence estimates from the AIHW were updated from the previous submission, which was reasonable. Estimates of *NTRK* fusion frequency, proportion with advanced disease at diagnosis and, where relevant, the proportion of patients eligible for later-line treatment were then applied to the estimated incident population for each tumour type to estimate the population eligible for larotrectinib treatment. These estimates were unchanged from the previous submission, except for the frequency of *NTRK* fusions in paediatric STS, where the resubmission applied an estimate of 0.68%. This was reasonable and consistent with previous MSAC and PBAC advice.
- 6.75 Uptake of *NTRK* fusion testing and larotrectinib treatment was assumed to vary between the tumour type subgroups. All paediatric patients were assumed to undergo testing and treatment. Uptake in adult patients with high *NTRK* fusion frequency types was assumed to increase from ■■■% in Year 1 to ■■■% by Year 3, and uptake in adults with low *NTRK* fusion frequency tumours was assumed to increase from ■■■% in Year 1 to ■■■% in all subsequent years. While higher uptake rates in adults with high *NTRK* fusion frequency tumour types have been assumed relative to the previous submission, these may still be an underestimate in Years 1-2. The ESCs considered that uptake in adults with low *NTRK* fusion frequency tumours was potentially overestimated given the uncertain clinical need of larotrectinib in this population.
- 6.76 Further, there may also be a risk of use outside the restrictions, given that the tumour types enrolled in the larotrectinib studies and included in the TGA approved indication are broader than the requested PBS listing. A sensitivity analysis presented by the resubmission assuming that all tumour types represented in the larotrectinib studies

could receive *NTRK* testing and larotrectinib treatment, increases the number of patients treated with larotrectinib from < 500 in Year 1 to < 500 in Year 6.

- 6.77 The resubmission estimated that approximately < 500 patients will grandfather to PBS subsidised larotrectinib upon listing. Grandfathered patients were assumed to receive the same number of larotrectinib scripts as incident cases (including initial scripts). This may not be reasonable as some treatment would have been provided to these patients prior to PBS listing.
- 6.78 The average daily doses applied in the resubmission are unchanged from the previous submission (188.6 mg in adults and 127.8 mg in paediatrics). The average treatment duration was assumed to be 2.5¹⁴ years based on the extrapolated time on treatment curve from the pooled overall larotrectinib analysis. When the larotrectinib time on treatment subgroup analyses are weighted according to the distribution of tumour types expected in clinical practice, the average treatment duration is estimated to be 3.6¹⁴ years (Table 30). However, the resubmission's analyses assume treatment beyond progression – if treatment is not allowed beyond progression, the estimated duration of treatment reduces to 3.1¹⁴ years. As the tumour type distribution in the overall larotrectinib data have limited applicability to the proposed clinical setting, the ESCs considered that treatment duration of larotrectinib was likely underestimated.
- 6.79 The resubmission expected that the listing of larotrectinib would result in a reduction in costs associated with SoC treatment. The resubmission has not considered that, where an active therapy is proposed to be substituted by larotrectinib, SoC would be displaced, rather than replaced in a proportion of patients.
- 6.80 As per the previous submission, the resubmission does not explicitly provide an epidemiological approach to estimate the number of patients eligible for *NTRK* fusion testing. Rather, the number of tests required to identify one patient with *NTRK* fusions has been applied to the number of patients estimated to receive larotrectinib. This approach implicitly assumes that the rate of uptake of both testing and treatment is the same; and that testing occurs at the time at which treatment decisions regarding larotrectinib are being taken. The estimates used are reasonable for the paediatric subgroups and the adults with high *NTRK* fusion frequency tumour types. However, in adult patients with low *NTRK* fusion tumour types, this may not be a reasonable approach, given that *NTRK* fusion testing can occur on diagnosis of advanced disease before initiation of first-line treatment, and that not all patients tested would be eligible for larotrectinib treatment on disease progression.
- 6.81 For each adult patient with a low *NTRK* fusion frequency tumour type treated with larotrectinib, the resubmission estimated that < 500 IHC tests were required. This approach does not account for IHC sensitivity, and so more IHC tests are required to identify one true positive patient. Further, as IHC test performance was based on one

¹⁴ Bayer affirms that the assumed average treatment duration was only provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

study with small patient numbers such that the specificity reported in some tumour types (i.e. 100%) is unlikely to be reproducible in clinical practice. Given the low prevalence estimates – particularly for colorectal cancer and NSCLC – small reductions in the specificity of IHC testing will lead to substantial increases in the number of NGS/FISH tests required.

- 6.82 The estimated use and financial implications of *NTRK* fusion testing and larotrectinib treatment is presented in Table 31.

Table 31: Estimated use and financial implications of *NTRK* testing and larotrectinib treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of <i>NTRK</i> fusion testing						
IHC utilisation						
Adults with low <i>NTRK</i> fusion frequency tumour types who receive larotrectinib	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. IHC tests required (█ ¹ per patient treated)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Revised (█ ¹ per patient) ^a	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
NGS/FISH utilisation						
Paediatric high <i>NTRK</i> fusion frequency patients who receive larotrectinib [A]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ ¹ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Adult high <i>NTRK</i> fusion frequency patients who receive larotrectinib [B]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ ¹ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Paediatric low <i>NTRK</i> fusion frequency patients who receive larotrectinib [C]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ ¹ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Adults low <i>NTRK</i> fusion frequency patients who receive larotrectinib [D]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ ¹ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of NGS/FISH tests	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated extent of use of larotrectinib						
No. grandfathered patients [E]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients likely to be treated with proposed medicine [A + B + C + D + E]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of patients likely to be treated with proposed medicine – November 2020 submission	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed ^b	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Revised ^c	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Net financial implications to the MBS						
Cost of <i>NTRK</i> fusion testing to the MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Revised ^d	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Cost offsets to the MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Revised ^e	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to the MBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Revised	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
November 2020 submission						
Net cost to the MBS (revised)	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net financial implications of to the PBS/RPBS						
Cost of larotrectinib to the PBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Revised ^c	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Cost offsets to the PBS	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Revised ^f	█ ³	█ ³	█ ³	█ ³	█ ³	█ ³
Net cost to the PBS	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Revised	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴
November 2020 submission						
Net cost to the PBS (revised)	█ ³	█ ⁵	█ ⁵	█ ⁶	█ ⁶	█ ⁷
Net financial implications						
Net cost to Government	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴	█ ⁴
Revised	█ ³	█ ³	█ ⁴	█ ⁴	█ ⁴	█ ⁴
November 2020 submission						
Net cost to Government (revised)	█ ⁴	█ ⁵	█ ⁵	█ ⁶	█ ⁶	█ ⁷

Source: Constructed during the evaluation from Section 4 and the 'A4.2_larotrectinib_PBACMSAC_Section4_June21_3June21' workbook included in the resubmission.

^a $1 / (\text{weighted prevalence} \times \text{weighted IHC sensitivity})$, where weighted prevalence was derived by dividing 47 patients estimated with *NTRK* fusions by the █⁹ patients eligible for later-line treatment. Weighted sensitivity 84.6% was applied.

^b Assuming █¹ scripts in adult and █¹ scripts per paediatric patient as estimated by the resubmission. These total number of scripts represent the total number of scripts for 2.5 years.

^c The number of larotrectinib scripts was revised during the evaluation to distribute scripts over the 2.5 year treatment duration assumed.

^d The number of IHC tests and costs were revised based on █¹ tests required to find one *NTRK* fusion positive patient and the cost of NGS/FISH was revised during the evaluation to account for the implications of the Greatest Permissible Gap on the NGS MBS rebate.

^e Revised to assume only one use of MBS item 13950 each time a patient presents for treatment and to correct for the erroneous doubling of services.

^f Prices were revised during the evaluation to use the efficient price for the average dose (as used in the economic evaluation) and SoC patient copayments were revised to assume only one copayment per original script of infusible PBS items (as per the Efficient Funding of Chemotherapy arrangements). Costs for lenvatinib and trifluridine+tipiracil are based on published prices.

FISH = fluorescence in situ hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; *NTRK* = neurotrophic tropomyosin receptor kinase.

The redacted values correspond to the following ranges:

¹ < 500

² 500 to < 5,000

³ \$0 to < \$10 million

⁴ \$10 million to < \$20 million

⁵ \$20 million to < \$30 million

⁶ \$30 million to < \$40 million

⁷ \$40 million to < \$50 million

⁸ 5,000 to < 10,000

⁹ 10,000 to < 20,000

- 6.83 The net costs to the PBS were most sensitive to the duration of larotrectinib treatment, the size of the eligible population (including tumour types eligible for larotrectinib treatment) and the frequency of *NTRK* fusions in the specified adult low frequency tumour types.
- 6.84 The net costs to the MBS were most sensitive to the incidence estimates applied, the tumour types included, the timing of *NTRK* testing, IHC specificity and cost and the split of NGS and FISH testing.

Quality use of medicines (QUM)

- 6.85 This has not changed since the previous submission (paragraphs 6.95 and 6.96, larotrectinib PSD, November 2020). A QUM issue will arise should larotrectinib be prescribed or be made available for a treatment line where it may substitute for more effective available therapies. Previously, DUSC considered that risk of use outside the restriction was low, especially if a pathology report is required as part of the written authority application.

Financial management – risk sharing arrangements

- 6.86 The previous submission's individual utilisation-based risk share arrangement, consisting of a duration-based cap and rebate, was removed from the current submission on the basis of PBAC advice (paragraphs 7.20, 5.08 larotrectinib PSD, November 2020). This is appropriate. No alternate risk sharing arrangements were proposed.

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

7 PBAC Outcome

Paediatric *NTRK* fusion population and adult high frequency *NTRK* fusion population

- 7.1 The PBAC deferred making its decision on whether to recommend the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (*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. The PBAC was of a mind to recommend the listing for paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (MASC and secretory breast carcinoma) on the basis that the incremental cost-effectiveness ratio (ICER) was acceptable at the proposed price, pending MSAC advice on the funding of the codependent *NTRK* testing.
- 7.2 The PBAC noted the input from health care professionals which highlighted the need for treatment options particularly for paediatric cancer patients. The PBAC reiterated there was a clinical need for effective therapies for patients with rare cancers harbouring *NTRK* fusions, for which there are few effective standard of care treatments. The PBAC noted the majority of tumour types in paediatric patients and the tumour types specified for the adult high frequency subgroup (MASC and secretory breast carcinoma) are rare cancers.

- 7.3 The PBAC noted that salivary gland cancer which was specified for the adult high frequency *NTRK* fusion population, was broader than MASC specified in the proposed MBS item descriptor. The PBAC considered it would appropriate for MASC to be specified for the adult high frequency *NTRK* fusion population instead of salivary gland cancer to align the PBS restriction with MBS item descriptor and noting the frequency of *NTRK* fusions in non-MASC salivary gland tumours is low.
- 7.4 The PBAC noted there remained insufficient evidence of a treatment benefit for patients continuing to receive larotrectinib following disease progression. The PBAC considered that including a criterion in the continuation restriction which limits treatment to patients who have not had radiographic progression would reduce the risk of use beyond progression.
- 7.5 The PBAC recalled its previous advice that specifying the names of the eligible tumour types in the PBS restrictions may reduce the risk of use beyond the intended populations. The PBAC noted that the resubmission specified tumour types for the adult subgroups only. The PBAC considered that not specifying the tumour types for the paediatric subgroups was appropriate noting the high clinical need and relatively low prevalence of paediatric cancer patients.
- 7.6 The PBAC recalled that, in its November 2020 consideration of larotrectinib, it had considered the claim of superior effectiveness compared to Standard of Care (SoC) was acceptable for the high frequency adult and paediatric populations but not sufficiently supported for the low frequency paediatric population.
- 7.7 The PBAC noted the resubmission was based on a naïve indirect comparison between updated pooled efficacy data (July 2020 data cut-off) from the same single-arm larotrectinib studies as in the previous submission (LOXO-001, NAVIGATE, and SCOUT) and SoC data from historical single-arm studies. The PBAC noted that, compared to the previous July 2019 data cut-off, there was an additional 52 patients and median follow-up for OS increased to 24 months from 15.8 months. The PBAC noted that, as per the previous submission, 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 OS not being reached for all tumour types combined.
- 7.8 The PBAC noted that an informative comparison of safety between larotrectinib and SoC was not feasible given the limited data. The PBAC noted there may be an increased risk of neurodevelopment impairment for paediatric patients the longer patients remain on treatment. The PBAC maintained that, overall, the available data indicated a manageable safety profile for larotrectinib, although there were insufficient data to assess the long-term safety of larotrectinib.
- 7.9 The PBAC recalled that, in November 2020, it advised that the price reduction should be of a magnitude sufficient to achieve an ICER within the range of \$70,000/QALY to \$80,000/QALY. The PBAC further recalled it previously advised that to determine the magnitude of the price reduction required, adjustments to the economic analysis including i) the most conservative OS and PFS extrapolations; ii) an *NTRK* fusion

frequency of 0.68% for paediatric STS; and iii) exclusion of the RSA rebate, should be applied to account for the uncertainties of the larotrectinib data.

- 7.10 The PBAC noted the resubmission presented a cost-utility analysis with a revised model structure, comparing (a) *NTRK* testing and larotrectinib treatment in patients identified with *NTRK* fusions and SoC treatment in those without, to (b) no testing, where all patients were treated with SoC. The PBAC noted that the main revised inputs to the economic analysis were consistent with those outlined in paragraph 7.8 and included a decrease in the time horizon from 20 to 15 years, updated *NTRK* fusion testing costs, updated larotrectinib data and a price reduction for larotrectinib. The PBAC noted the resulting ICER for the adult high *NTRK* frequency subgroup and all paediatric patients combined was \$75,000 to < \$95,000/QALY when the distribution of tumour types were revised to reflect the distribution in the tested Australian population (rather than the treated population) and the most conservative OS and PFS parametric models were applied for the high *NTRK* fusion frequency tumour types. While the PBAC considered the treatment benefit of larotrectinib in the paediatric low frequency subgroup was uncertain, it noted that this subgroup did not have a substantial effect on the ICER. The PBAC noted there remained uncertainty around the incremental benefit modelled for larotrectinib overall given the lack of direct comparative data, use of historical SoC data, small patient numbers across studies, immaturity of the data and heterogeneity within and between tumour types. However, the PBAC considered the revised ICER was acceptable at the proposed price for paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours, in the context of the high unmet clinical need for effective treatments for these patient populations.
- 7.11 The PBAC noted that the epidemiological approach used to estimate the number of patients eligible for treatment with larotrectinib remained generally unchanged from the previous submission. The PBAC noted that the financial estimates appropriately revised the frequency of *NTRK* fusions in paediatric STS to 0.68%. The PBAC agreed with the ESCs that the 2.5¹⁵ year treatment duration for larotrectinib applied in the financial estimates was likely an underestimate, noting that this treatment duration was based on the pooled overall larotrectinib analysis which does not reflect the distribution of tumour types likely to be observed in Australian clinical practice. The PBAC noted that the financial estimates also assumed treatment with larotrectinib beyond progression. The PBAC noted that when the larotrectinib time on treatment subgroup analyses are weighted according to the distribution of tumour types expected in clinical practice and treatment is not allowed beyond progression, the average treatment duration is estimated to be 3.64¹⁵ years in the combined paediatric *NTRK* fusion population and adult high frequency *NTRK* fusion population. The PBAC

¹⁵ Bayer affirms that the assumed average treatment duration was only provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

considered an RSA would be appropriate to manage the risk of use in the low frequency adult population and a longer average treatment duration.

Outcome:

Deferred

Adult low frequency *NTRK* fusion population

- 7.12 The PBAC did not recommend the listing of larotrectinib for the treatment of adult patients with low frequency *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. The PBAC considered that the ICER for this population remained high and uncertain. Further, the PBAC considered there is less unmet clinical need within this patient population given there are effective alternative treatments available for adult low frequency *NTRK* fusion tumours.
- 7.13 The PBAC noted the resubmission specified four specific tumour types for the adult low frequency subgroup: adult STS; CRC; thyroid cancer, and NSCLC. The PBAC noted that the resubmission specified new comparators for NSCLC (docetaxel and placebo), thyroid cancer (lenvatinib) and CRC (trifluridine/tipiracil) and considered these were more representative of current SoC in the last treatment line setting where larotrectinib is proposed to be used in the adult low frequency subgroup.
- 7.14 The PBAC considered that an incremental benefit of larotrectinib compared to SoC in the adult low frequency subgroup was not clearly supported by the additional larotrectinib single-arm data and noted that the data remained immature at the latest data cut. The PBAC noted that the limited and uncertain nature of the available data was reflected in the latest Kaplan-Meier curves where a small number of additional patients resulted in significant change to the curves.
- 7.15 The PBAC maintained its previous consideration that the claim of superior effectiveness compared to SoC for the low frequency adult population was not sufficiently supported. Further, the PBAC considered there is less unmet clinical need within the low frequency adult population given there are existing effective therapies for several adult low frequency tumour types and the uncertainty around the incremental benefit of larotrectinib compared to these therapies.
- 7.16 The PBAC noted that the ICER for the adult low frequency subgroup was \$75,000 to < \$95,000/QALY when the larotrectinib data used in the analysis was restricted to adult low frequency tumour types and the distribution of tumour types were revised to reflect the distribution in the tested Australian population. The PBAC noted that the ICER was higher than the range of \$70,000/QALY to \$80,000/QALY which it previously specified for determining the magnitude of price reduction for larotrectinib. The PBAC considered the ICER was uncertain and likely underestimated given there was insufficient evidence to support an incremental benefit compared to SoC. The PBAC noted that the analysis for the adult low frequency tumour subgroup was particularly sensitive to the time horizon, OS and PFS extrapolation and duration of lenvatinib SoC treatment duration. The PBAC noted that the ICER increased to \$155,000 to <

\$255,000/QALY when i) the time horizon was reduced from 15 years to 5 years; ii) the most conservative OS and PFS extrapolations were used; and iii) the lenvatinib treatment duration was reduced from 39.6 months to the duration of 17.45 months, which the Committee had previously considered for lenvatinib. The PBAC advised that, given there would unlikely be sufficient data forthcoming to address the uncertainty around the effectiveness of larotrectinib, a further substantial price reduction would be required to achieve a cost-effective price. The PBAC advised that the magnitude of the price reduction required in order to achieve an ICER within the range of \$70,000/QALY to \$80,000/QALY should be determined using more conservative extrapolations, a shorter time horizon and a reduced lenvatinib treatment duration.

- 7.17 The PBAC noted that the financial estimates assumed that uptake in adult patients with low *NTRK* fusion frequency tumours would be ■% in Year 1 and ■% in subsequent years. The PBAC considered that assumed uptake was likely overestimated given the uncertainty regarding uptake of *NTRK* testing in the adult low frequency subgroup.

Outcome:
Rejected

Addendum from the March 2022 PBAC Meeting:

8 Background

- 8.1 At its November 2021 meeting, the PBAC deferred making its decision on whether to recommend the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (*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. The PBAC was of a mind to recommend the listing for paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (MASC and secretory breast carcinoma) on the basis that the incremental cost-effectiveness ratio (ICER) was acceptable at the proposed price, pending MSAC advice on the funding of the co-dependent *NTRK* testing. The PBAC intended to not recommend the listing of larotrectinib for the treatment of adult patients with low frequency *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.
- 8.2 At its meeting on 25-26 November 2021, 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.
- 8.3 Overall, MSAC agreed with the ESCs and considered that there continued to be limited evidence of the analytical performance of the proposed tests (i.e. NGS, FISH and IHC). However, based on the limited evidence, MSAC also concluded that, although analytical performance varied across RNA-NGS, DNA-NGS and FISH, this was within acceptable limits for paediatric patients or adult patients with high-frequency *NTRK* gene fusion cancer types. MSAC did not support public funding for adult patients with any type of tumour harbouring *NTRK* fusion at low frequency due to poorer test performance and in alignment with the PBAC's intention to not recommend listing larotrectinib in this population on the PBS. Thus, MSAC advised that the proposed MBS item for IHC testing prior to *NTRK* fusion testing was not required.
- 8.4 MSAC advised that separate MBS items should be created for the two separate methodologies (i.e. NGS and FISH) due to their differing costs and performance and the need to allow time for pathology laboratories to develop the capacity to provide NGS-based services. MSAC also considered that the two cancer types with high frequency of *NTRK* fusion in adults: mammary analogue secretory carcinoma of the salivary gland or secretory breast cancer, should be specified in the item descriptor.

9 Current situation

- 9.1 The sponsor provided revised financial estimates to address the issues raised in the November 2021 PBAC public summary document (PSD). Key changes to the financial estimates included the following:

- The estimates of patient numbers have been revised to include only the paediatric population and adult high-frequency *NTRK* fusion population.
- The estimate of the per patient script volume has been revised to reflect the average treatment duration of 3.64 years¹⁶ in the combined paediatric *NTRK* fusion population and adult high-frequency *NTRK* fusion population.
- Scripts have been applied across years of treatment to account for initial and continuing treatment. Previously, scripts were applied within the same year rather than split across years.
- The estimated number of grandfather patients has been reduced to reflect the number of grandfather patients within the paediatric population and adult high-frequency *NTRK* fusion population.

9.2 The revised financial estimates are presented in the Table below.

¹⁶ Bayer affirms that the assumed average treatment duration was only provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

Table 1: Revised estimated use and financial implications of *NTRK* testing and larotrectinib treatment

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use of <i>NTRK</i> fusion testing						
NGS/FISH utilisation ^a						
Paediatric high <i>NTRK</i> fusion frequency patients who receive larotrectinib [A]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Adult high <i>NTRK</i> fusion frequency patients who receive larotrectinib [B] ^b	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Paediatric low <i>NTRK</i> fusion frequency patients who receive larotrectinib [C]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
No. NGS/FISH tests required (█ per patient)	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of NGS/FISH tests	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Estimated extent of use of larotrectinib						
No. grandfathered patients [D]	█ ¹	-	-	-	-	-
Number of patients likely to be treated with proposed medicine [A + B + C + D]	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Number of scripts dispensed	█ ¹	█ ³	█ ³	█ ³	█ ³	█ ³
Net financial implications to the MBS						
Cost of <i>NTRK</i> fusion testing to the MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Cost offsets to the MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to the MBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net financial implications of to the PBS/RPBS						
Cost of larotrectinib to the PBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Cost offsets to the PBS ^c	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net cost to the PBS	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²
Net financial implications						
Net cost to Government	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²	\$█ ²

Source: Table 2 of the pre-PBAC Response, 'Attachment 1-Item 7.07_1602.1 Larotrectinib_PBACMSAC_UCM workbook_Jan2022' workbook

Markups and MBS item costs have been updated to reflect July 2021 updates. PBS items have been updated to reflect the January 2022 schedule.

^a Cost of NGS testing was revised to \$1,000 as per MSAC advice (p6 of Public Summary Document for Application 1602.1)

^b the uptake rate in Year 1 and 2 for adult high frequency *NTRK* fusion patients was revised to 100% as per ESCs advice (Paragraph 6.75 November 2021 larotrectinib Minutes).

^c Cost offsets for larotrectinib and trifluridine+tipiracil are based on published prices.

FISH = fluorescence *in situ* hybridisation; IHC = immunohistochemistry; NGS = next generation sequencing; *NTRK* = neurotrophic tropomyosin receptor kinase.

The redacted values correspond to the following ranges:

¹ < 500

² \$0 to < \$10 million

³ 500 to < 5,000

9.3 The pre-PBAC Response proposed revised published prices to align with the reimbursement of larotrectinib in other countries. No changes were proposed to the effective price.

Revised published prices

Form	Published AEMP
Larotrectinib, 100 mg, oral capsules	<u>November 2021</u> \$ [REDACTED] <u>Revised</u> \$ [REDACTED]
Larotrectinib, 25 mg, oral capsules	<u>November 2021</u> \$ [REDACTED] <u>Revised</u> \$ [REDACTED]
Larotrectinib, 20 mg/ml, 1 × 100 ml bottle solution, oral administration	<u>November 2021</u> \$ [REDACTED] <u>Revised</u> \$ [REDACTED]

Source: Table 1 and Table 2 of the pre-PBAC Response

9.4 The pre-PBAC Response indicated the sponsor was willing to enter a Risk Sharing Arrangement with subsidisation caps based on the estimated drug cost to the PBS of listing larotrectinib and a [REDACTED] % rebate for expenditure above the caps.

9.5 The pre-PBAC Response accepted the following amendments to the restriction previously advised by the PBAC:

- Specifying MASC for the adult high frequency NTRK fusion population instead of salivary gland cancer to align the PBS restriction with MBS item descriptor (paragraph 7.3, November 2021 larotrectinib PSD).
- Including a criterion in the continuation restriction which limits treatment to patients who have not had radiographic progression to reduce the risk of use beyond progression (paragraph 7.4, November 2021 larotrectinib PSD).
- Limiting treatment duration under the grandfather restriction to 3 months consistent with the proposed initial treatment restriction (paragraph 2.1, November 2021 larotrectinib PSD).

10 PBAC Outcome

10.1 The PBAC recommended the listing of larotrectinib for the treatment of patients with tropomyosin receptor kinase (*NTRK*) fusion tumours that are either unresectable locally advanced, metastatic, or locally advanced and unsuitable for surgery (i.e. would otherwise require disfiguring surgery or limb amputation to achieve a complete surgical resection). The PBAC recommended the listing for paediatric patients with *NTRK* fusion tumours and adult patients with high frequency *NTRK* fusion tumours (specifically MASC and secretory breast carcinoma) on the basis that the incremental cost-effectiveness ratio was acceptable at the proposed price and noting that MSAC

supported funding the co-dependent *NTRK* testing to determine eligibility for treatment with larotrectinib in all paediatric patients, and adult patients with high-frequency *NTRK* fusion cancer types. The PBAC did not recommend this listing extend to adult patients for low frequency *NTRK* fusion tumours for the reasons stated in its November 2021 PSD.

- 10.2 The PBAC noted the revised financial estimates appropriately reflect the estimated treatment duration in the combined paediatric *NTRK* fusion population and adult high frequency *NTRK* fusion population of 3.64 years¹⁷, when the larotrectinib time on treatment subgroup analyses are weighted according to the distribution of tumour types expected in clinical practice and treatment is not allowed beyond progression. The PBAC maintained its previous advice that an RSA would be appropriate to manage the risks of use in the low frequency adult population and of a longer average treatment duration.
- 10.3 The PBAC reiterated that an Authority Required (In Writing) listing would be appropriate for initial treatment and an Authority Required (telephone/online PBS Authorities system) listing would be appropriate for continuing treatment, as the combination of high price and risk in use in adult low frequency *NTRK* tumours and tumours without *NTRK* fusion are significant enough to warrant an 'in-writing only' type listing at treatment initiation. The PBAC advised that the written authority application for both paediatric and adult patients should detail confirmation of a positive *NTRK* gene fusion test. The PBAC advised that the authority application for adult patients should include details of tumour histology type to limit use to MASC and secretory breast carcinoma, the tumour types specified in the restriction for adult patients.
- 10.4 The PBAC considered that a separate grandfather restriction would not be required given that grandfather patients would be eligible under the initial restrictions (if they meet the PBS initiation criteria).
- 10.5 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were met. Specifically the PBAC found that in the circumstances of its recommendation for larotrectinib:
 - a) The treatment is expected to provide a substantial and clinically relevant improvement in efficacy over standard of care in terms of overall survival;
 - b) The treatment is expected to address a high and urgent unmet clinical need in patients with *NTRK* fusion tumours, noting the majority of tumour types in paediatric patients and the tumour types specified for the adult high frequency subgroup (MASC and secretory breast carcinoma) are rare cancers with limited treatment options;

¹⁷ Bayer affirms that the assumed average treatment duration was only provided for the purposes of informing the PBAC consideration. Interpretation of the results and their application should therefore be limited to seeking to understand the basis for the PBAC outcome and should not be used for any other purpose.

c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A based on the preceding findings.

10.6 The PBAC considered that larotrectinib should be exempt from the early supply rule as the dosage regimen is not standard for paediatric patients.

10.7 PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

11 Recommended listing

Add new medicinal product as follows:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. 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, 100 mL	NEW	1	1	2	Vitrakvi
		Early Supply Rule applies? Yes Max.qty (packs) multiplier = 3 Repeat increases: nil			
Restriction Summary / Treatment of Concept:					
Category / Program: General Schedule (Code: GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing only via post/HPOS upload)					
NOTE: 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.					
NOTE: No increase in the maximum number of repeats may be authorised.					
NOTE: Special pricing arrangements apply					
Episodicity: [blank]					
Severity: [blank]					
Condition: Solid tumours (of any type) with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion where treatment is/was initiated in a child					
Indication: Solid tumours (of any type) with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion where treatment with this drug is/was initiated in a child					
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 – 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					

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	Clinical criteria:
	The condition must be metastatic disease; or
	The condition must be both: (i) locally advanced, (ii) unresectable; or
	The condition must be both: (i) locally advanced, (ii) require disfiguring surgery/limb amputation to achieve complete surgical resection
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised systemic 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
	Population criteria:
	Patient must be/have been under 18 years of age (i.e. prior to their 18 th birthday) at treatment initiation with this drug
	Prescribing Instructions:
	The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) 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).
	NOTE: 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. EST 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 authority to prescribe should 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
Restriction Summary / Treatment of Concept:	
	Episodicity: [blank]
	Severity: [blank]
	Condition: Solid tumours (of certain specified types) with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
	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 – 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

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	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 a mammary analogue secretory carcinoma of the salivary gland confirmed through a pathology report (of any date); or
	The condition must be a secretory breast carcinoma confirmed through a pathology report (of any date)
	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 both: (i) locally advanced, (ii) require disfiguring surgery/limb amputation to achieve complete surgical resection
	AND
	Clinical criteria:
	The treatment must be the sole PBS-subsidised systemic 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
	Population criteria:
	Patient must be aged 18 years or older
	Prescribing Instructions: The authority application must be made in writing and must include: (1) a completed authority prescription form; and (2) 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).
	Prescribing Instructions: Provide the following evidence if different to that provided to substantiate the NTRK gene fusion, to establish the carcinoma type (salivary gland/secretory breast carcinoma) being treated: (i) the date of the pathology report, (ii) the name of the pathology service provider, (iii) the unique identifying number/code linking the pathology result to the patient

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, 100 mL	NEW	1	1	5	Vitrakvi
			Max.qty (packs) multiplier = 3 Repeat increases: nil		
Restriction Summary / Treatment of Concept:					
Category / Program: General Schedule (Code: GE)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (telephone/online PBS Authorities system)					
Episodicity: [blank]					
Severity: [blank]					
Condition: Solid tumours with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion					

	Indication: Solid tumours with confirmed neurotrophic tropomyosin receptor kinase (NTRK) gene fusion
	Treatment phase: Continuing treatment
	Treatment criteria:
	Patient must be undergoing continuing PBS-subsidised treatment commenced through an 'Initial treatment' listing
	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.
	Prescribing instructions: Where radiographic progression is observed, mark any remaining repeat prescriptions with the word 'cancelled'.
	NOTE: No increase in the maximum number of repeats may be authorised.
	NOTE: Special pricing arrangements apply
	NOTE: 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. EST Monday to Friday).
	NOTE: 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.

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

12 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.

13 Sponsor's Comment

Bayer welcomes the PBAC's decision to recommend larotrectinib (Vitrakvi®) for reimbursement on the PBS for the treatment of children who are diagnosed with NTRK gene fusion positive tumours, as well as for adults with a NTRK fusion-positive mammary analogue secretory cancer of salivary gland or secretory breast cancer. This is a major step forward in the fight against childhood and rare cancers.