

7.07 SELUMETINIB, Capsule 10 mg, Capsule 25 mg, Koselugo[®], Alexion Pharmaceuticals Australasia Pty Ltd

1 Purpose of resubmission

- 1.1 The Facilitated Resolution Pathway resubmission requested a Section 85, General Schedule Authority Required (Written), listing for selumetinib for the treatment of symptomatic, inoperable plexiform neurofibroma(s) (PN) in paediatric patients aged two years and over with neurofibromatosis (NF1).
- 1.2 Listing was requested on the basis of a cost-utility analysis versus best supportive care (BSC).

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

Component	Description
Population	Children aged ≥ 2 years and diagnosed ≤ 18 years with NF1 and symptomatic ^a , inoperable ^b PN
Intervention	Selumetinib 25 mg/m ² BSA orally twice daily until unacceptable tolerability or disease progression
Comparator	Best supportive care (no active treatment)
Outcomes	ORR assessed by centralised volumetric MRI of the target PN, DoR, PFS, clinical outcomes including pain, motor dysfunction, airway dysfunction, bowel/bladder dysfunction, vision dysfunction, disfigurement, HRQoL, safety and tolerability.
Clinical claim	In children with NF1 and symptomatic, inoperable PN, treatment with selumetinib is more effective than supportive care in reducing PN volume, reducing pain, improving functional assessment scores and improving HRQoL. Selumetinib has an acceptable safety and tolerability profile for chronic treatment in children.

Source: Table 1.1 of the resubmission.

BSA = body surface area; DoR = duration of response; HRQoL = health-related quality of life; MRI = magnetic resonance imaging; NF1 = neurofibromatosis type 1; ORR = objective response rate; PFS = progression-free survival; PN = plexiform neurofibroma(s).

^a Definition of symptomatic: PN has to cause significant morbidity, such as (but not limited to) head and neck PN that can compromise the airway or great vessels, paraspinal PN that can cause myelopathy, brachial or lumbar plexus PN that can cause nerve compression and loss of function, PN that can result in major deformity (e.g., orbital PN) or significant disfiguring, PN of the extremity that can cause limb hypertrophy or loss of function, and painful PN.

^b Definition of inoperable: Adequate tumour resection cannot be done safely or without causing unacceptable morbidity.

Strikethrough text indicates change to the requested population from the July 2022 resubmission.

2 Background

Registration status

- 2.1 Selumetinib was TGA registered on 2 December 2021 for the treatment of paediatric patients aged 2 years and above, with NF1 who have symptomatic, inoperable PN(s).

Previous PBAC consideration

- 2.2 At the November 2022 PBAC meeting, the PBAC did not recommend selumetinib for the treatment of symptomatic, inoperable PN in paediatric patients with NF1 (paragraph 7.1, selumetinib Public Summary Document (PSD), November 2022 PBAC

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meeting). A Facilitated Resolution Pathway workshop was held for selumetinib in April 2023 to explore feasible options to address the issues identified by the PBAC.

2.3 Table 2 summarises the key matters of concern from the November 2022 PBAC submission and how they were addressed in the resubmission.

Table 2: Summary of key matters of concern

Component	Matter of concern	How the resubmission addresses it
Restriction	The Secretariat questioned the suitability of a Section 100 Highly Specialised Drug Program (HSDP) listing (paragraph 3.5, selumetinib PSD, Nov 2022 PBAC meeting).	Addressed. The resubmission requested a Section 85 - General Schedule listing.
	The PBAC stated that the initial supply restriction should align more closely with the SPRINT trial Stratum I and specify that patients have: (i) the ability to swallow a whole capsule, and (ii) a Karnofsky or Lansky Performance score of $\geq 70\%$ (paragraph 7.16, Selumetinib, PSD, Nov 2022 PBAC meeting).	Addressed. These criteria were added to the proposed initial restriction in the resubmission.
	The PBAC stated that there was quality use of medicine issues associated with the large capsule size (paragraph 7.19, selumetinib PSD, Nov 2022 PBAC meeting).	Partially addressed. The dosage form remained the same, however, the resubmission added the criterion “patients must be able to swallow selumetinib capsules” to the proposed initial restriction.
	The PBAC stated that any future restriction required the addition of a definition for progression and a clear stopping rule (paragraph 7.17, selumetinib PSD, Nov 2022 PBAC meeting).	Addressed. The resubmission proposed a ‘First Continuing’ restriction at six months for the assessment of tolerability followed by ‘Subsequent Continuing’ restriction at 12 months for the assessment of tolerability and response to treatment defined as stability or improvement of the clinical criteria and that relevant imaging has not shown an increase in tumour size of $\geq 20\%$.
Clinical effectiveness	The PBAC requested that a resubmission should present any available data for adult patients (paragraph 7.18, selumetinib PSD, Nov 2022 PBAC meeting).	Addressed. The resubmission presented results from: <ul style="list-style-type: none"> • NCT02407405: a Phase II clinical trial of selumetinib in adult patients. • A subgroup analysis on a cohort (n = 10, 20%) of patients who turned 18 whilst enrolled in the SPRINT trial Stratum I.
	The PBAC was moderately certain that selumetinib demonstrated superior efficacy compared to supportive care in patients with symptomatic inoperable PN but noted a number of uncertainties remained (paragraph 7.8, selumetinib PSD, Nov 2022 PBAC meeting).	Not addressed. The resubmission did not present any additional data or analyses to account for the uncertainty in the effectiveness claim.
	The PBAC considered the claim that selumetinib was non-inferior in terms of safety compared to supportive care could not be supported given the lack of comparative data (paragraph 7.10, selumetinib PSD, Nov 2022 PBAC meeting).	Not addressed. The resubmission did not present any comparative data.

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Component	Matter of concern	How the resubmission addresses it
Economic evaluation	The PBAC noted that a significant price reduction will be required for selumetinib to be cost-effective (paragraph 7.20, selumetinib PSD, Nov 2022 PBAC meeting).	Partially addressed. The resubmission proposed a price reduction of █████% on effective AEMP; however, the ICER remained high.
	The PBAC stated that there were number of issues with the economic model, including <ul style="list-style-type: none"> • Time horizon • Application of differential discount rate • Cost of monitoring for selumetinib • Sources and application of differential utilities for PFS health state • Extrapolation function for PFS (selumetinib) • Extrapolation function for TTD • Standard mortality ratio applied (paragraph 7.11, selumetinib PSD, Nov 2022 PBAC meeting).	Addressed and revised. The following revisions were made: <ul style="list-style-type: none"> • Time horizon revised to 50 years. • Applied uniform 5% discount rate to costs and outcomes • Included ophthalmological monitoring costs • Uniform PFS utility score of 0.74 applied to both arms • Lognormal extrapolation for PFS applied to both arms • Maintained Weibull extrapolation for the TTD. • Maintained SMR of 2.02 based on Duong et al. (2011)
Financial estimates	The PBAC noted the following issues: <ul style="list-style-type: none"> • The uncertainty regarding the proportion of patients with symptomatic, inoperable PN • The assumed uptake rate of 95% • The imprecise approach used to estimate the dose and number of prescriptions • The inappropriate application of time duration to a prevalent patient population by using extrapolated TTD survival curve (paragraph 7.14, selumetinib PSD, Nov 2022 PBAC meeting).	Addressed and revised. The following revisions were made: <ul style="list-style-type: none"> • Proportion of patients with NF1 PN was revised to 67% from 74%. • The eligible patient population was split into (i) patients aged <6 years (ii) patients aged ≥6 years. Different uptake rates were applied to both cohorts based on the revised eligibility criteria. • Inclusion of BSA distribution from SPRINT trial Stratum I to determine the doses and number of prescriptions. • TTD was not applied to estimate the financial implications of selumetinib.
	The PBAC stated that a fixed cost per patient per year would be preferable for selumetinib (paragraph 7.13, selumetinib PSD, Nov 2022 PBAC meeting). The PBAC considered that a RSA would be required and a rebate of 100% for use exceeding the caps would likely be appropriate (paragraph 7.15, selumetinib PSD, Nov 2022, PBAC meeting).	Addressed. The resubmission proposed a fixed maximum cost per patient based on a BSA of █████m ² and a RSA with a █████% rebate above the overall expenditure cap.

Source: Table 1.2 of the resubmission.

AEMP = approved ex-manufacturer price; BSA = body surface area; NF1 = neurofibromatosis type 1; PFS = progression-free survival, PN = plexiform neurofibroma(s); SMR = standard mortality rate; TTD = time-to-treatment discontinuation.

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

3 Requested listing

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELUMETINIB					
Selumetinib 10 mg capsule, 60	Published: \$7,112.13 Effective: \$█	1	60	5	Koselugo
Selumetinib 25 mg capsule, 60	Published: \$17,537.13 Effective: \$█	1	60	5	Koselugo

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Category / Program: General Schedule - 85
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing)
Episodicity: Chronic treatment
Severity: Symptomatic, inoperable plexiform neurofibroma(s)
Condition: Neurofibromatosis type 1 (NF1)
Indication: Treatment of symptomatic, inoperable PN in patients with NF1
Treatment Phase: Initial
Clinical criteria:
The PN must cause significant symptoms/morbidity, disability, disfigurement or impairment of normal body function
OR
Clinical criteria:
The PN is likely to lead to significant symptoms/morbidity, disability, disfigurement or impairment of normal body function
AND
Clinical criteria:
Complete PN resection cannot be done safely or without causing unacceptable morbidity
Treatment criteria:
Must be treated by a specialist physician with expertise in neurofibromatosis or in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in neurofibromatosis or in consultation with a centre with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
Population criteria:
Patients must be ≥ 2 years and ≤ 18 years of age with symptomatic, inoperable PN
AND
Population criteria:
Patients must be able to swallow selumetinib capsule
AND
Population criteria:
Patients must have a Karnofsky [^] or Lansky [#] Performance Score of $\geq 70\%$ [^] Schag et al. 1984 [#] Lansky et al 1987
Administrative Advice: Significant symptoms/morbidity are symptoms such as (but not limited to) head and neck PN that can compromise the airway or great vessels, paraspinal PN that can cause myelopathy, brachial or lumbar plexus PN that can cause nerve compression and loss of function, PN that can result in major deformity (e.g., orbital PN) or significant disfiguring, PN of the extremity that can cause limb hypertrophy or loss of function, and painful PN.
Administrative Advice: 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). At the time of the authority application, details (result and date of result) of relevant imaging report must be provided.
Administrative Advice: Special Pricing Arrangements apply
Treatment Phase: First Continuing
Clinical criteria:
Must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Must be tolerating treatment

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Treatment criteria:
Must be treated by a specialist physician with expertise in neurofibromatosis or in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in neurofibromatosis or in consultation with a centre with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
Population criteria:
Patients must be 2 years or older
Administrative Advice: 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).
Treatment Phase: Subsequent continuing
Clinical criteria:
Must have previously received PBS-subsidised treatment with this drug for this condition
AND
Clinical criteria:
Must be tolerating treatment
AND
Clinical criteria:
Patients must have stabilisation of disease or adequate response to treatment. Adequate response is defined as: Stability or improvement of the clinical criteria as per the initial restriction AND Relevant imaging has not shown an increase in tumour size of 20% or more.
Treatment criteria:
Must be treated by a specialist physician with expertise in neurofibromatosis or in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in neurofibromatosis or in consultation with a centre with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
Population criteria:
Patients must be 2 years or older
Administrative Advice: 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). At the time of the authority application, details (result and date of result) of the imaging report must be provided.
Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – ‘Grandfather’ arrangements
Clinical criteria:
Patient must have previously received treatment with this drug for this condition prior to PBS listing
AND
Clinical criteria:
The PN must have caused significant symptoms/morbidity, disability, disfigurement or impairment of normal body function prior to commencing treatment with selumetinib
OR
Clinical criteria:

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The PN was likely to lead to significant symptoms/morbidity, disability, disfigurement or impairment of normal body function prior to commencing treatment with selumetinib
AND
Clinical criteria:
Complete PN resection cannot be done safely or without causing unacceptable morbidity
AND
Clinical criteria:
If < 1 year since commencement of selumetinib treatment: Patient must be tolerating treatment.
OR
Clinical criteria:
If ≥ 1 year since commencement of selumetinib treatment: Patients must be tolerating treatment and patients must have stabilisation of disease or adequate response to treatment. Adequate response is defined as: Stability or improvement of the clinical criteria
AND
Relevant imaging has not shown an increase in tumour size of 20% or more
Treatment criteria:
Must be treated by a specialist physician with expertise in neurofibromatosis or in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
AND
Treatment criteria:
Must be treated in a centre with expertise in neurofibromatosis or in consultation with a centre with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
Population criteria:
Patients must be 2 years or older
Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the relevant 'Continuing' treatment phase criteria. This grandfather restriction will cease to operate from 12 months after the date specified in the clinical criteria.

- 3.1 The requested effective ex-manufacturer price (EMP) was █████% lower than that proposed in the previous submission, equating to an effective EMP of \$| (as compared to \$|) for the 10 mg pack and \$| (as compared to \$|) for the 25 mg pack.
- 3.2 The ESC noted that the proposed restrictions in the resubmission incorporated all changes suggested by the PBAC at its November 2022 meeting as well as the outcomes of the Facilitated Resolution Pathway workshop:
- The clinical criteria of the proposed initial restriction were revised to identify two categories of patients: 1) those with significant symptoms (see paragraph 4.4), and 2) those who have PNs likely to lead to significant symptoms (see paragraph 4.5). The proposed population in the resubmission was broader than that in the original submission, which was restricted to patients with symptomatic PN. The broadening of the restriction aligned with the advice received in the workshop that it would potentially be beneficial for some patients to receive treatment before they develop PN-related morbidity (i.e., symptoms).
 - The resubmission proposed a 'First Continuing' restriction at six months for the assessment of tolerability followed by 'Subsequent Continuing' restriction at 12 months for the assessment of tolerability and response to treatment. This was

consistent with the SPRINT trial Stratum 1, given median time to response in the trial was eight months, and was supported by the advice received at the workshop.

- The clinical criteria of the proposed ‘Subsequent Continuing’ restriction included the definition for evaluation of disease stabilisation and adequate response (defined as stability or improvement of the clinical criteria and relevant imaging that has not shown an increase in tumour size of $\geq 20\%$ compared to baseline). This was appropriate and consistent with the SPRINT trial Stratum I and supported by the advice received at the workshop.
- The population criterion was amended to specify that treatment with selumetinib should be initiated, rather than NF1 being diagnosed, between the ages of two and 18 years. This was appropriate and consistent with the previous PBAC advice that it would be reasonable for patients who were less than 18 years at commencement of selumetinib treatment to continue to receive selumetinib as an adult (paragraph 7.18, selumetinib PSD, November 2022 PBAC Meeting).
- The treatment criterion was revised to specify that patients must be treated by or in consultation with a specialist physician with expertise in neurofibromatosis. This was appropriate and consistent with the outcome of the workshop.
- Requirement of Karnofsky or Lansky Performance Score of $\geq 70\%$. This was appropriate and consistent with the eligibility criteria of the SPRINT trial Stratum I (paragraph 7.16, selumetinib PSD, November 2022 PBAC meeting).
- Addition of “ability to swallow a whole selumetinib capsule” as a population criterion. This was appropriate and consistent with the inclusion criteria of the SPRINT trial Stratum I (paragraph 7.16, selumetinib PSD, November 2022 PBAC meeting).

- 3.3 The Pre-Sub-Committee Response (PSCR) suggested amending the criterion in the grandfather supply listing to allow patients who have been receiving off-label trametinib (or those on trials for mirdametinib or dabrafenib) to transition to PBS subsidised selumetinib as follows:

‘Patient must have previously received treatment with ~~this drug~~ mitogen-activated protein kinase (MEK) inhibitor for this condition prior to [PBS listing date].’

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

4 Population and disease

- 4.1 NF1 is a rare, incurable, autosomal-dominant genetic disorder that is caused by germline mutations in the NF1 tumour suppressor gene. NF1 is a highly heterogenous disease with a wide range of clinical manifestations involving multiple organ systems,

with symptoms affecting nervous system, skin, bones, and eyes. The prevalence rate of NF1 is approximately one in 2,500-3,000 people in Australia.^{1,2}

- 4.2 Approximately 30% of the patients with NF1 develop PN. PN are non-malignant peripheral nerve sheath tumours which may cause significant morbidities, including pain, disfigurement, motor function deficits, neurological dysfunction, and in the most severe cases, life-threatening complications due to compression of vital structures. PN associated with NF1 has a substantial burden on the quality of life of patients, their families and carers.
- 4.3 Most patients are diagnosed as children and experience a higher rate of PN growth during early childhood, which gradually slows with age. The PBAC previously noted that the benefit of treatment with selumetinib was likely to be greatest in younger patients as PN growth rate is highest in these patients (paragraph 7.13, selumetinib PSD, November 2022 PBAC meeting). The resubmission stated that, while the growth of PN slows down in adult patients, tumour growth is still experienced by patients across all age categories. Additional findings from a 10-year follow-up study by Ly et al. (2023) found that 17.4% (8/46) adult patients with NF1 experienced PN growth. Of note, 62.8% (160/255) of internal neurofibromas and 56% (70/125) of PN shrank spontaneously without being exposed to systemic therapy in Ly et al. (2023).
- 4.4 PN is defined as ‘symptomatic’ by the resubmission (and in the restriction) if it causes significant morbidity, such as (but not limited to):
- head and neck PN that could compromise the airway or great vessels;
 - paraspinal PN that could cause myelopathy;
 - brachial or lumbar plexus PN that could cause nerve compression and loss of function;
 - PN that could result in major deformity (e.g., orbital PN) or significant disfiguring;
 - PN of the extremity that could cause limb hypertrophy or loss of function; and
 - painful PN.
- 4.5 ‘Patients at risk of developing significant PN morbidity’ were defined by the resubmission (and in the restriction) as those who did not have clinically significant PN-related morbidity but had the potential of developing any of the aforementioned significant PN-morbidities. PN was defined as ‘inoperable’ if it cannot be completely

¹ Children’s Tumour Foundation, About Neurofibromatosis type 1 (NF1), [https://www.ctf.org.au/page/109/types-of-nf#:~:text=types%20of%20NF-Neurofibromatosis%20Type%201%20\(NF1\),on%20or%20under%20the%20skin](https://www.ctf.org.au/page/109/types-of-nf#:~:text=types%20of%20NF-Neurofibromatosis%20Type%201%20(NF1),on%20or%20under%20the%20skin).

² The Royal Children’s Hospital Melbourne, Neurofibromatosis type 1 (NF1) [https://www.rch.org.au/kidsinfo/fact_sheets/Neurofibromatosis/#:~:text=Neurofibromatosis%20\(NF\)%20is%20a%20group,in%203000%20people%20in%20Australia](https://www.rch.org.au/kidsinfo/fact_sheets/Neurofibromatosis/#:~:text=Neurofibromatosis%20(NF)%20is%20a%20group,in%203000%20people%20in%20Australia).

resected without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity.

- 4.6 The resubmission, following advice received at the Facilitated workshop, also targeted patients at risk of developing significant PN morbidity. This was broader compared to the previous submission, which was restricted to patients with symptomatic PN. The resubmission presented efficacy data for patients at risk of developing significant PN morbidity from the SPRINT trial (Stratum II).
- 4.7 Selumetinib is a selective inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK 1 and 2). MEK 1 and 2 are key components of the cellular growth signalling cascade which is overactive in NF1 due to mutations in the NF1 tumour suppressor gene. Inhibition of MEK prevents PN growth and promotes PN shrinkage by reducing cell proliferation and preventing abnormal cell survival.
- 4.8 Currently, there are no approved pharmacological treatments for symptomatic, inoperable PN in paediatric patients with NF1. Treatment options are limited to symptomatic and supportive treatment, such as pain medication, debulking surgery or interventions (e.g., tracheostomy to alleviate severe airway morbidities). Trametinib (a MEK inhibitor) is used off-label to treat NF1 PN in Australia and there is an ongoing local clinical trial³. Several other MEK inhibitors, such as binimetinib and mirdametinib, and the tyrosine kinase inhibitor (TKI) cabozantinib are currently being trialled among paediatric and adult patients for NF1 PN.⁴ The current and proposed clinical management algorithms remained unchanged from the previous submission. Selumetinib was proposed as an alternative to supportive care available to patients with NF1 PN in Australia. Additionally, concomitant symptomatic and supportive management may be required with selumetinib.

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

5 Comparator

- 5.1 The resubmission nominated best supportive care (BSC), which consists of palliative care and symptomatic management, as the main comparator. The PBAC previously accepted BSC to be the appropriate comparator (paragraph 7.4, selumetinib PSD, November 2022 PBAC meeting).

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

³ Trametinib in Neurofibromatosis Type 1 associated tumours (TiNT) (ACTRN12620001229965). <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=379244>

⁴ Armstrong A., Belzberg A., et al., (2023), 'Treatment decisions and the use of MEK inhibitors for children with neurofibromatosis type 1-related plexiform neurofibromas', BMC Cancer, 23. <https://doi.org/10.1186/s12885-023-10996-y>

6 Consideration of the evidence

Sponsor hearing

- 6.1 There was no hearing for this item. The PBAC recalled that in November 2022 the sponsor hearing provided a clinical perspective on treating this uncommon disease.

Consumer comments

- 6.2 The PBAC noted and welcomed the input from individuals (22), health care professionals (2) and organisations (2) via the Consumer Comments facility on the PBS website. The comments from individuals described the physical and psychological burden of the disease and the high unmet clinical need for effective therapies for NF1 patients with PN. The comments also described a range of benefits of treatment with selumetinib including stabilisation and reduction of tumour size, pain reduction, avoidance of surgery and improvements in quality of life. Contributors described the difficulties in managing the pain associated with the condition, the limited surgical options for some tumours due to their location, the need for repeated surgeries and the complications associated with the tumours and the surgeries. There was strong consumer support for this listing. The comments from the health professionals described the dramatic effects on quality of life and disability associated with selumetinib and its tolerable safety profile.
- 6.3 Input from the Children's Tumour Foundation described the lack of available therapies for patients with NF1 and the clinical need for affordable treatment options. The input also described the debilitating physical and psychological effects of tumours on NF1 patients and the complications associated with surgery.
- 6.4 The PBAC noted the advice received from the National Paediatric Medicines Forum clarifying the likely use of selumetinib in clinical practice. The PBAC specifically noted the unmet clinical need for effective treatments for NF1 that offered an alternative treatment to conventional chemotherapy and surgery. The PBAC noted that this advice was supportive of the evidence provided in the submission.

Clinical studies/trials

- 6.5 As in the November 2022 submission, the resubmission presented two unanchored indirect treatment comparisons (ITC) of selumetinib and BSC for the treatment of paediatric patients with NF1 PN, based on:
- The SPRINT trial Stratum I (N=50) a Phase II, open label, single-arm study of selumetinib in paediatric patients (aged ≥ 2 years and ≤ 18 years) compared to an age and maximum duration of follow-up matched cohort from the National Cancer Institute Natural History (NCI NH; N=92), a longitudinal, observational, natural history study of patients (children, adolescents and adults) with a confirmed diagnosis of NF1 or a confirmed NF1 mutation.
 - Patients with progressive PN from the SPRINT trial Stratum I (N=21) compared to the placebo arm of the 01-C-0222 trial (N=29), a Phase II, randomised, double-

blind, placebo-controlled trial comparing tipifarnib (an experimental treatment) to placebo in children and young adults (aged 3 to 25 years) with NF1 and unresectable, progressive PN.

- 6.6 In response to the PBAC's request to present any available data for adult patients (paragraph 7.18, selumetinib PSD, November 2022 PBAC meeting), the resubmission presented clinical evidence from the following:
- Study NCT02407405 (N=23), an ongoing, open-label, single-site study of selumetinib in patients aged ≥ 18 years with NF1 and symptomatic, inoperable, progressive PN.
 - A post-hoc subgroup analysis of the SPRINT trial Stratum I (N=10), which informed the efficacy and safety of selumetinib in patients who turned 18 years during the clinical trial.
- 6.7 Additionally, the resubmission presented results from the SPRINT trial Stratum II (N=25), a Phase II, open-label, single arm study of selumetinib in children (aged ≥ 2 years and ≤ 18 years) with NF1 and inoperable PN with no significant clinical morbidity (i.e., asymptomatic) but with the potential for significant clinical PN-related morbidity. Determination of the absence of clinically significant morbidity and potential morbidities, as defined in paragraph 4.4 and 4.5, was made by investigators based on clinical and imaging evaluations at baseline.
- 6.8 Details of the studies presented in the resubmission are provided in Table 3. The details and results from the SPRINT trial Stratum I, NCI NH study and the 01-C-0222 trial remain unchanged from those presented in the November 2022 submission.

Table 3: Trials/studies and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
Selumetinib studies		
SPRINT Phase II	A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas.	August 2019
	A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (SPRINT). Long Term Efficacy and Safety Update.	April 2022
	A Phase I/II Study of the Mitogen Activated Protein Kinase (MEK) 1 Inhibitor Selumetinib (AZD6244; HYD Sulfate) in Children with Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas (PN) (SPRINT Phase II Stratum 2)	December 2019
	Gross A, Wolters P et al. Selumetinib in children with inoperable plexiform neurofibromas.	<i>New England Journal of Medicine</i> 2020; 382, 1430-1442
	Gross A, Glassberg B et al. Selumetinib in Children with Neurofibromatosis Type 1 and Asymptomatic Inoperable Plexiform Neurofibroma At Risk for Developing Tumor-Related Morbidity.	<i>Neuro-oncology</i> 2022; 24 (11): 1978-1988.
Gross A, Dombi E et al. Long-Term Safety and Efficacy of Selumetinib in Children with Neurofibromatosis Type 1 on a Phase 1/2 Trial for Inoperable Plexiform Neurofibromas.	<i>Neuro-oncology</i> 2023; 25 (10): 1883-1894.	
Glassberg B, Gross A et al. Selumetinib in children with clinically asymptomatic inoperable NF1 related plexiform neurofibromas.	<i>Pediatric Blood and Cancer</i> 2020; 67.	

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Trial ID	Protocol title/ Publication title	Publication citation
	Gross A, Wolters P et al. SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas.	<i>Neuro-Oncology</i> 2018; 20, i143-i144.
	Gross A, Baldwin A et al. Phase II Study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas.	<i>Journal of Clinical Oncology</i> 2016; 34.
	Gross A, Wolters P et al. SPRINT: Phase II study of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886) in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas.	<i>Journal of Clinical Oncology</i> 2018; 36.
	Jackson S, Baker E et al. The effect of selumetinib on spinal neurofibromas in patients with NF1.	<i>Neuro-Oncology</i> 2018; 20, vi237
	Jackson S, Baker E et al. The MEK inhibitor selumetinib reduces spinal neurofibroma burden in patients with NF1 and plexiform neurofibromas	<i>Neuro-Oncology Advances</i> 2020; 2, vdaa095
SPRINT Phase I (NCT01362803)	AZD6244 Hydrogen Sulfate for Children With Nervous System Tumors Dombi E, Baldwin A et al. Activity of selumetinib in neurofibromatosis type 1-related plexiform neurofibromas. Fisher M, Marcus L et al. Selumetinib (AZD6244) hydrogen sulfate, a MEK1/2 inhibitor, in children with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNS): A Phase I study. Widemann B, Marcus L et al. Phase I study of the MEK1/2 inhibitor selumetinib (AZD6244) hydrogen sulfate in children and young adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PNS).	<i>New England Journal of Medicine</i> 2016; 375,2550-2560. <i>Neuro-Oncology</i> 2014; 16, i129 <i>Journal of Clinical Oncology</i> 2014; 32.
NCT02407405	MEK 1/2 Inhibitor Selumetinib (AZD6244 Hydrogen Sulfate) in Adults With Neurofibromatosis Type 1 (NF1) and Inoperable Plexiform Neurofibromas Coyne G, Gross A et al. Phase II trial of the MEK 1/2 inhibitor selumetinib (AZD6244, ARRY-142886 Hydrogen Sulfate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Coyne G, Gross A et al. Abstract PR07: Phase II Trial of the MEK 1/2 inhibitor selumetinib (AZD6344, ARRY-142886 hydrogen sulphate) in adults with neurofibromatosis type 1 (NF1) and inoperable plexiform neurofibromas (PN). Jackson S, Baker E et al. The effect of selumetinib on spinal neurofibromas in patients with NF1. Jackson S, Baker E et al. The MEK inhibitor selumetinib reduces spinal neurofibroma burden in patients with NF1 and plexiform neurofibromas	<i>Journal of Clinical Oncology</i> 2020; 38: 3612-3612 <i>Molecular Cancer Therapeutics</i> 2019; 18, PR07-PR07. <i>Neuro-Oncology</i> 2018; 20, vi237 <i>Neuro-Oncology Advances</i> 2020; 2, vdaa095
Supportive care studies		
NH study (NCT00924196)	Akshintala S, Baldwin A et al. Longitudinal evaluation of peripheral nerve sheath tumours in neurofibromatosis type 1: growth analysis of plexiform neurofibromas and distinct nodular lesions. Akshintala S, Dombi E et al. Predictors of plexiform neurofibroma growth in patients with neurofibromatosis 1 (NF1). Dagalakis U, Lodish M et al. Puberty and plexiform neurofibroma tumour growth in patients with neurofibromatosis type 1. Gross A, Singh G et al. Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1. Hou Y, Allen T et al. Predictors of cognitive development in children with neurofibromatosis type 1 and plexiform neurofibromas. Kim A, Gillespie A et al. Characteristics of children enrolled in treatment trials for NF1-related plexiform neurofibromas.	<i>Neuro-Oncology</i> 2020; 22, 1368-1378. <i>Pediatric Blood and Cancer</i> 2014; 61, S32-S33. <i>Journal of Pediatrics</i> 2014; 164, 620-624. <i>Neuro-Oncology</i> 2018; 20, 1643-1651. <i>Developmental Medicine and Child Neurology</i> 2020; 62, 977-984. <i>Neurology</i> 2009; 79, 1273-1279

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Trial ID	Protocol title/ Publication title	Publication citation
	<p>Loucas C, Wolters P et al. Verbal learning and memory in youth with neurofibromatosis type 1 and plexiform neurofibromas: Relationships with disease severity.</p> <p>Meany H, Dombi et al. 18-fluorodeoxyglucose-positron emission tomography (FDG-PET) evaluation of nodular lesions in patients with neurofibromatosis type 1 and plexiform neurofibromas or malignant peripheral nerve sheath tumours (MPNST).</p> <p>Ngyuen R, Dombi E et al. Characterization of spinal findings in children and adults with neurofibromatosis type 1 enrolled in a natural history study using magnetic resonance imaging.</p> <p>Widemann B. Natural history of peripheral nerve sheath tumours in NF1: Identification and characterization of malignant precursor lesions.</p> <p>Wolters P, Burns K et al. Pain interference in youth with neurofibromatosis type 1 and plexiform neurofibromas and relation to disease severity, social-emotional functioning, and quality of life.</p>	<p><i>European Journal of Paediatric Neurology</i> 2022; 38, 7-12.</p> <p><i>Pediatric Blood and Cancer</i> 2013; 60, 59-64.</p> <p><i>Journal of Neuro-Oncology</i> 2015; 121, 209-215.</p> <p><i>Clinical Cancer Research</i> 2018; 24.</p> <p><i>American Journal of Medical Genetics</i> 2015; Part A, 167, 2103-2113.</p>
Study 01-C0222 (NCT00021541)	<p>R115777 to Treat Children With Neurofibromatosis Type 1 and Progressive Plexiform Neurofibromas</p> <p>Widemann B, Dombi E et al. Phase 2 randomized, flexible crossover, double-blinded, placebo-controlled trial of the farnesyltransferase inhibitor tipifarnib in children and young adults with neurofibromatosis type 1 and progressive plexiform neurofibromas.</p>	<p><i>Neuro-Oncology</i> 2014; 16, 707-718.</p>

Source: Table 2.11 of the resubmission.

6.9 The key features of the included evidence are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Outcome(s)	Use in modelled evaluation
Selumetinib						
SPRINT trial (Stratum I)	50	OL, MC Median follow-up of 4 years	Low to Moderate ^a	Children aged ≥2 years and ≤18 years with NF1 and symptomatic, inoperable PN	ORR; PN growth; DoR; PFS; TTP; TTR; PROs and functional outcomes; safety and tolerability	PFS, TTD
SPRINT trial (Stratum II)	25	OL, MC NR	Low to Moderate ^a	Children aged ≥2 years and ≤18 years with NF1 and inoperable PN with no significant clinical morbidity but potential for significant clinical PN-related morbidity	ORR; PN growth; DoR; PFS; TTR; PROs and functional outcomes; safety and tolerability	Not used
NCT02407405	23	OL, Simon's 2-stage Ongoing trial	Unclear	Patients aged ≥18 years with NF1, symptomatic, inoperable, progressive PN	ORR, PD studies on pre/on-treatment biopsies of PN and cutaneous neurofibromas, PROs and functional outcomes	Not used
BSC						
NH Study	250	OB Median follow-up of 6.6 years	Low to Moderate ^a	Patients (children, adolescents, and adults) with a confirmed diagnosis of NF1 or a confirmed NF1 mutation	PFS, PN growth rate	PFS
01-C-0222 trial (Phase A)	60	R, DB NR	Low	Children and young adults (aged 3 to 25 years) with NF1 and unresectable, progressive PN	TTP, PFS	Not used

Source: Table 2.13 ; Table 2.15 ; Table 2.23 and Section 2.3 of the resubmission.

BMD = bone mineral density; DB = double blind; DoR = duration of response; HRQoL = health-related quality of life; MC = multi-centre; NF1 = neurofibromatosis type 1; NH = Natural History; NR = not reported; OB = observational; OL = open label; ORR = objective response rate;

OS = overall survival; PD = pharmacodynamic; PFS = progression-free survival; PN = plexiform neurofibroma(s); PRO = patient-reported outcomes; R = randomised; TTP = time to progression; TTR = time to response.

^a Risk of bias in non-randomised studies of interventions (ROBINS-I) was used to estimate the risk of bias.

Comparative effectiveness

Paediatric population

- 6.10 The results of SPRINT trial Stratum I presented in the resubmission were unchanged from the November 2022 submission and are summarised below.
- 6.11 In Stratum I, 46 of 48 patients (95.8%) experienced a reduction from baseline in target PN volume and 34 of 50 patients (68%) had a confirmed partial response (cPR; which was defined as PN volume decrease of $\geq 20\%$ compared to baseline on consecutive examinations at least 3 months apart). Median progression free survival (PFS; which was defined as PN volume increase of $\geq 20\%$ compared to baseline) was not reached in Stratum I. The trial reported clinically meaningful improvements in a number of functional and patient-reported outcomes.
- 6.12 The results of the two unanchored ITCs based on the SPRINT trial Stratum I data compared to NH study and the 01-C-0222 trial presented in the resubmission were unchanged from the November 2022 submission, and are summarised below:
- Selumetinib was associated with a -5.1% (95% CI: -27.3, 19.0) PN volume change (decrease) per year in Stratum I compared to 15.1% (95% CI: -3.7, 126.2) PN volume change (increase) per year in the age-matched cohort of the NH study.
 - Median PFS was not reached in Stratum I compared to 1.3 years (95% CI: 1.1, 1.6) in the NH age matched cohort.
 - The proportion of patients without progression after five years was 69.7% (95% CI: 50.8, 82.5) in Stratum I compared with 18.2% (95% CI: 10.8, 27.1) in the NH study.
 - In the subgroup of patients with progressive PN, the proportion of patients without progression after two years was 94.7% (95% CI: 80.6, 98.7) in Stratum I, compared to 20.6% (95% CI: 7.7, 37.8) in the placebo arm of 01-C-0222 trial.
- 6.13 The resubmission presented additional data from the SPRINT trial Stratum II to inform efficacy of selumetinib in paediatric patients at risk of developing PN related morbidities. In Stratum II (asymptomatic), a total of 18 of 25 patients (72%) had a cPR. This was consistent with the results from Stratum I (symptomatic), where 68% of patients had a cPR. Consistent with Stratum I (symptomatic), the median PFS was not reached; however, the proportion of patients who were progression free at week 48 was higher in Stratum II (asymptomatic; 86.6%) compared to Stratum I (symptomatic; 69.7%). The median PN volume change from baseline to best response was -32.7% (IQR: -39.7, -16.8%). Most functional and patient-reported outcomes, including visual, motor, bowel/bladder, or airway function were within normal limits and did not clinically or statistically improve or worsen during treatment with selumetinib.
- 6.14 The efficacy of selumetinib in Stratum II (asymptomatic) was comparable with that observed in Stratum I (symptomatic). However, the resubmission did not present any

comparative data with BSC to support the use of selumetinib in patients at risk of developing significant PN morbidity.

Adult population

- 6.15 The resubmission presented a post-hoc subgroup analysis of SPRINT trial Stratum I, which informed the efficacy and safety of selumetinib in paediatric patients who progress into adulthood (turned 18 years during the clinical trial; N=10). The mean age at last exposure to selumetinib was 20.1 years (range: 18.2 - 22.5 years)⁵ in the *post-hoc* subgroup.
- 6.16 A summary of best objective response rate (BOR) and PFS in the *post-hoc* subgroup population of the SPRINT trial Stratum I is presented in Table 5. A total of 9 (90%) patients in the subgroup achieved cPR⁶.

Table 5: Summary of BOR and PFS in post-hoc subgroup population of the SPRINT trial Stratum I

	Patients ≥18 years; N=10, n (%)
Best Objective Response	
Confirmed partial response	9 (90)
Partial response (cPR and PR)	9 (90)
Insufficient volume change (SD)	1 (10)
Not evaluable	0
Progression-free survival	
Alive and progression free	8 (80)
Discontinued study	1 (10)
Progression	1 (10)
Lost to follow-up	0
Withdraw consent	0

Source: Table 2.49 and Table 2.50 of the resubmission.

cPR = confirmed partial response; PR = partial response; n = number of participants reporting data; N = total participants in group; SD = stable disease.

* Note that the results presented in Table 5 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the SPRINT trial. 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.

- 6.17 The resubmission also presented efficacy data from Study NCT02405047, an ongoing study of selumetinib in adult patients with NF1 PN. The study reported that 16 of 23 patients (69%) had a PR and 13 of 23 patients (81%) had a cPR. There were no reports of disease progression. Time to response was 11 months (range: 5, 25 months). The

⁵ Note that the results presented in paragraph 6.15 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the SPRINT trial. 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.

⁶ Note that the results presented in paragraph 6.16 are derived from post-hoc analyses conducted by the applicant specifically for the purposes of informing the PBAC consideration. These analyses were not part of the pre-specified statistical plan for the SPRINT trial. 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.

median PN volume change from baseline to best response was -22% (range: -41%, 5.5%). Patient-reported outcomes, including target tumour pain intensity and pain interference scores, significantly improved. However, the results from Study NCT02405047 were uncertain due to the absence of baseline demographics and disease characteristics and as only preliminary data were available from two conference abstracts. The baseline demographics and disease characteristics were presented in the PSCR. The ESC noted that the baseline characteristics were comparable to the paediatric population of Stratum I of the SPRINT trial.

Comparative harms

Paediatric Population

- 6.18 Safety data for the SPRINT trial Stratum I remained unchanged from the previous submission. In Stratum I, 34 (68%) patients experienced any severe adverse event (AE) (Grade ≥ 3), 15 (30%) patients experienced a serious AE and 6 (12%) had an AE leading to treatment discontinuation. The most frequently reported severe AEs (Grade ≥ 3) were diarrhoea (16%), hypoxia (8%), paronychia (8%), pyrexia (8%), vomiting (8%) and increased weight (8%). A total of 26 (52%) patients discontinued treatment as of data cut-off of March 2021, with reasons for discontinuation including adverse event (6 patients), disease progression (6 patients), investigator discretion (6 patients), patient not willing to continue (3 patients), complicating illness (2 patients), treatment period completed (1 patient), non-compliance with protocol (1 patient) and other (1 patient).
- 6.19 In the SPRINT trial Stratum II, all patients (100%) experienced at least one AE related to study drug; however, most of the AEs were either grade 1 or 2 (97.7%). The most frequently reported AEs were rash (acneiform, maculopapular, dry skin), headache, gastrointestinal symptoms (nausea, vomiting), asymptomatic elevation of creatine phosphokinase, and paronychia. Five patients (20%) required dose reductions due to AEs and one patient discontinued treatment due to persistent asymptomatic lipase elevation. Of note, no patient developed central serous retinopathy or other vision-threatening ocular toxicities which have been attributed to this drug in other settings.

Adult population

- 6.20 Overall, the post-hoc subgroup analysis of SPRINT trial Stratum I demonstrated comparable safety results to the whole trial population.
- 6.21 In Study NCT02407405, a total of 21/23 (91%) patients experienced Grade ≥ 3 AEs; 5 patients (24%) with transaminitis, 1 patient (5%) with rash, and 1 patient (5%) with pancreatic enzyme elevation. Dose reduction occurred in two patients (9.5%) due to AEs and eight patients discontinued treatment.

Benefits/harms

- 6.22 The unanchored indirect comparison presented in the resubmission did not allow for a quantitative comparison of the benefits and harms of selumetinib and supportive care. Accordingly, a benefits/harms table has not been presented.

Clinical claim

- 6.23 The resubmission maintained that selumetinib is superior in terms of effectiveness and non-inferior in terms of safety compared to BSC.
- 6.24 The PBAC had previously considered the claim of superior comparative efficacy was adequately supported in patients with symptomatic, inoperable PN; however, it noted uncertainties due to the small sample size of the SPRINT trial, unanchored ITCs, transitivity issues, lack of established MCIDs, and absence of clinical evidence in adult patients (paragraph 6.48, selumetinib PSD, November 2022 PBAC Meeting). These concerns remain outstanding, with the exception of new clinical evidence in adult patients (see paragraph 6.27).
- 6.25 The efficacy data presented for patients at risk of developing PN morbidity from the SPRINT trial Stratum II (asymptomatic) was comparable to that observed in SPRINT trial Stratum I (symptomatic). Overall, the ESC considered that the claim of superior comparative efficacy in patients with asymptomatic PN was likely to be supported; however, as no comparative data to support the use of selumetinib in patients at risk of developing significant PN morbidity were presented in the resubmission the magnitude of the benefit is uncertain.
- 6.26 The ESC considered that the efficacy data presented for adult patients supported the clinical benefit of selumetinib in adult population; however, the magnitude of the benefit was uncertain as:
- there was no direct comparison of selumetinib with BSC in the adult population (e.g., comparison with adult patients in the Natural History (NH) study);
 - the subgroup analysis of the SPRINT trial Stratum I was *post hoc* and only preliminary results from Study NCT02407405 were available; and
- 6.27 Overall, the PBAC considered that the claim of superior comparative effectiveness was reasonable.
- 6.28 The PBAC had previously considered that the claim of non-inferior comparative safety was not adequately supported given the lack of comparative data (paragraph 7.10, selumetinib PSD, November 2022 PBAC meeting). Based on the data presented, the ESC considered that a claim of an inferior, but manageable, safety profile compared to BSC would be reasonable.
- 6.29 The PBAC agreed with ESC and considered that an inferior, but manageable, safety profile compared to BSC was reasonable.

Economic analysis

- 6.30 The resubmission again presented a cost-utility analysis (CUA) of selumetinib compared to BSC.
- 6.31 In November 2022, the PBAC considered that there were a number of issues with the economic model that reduced its reliability for decision-making (paragraph 7.11, selumetinib PSD, November 2022 PBAC meeting). The ESC had considered that the

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incremental cost effectiveness ratio (ICER) of \$95,000 to < \$115,000 per quality adjusted life year (QALY) gained presented in the submission was optimistic. The ESC presented a revised base case ICER of \$155,000 to < \$255,000 per QALY gained⁷ based on a 50-year time horizon, a constant discount rate of 5% to both costs and outcomes, lognormal extrapolation for PFS, and uniform utility values for PFS (paragraph 6.80 and 6.81, selumetinib PSD, November 2022 PBAC meeting).

- 6.32 The PBAC considered that based on the economic model respecified by ESC, selumetinib was likely to be cost-effective at an ICER of less than \$75,000 to < \$95,000 per QALY gained (paragraph 7.12, selumetinib PSD, November 2022 PBAC meeting) and noted that a significant price reduction would be required (paragraph 7.20, selumetinib PSD, November 2022 PBAC meeting). Additionally, the PBAC considered that a fixed cost per patient per year would be preferable for selumetinib as it would reduce the cost-effectiveness concerns relating to use in older patients (including adults) and any change in average BSA over time (paragraph 7.13, selumetinib PSD, November 2022 PBAC meeting).
- 6.33 The resubmission revised the inputs in the economic model based on the ESC and PBAC's advice in November 2022. Table 6 presents the inputs used in the resubmission along with those used in the November 2022 submission and ESC and PBAC's recommendations.

⁷ This increased to \$335,112 per QALY when corrected TTD data were used (see paragraph 6.39)

Table 6: Summary of inputs used in November 2022 submission and the current resubmission.

Parameter	November 2022 submission	PBAC and ESC recommendations	March 2024 resubmission
Time horizon	100 years (pre-PBAC response = 75 years).	50 years	50 years
Discount rate	Differential discount rate applied: 5% on costs 5% on outcomes until 18 years; 3% from 18 to 24 years; and 1.5% from the age of 24 years (The pre-PBAC response applied a 5% discount rate to outcomes up to 24 years; and 3.5% beyond 24 years.)	Constant discount rate of 5% to costs and outcomes.	Constant discount rate of 5% to both cost and outcomes.
Disease monitoring cost	Two MRIs would be used for routine disease monitoring. (MBS fees were updated in the pre-PBAC response.)	The submission might have underestimated the cost associated with the additional tests required to monitor toxicity with the use of selumetinib.	Cost of ophthalmological visits was included.
Utility values for PFS	PFS in selumetinib = 0.740 PFS in BSC = 0.625	Uniform utility values to the PFS health state for both the selumetinib and BSC arms.	Uniform PFS utility of 0.740 used for both the selumetinib and BSC arms.
Extrapolation function for PFS	Applied exponential distribution to PFS in the selumetinib arm and lognormal distribution to PFS in the BSC arm. (The pre-PBAC response accepted the lognormal extrapolation for both treatment arms.)	Lognormal extrapolation for PFS in selumetinib arm.	Lognormal extrapolation for PFS in selumetinib arm.
Extrapolation function for TTD	Applied Weibull extrapolation	While the Weibull distribution may be reasonable, the model was very sensitive to the extrapolation assumptions.	Weibull extrapolation (based on corrected TTD data).
Effective AEMP	10 mg: \$ 25 mg: \$	A significant price reduction would be required to be cost-effective.	A % price reduction in the effective AEMP was proposed (10 mg: \$; 25 mg: \$). The resubmission also proposed a fixed maximum cost per patient per year corresponding to a BSA of m ² .
ICER	\$ ¹ per QALY gained. (pre-PBAC response = \$ ² per QALY gained).	The ESC revised base case was \$ ^{2*} per QALY gained. The PBAC considered an ICER of \$ ³ per QALY gained would be cost effective.	\$ ² per QALY gained

Source: Table 3-3 of the resubmission.

AE = adverse event; BSA = body surface area; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; MRI = magnetic resonance imaging; N/A = not applicable; PFS = progression-free survival; PSCR = Pre-Sub-Committee Response; PSD = Public Summary Document; TTD = time to treatment discontinuation.

* This increased to \$255,000 to < \$355,000 per QALY when corrected TTD data were used (see paragraph 6.39)

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$155,000 to < \$255,000

³ \$75,000 to < \$95,000

6.34 Key components of the economic evaluation are presented in Table 7.

Table 7: Summary of model structure, key inputs and rationale

Component	Summary
Treatments	Selumetinib vs BSC
Time horizon	50 years in the model base case versus 6 years in the SPRINT trial Stratum I
Outcomes	QALYs
Methods used to generate results	Partitioned survival model (i.e. area under the curve)
Health states	Non-progressive, progressive disease, or death
Cycle length	12 months
Allocation to health states	PFS KM were derived from the SPRINT trial Stratum I for selumetinib and NH study for BSC and were extrapolated using parametric survival models.
	Updated and corrected treatment discontinuation was implemented via parametric extrapolation of patient-level TTD from the SPRINT trial Stratum I.
	OS for both selumetinib and BSC was estimated using general population mortality from the ABS adjusted based on the SMR for patients with NF1 reported in Duong et al. 2011.
Extrapolation method	For PFS, lognormal parametric distribution was applied to both selumetinib and BSC arm. For TTD, an updated and corrected Weibull parametric distribution was applied to the selumetinib arm.
	86% of QALYs (undiscounted) and 17% of costs (undiscounted) occur in the extrapolated period.
Health related quality of life	TTO study conducted as presented in the previous submission.
	Progression-free = 0.74; Progressed = 0.51
Discount rate	Uniform discount rate of 5% applied to both cost and outcomes

Source: Table 3-4 of the resubmission and 'Selumetinib Section 3 workbook' Excel workbook.

ABS = Australian Bureau of Statistics; BSC = best supportive care; KM = Kaplan-Meier; NF1 = neurofibromatosis type 1; NH = Natural History study; OS = overall survival; PFS = progression-free survival; PN = plexiform neurofibroma(s); QALY = Quality-adjusted life-years; SMR = standardised mortality ratio; TTD = treatment-to-discontinuation; TTO = time trade off.

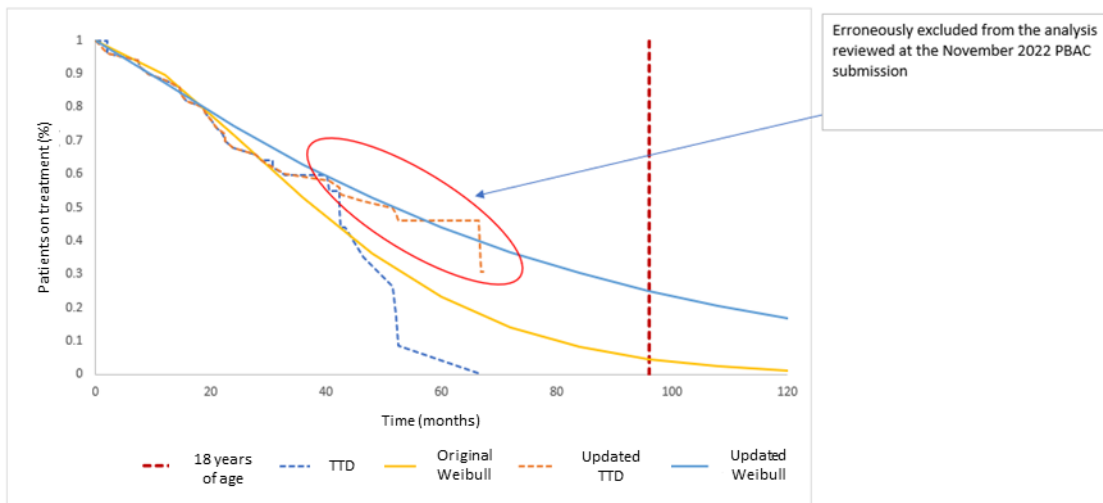
6.35 The partitioned survival model structure was unchanged in the resubmission. The model consisted of three health states:

- Non-progressed disease (on-treatment and off-treatment);
- Progressed disease (defined as $\geq 20\%$ increase in PN tumour size from baseline, or, if a patient had a partial response, then defined as an increase of at least 20% from the best response measured by volumetric MRI analysis); and
- Death.

6.36 The approach taken in the resubmission remained the same as in the previous submission with observed Kaplan-Meier (KM) function curves (PFS and time to treatment discontinuation (TTD)) used up until 72 months (6 years) and parametric distributions with best relative fit applied to extrapolate the KM function curves over a time horizon of 50 years.

6.37 The resubmission stated that the survival data informing the TTD in the previous submission erroneously excluded data recorded between 40 and 68 months (Figure 1). The resubmission presented a corrected Weibull extrapolation, which increased the proportion of patients on treatment, thereby increasing the total cost of treatment with selumetinib. The Weibull extrapolation had the third best relative fit to the corrected data (the log logistic was the best fit and lognormal the second best fit – see paragraph 6.40 for the effects on the ICER).

Figure 1: Updated TTD analysis



Source: Figure 3-1 of the resubmission.
TTD = time to treatment discontinuation.

- 6.38 The submission stated the source of the discrepancy in the TTD data was due to a data programming issue when parametric TTD distribution curves were being generated. The resubmission further stated that the validity of the results was confirmed through independent analysis. The updates made to the cost effectiveness model were reviewed internally by two independent reviewers and by one independent external reviewer, confirming consistency of results. However, the absence of patient-level data from the SPRINT trial Stratum I meant that the updated KM TTD curves presented in the resubmission could not be independently verified during the evaluation. Using the corrected TTD data in the ESC revised base case increased the ICER by 1% (from \$155,000 to < \$255,000 per QALY gained to \$255,000 to < \$355,000 per QALY gained).
- 6.39 In November 2022, the ESC considered that while the use of a Weibull distribution for selumetinib TTD may have been reasonable, the model was very sensitive to the extrapolation assumptions, with the use of loglogistic function (the next best fit according to AIC and BIC statistics) increasing the ICER by 1% (paragraph 6.71, selumetinib PSD, November 2022 PBAC meeting). The corrections to the TTD curve meant that the economic model presented in the resubmission was not as sensitive to the use of different extrapolation functions. In the resubmission, using the loglogistic function increased the ICER by 1%.
- 6.40 The resubmission presented data from the NH study, which demonstrated that PN growth rates plateaued as patients got older. Additionally, the resubmission stated that clinical experts in the UK had advised that patients continuing treatment beyond the age of 18 would be those with life-threatening PN growth, estimating this to be around 10% of the eligible population (NICE evaluation 2022). Consequently, it was unlikely that the long tail of the extrapolation distributions past the age of 18 (dotted red line in Figure 1) accurately reflected clinical practice. Therefore, the base case of the economic evaluation applied an 80% discontinuation year on year from the age of 18.

6.41 Table 8 provides the results of the updated economic evaluation, and the ESC revised base case from November 2022 is included for reference.

Table 8: Results of the stepped economic evaluation

Step and component	Selumetinib	Best supportive care	Increment
Step 1: trial-based costs and outcomes			
Costs	\$	\$0.00	\$
QALY	4.06	3.22	0.84
Incremental cost/extra QALY gained			\$ ¹
Step 2: time horizon extended to 50 years			
Costs	\$	\$0.00	\$
QALY	28.84	22.68	6.16
Incremental cost/extra QALY gained			\$ ²
Step 3: discounting (5% for both costs and outcomes) included			
Costs	\$	\$0.00	\$
QALY	11.44	9.00	2.44
Incremental cost/extra QALY gained			\$ ³
Step 4: incorporation of medical resource costs			
Costs	\$	\$10,467	\$
QALY	11.44	9.00	2.44
Incremental cost/extra QALY gained (base case)			\$ ³
Previous submission, November 2022 (ESC revised base case) ^a			
Costs	\$	\$10,314	\$
QALY	11.44	9.04	2.40
Incremental cost/extra QALY gained (base case)			\$ ^{3 b}

Source: Table 3-17 of the resubmission and Table 10, selumetinib PSD, November 2022 PBAC meeting.

ESC = economic sub-committee; QALY = quality-adjusted life years.

^a The November 2022 ESC revised base case applied a 50-year time horizon, lognormal distribution for PFS in selumetinib arm, constant discount rate of 5% to both costs and outcomes, and uniform utility values.

^b This ICER increased to \$255,000 to < \$355,000 per QALY when corrected TTD data were used.

The redacted values correspond to the following ranges:

¹ \$455,000 to < \$555,000

² \$75,000 to < \$95,000

³ \$155,000 to < \$255,000

6.42 For patients treated with selumetinib over a time horizon of 50 years, the economic evaluation estimated the following:

- Cost of selumetinib was \$| (undiscounted) (compared to \$| in the previous submission);
- A mean duration of treatment of approximately 5.75 years, as compared to 4.05 years in the previous model;
- Approximately 28.84 QALYs gained (undiscounted), resulting in an improvement of approximately 6.16 QALYs over BSC.

6.43 Based on the economic model presented in the resubmission, treatment with selumetinib was associated with an incremental cost per QALY gained of \$155,000 to < \$255,000 compared to BSC, for the treatment of inoperable and symptomatic PN in paediatric patients with NF1. In November 2022, PBAC considered that selumetinib would likely be cost effective at an ICER less than \$75,000 to < \$95,000 per QALY gained.

6.44 The following table provides the results from the November 2022 model, and steps through the changes made to generate the resubmission model.

Table 9: Stepped changes to the November 2022 model

	Incremental costs (\$)	Incremental QALYs	ICER (\$/QALY) (\$)	% change to ICER
November 2022 submission				
Submission base case		5.54	1	-
- Time horizon of 50 years		4.70	2	
- A constant discount rate of 5% to both costs and outcomes		2.73	3	
- Lognormal distribution for PFS in selumetinib arm		2.56	3	
- Uniform PFS utility values		2.40	3	
ESC revised base case (includes all the above changes)		2.40	3	-
Current resubmission				
- ESC revised base case + corrected TTD KM data		2.44	4	a
Impact of changing model inputs on the results of ESC revised base case + corrected TTD KM data				
- Updated healthcare resource utilisation costs (MRI, ophthalmologist, and pain medication)		2.44	4	
- A fixed maximum cost per patient per year corresponding to a BSA of m ²		2.44	4	-
- A % price reduction in the effective AEMP (from \$ to \$ for the 10 mg pack and from \$ to \$ for the 25 mg pack).		2.44	3	-
Resubmission base case (includes all the above changes)		2.44	3	-

Source: Selumetinib PSD, November 2022 and Selumetinib Section 3 Workbook.

AEMP = approved ex-manufacture price; BSA = body surface area; ESC = economic sub-committee; ICER = incremental cost-effectiveness ratio; PFS = progression-free survival; QALY = quality-adjusted life years; TTD = time to treatment discontinuation.

^a Percentage change in the ICER was compared to the ESC revised base case from November 2022 submission.

The redacted values correspond to the following ranges:

¹ \$95,000 to < \$115,000

² \$115,000 to < \$135,000

³ \$155,000 to < \$255,000

⁴ \$255,000 to < \$355,000

6.45 Table 10 presents the results of sensitivity analyses.

6.46 In the economic model, the median age was 10.2 years and the mean BSA for patients was 1.127m² with a maximum cost of treatment per patient per year based on a BSA of | m² (maximum cost = \$|, see Table 11 below). Sensitivity analyses using varying maximum costs of treatment per patient per year are included in the table below.

Table 10: Results of sensitivity analyses

	Incremental cost (\$)	Incremental QALY	ICER (\$)	% change from base case
Base case		2.44	1	-
Discount rate (base case 5%)				
• 0% costs and outcomes		6.16	2	-
• 3.5% costs and outcomes		3.07	3	-
Time horizon (base case 50 years)				
• 40 years		2.32	1	
• 72 years		2.54	1	-
Caregiver utility (not included in base case)				
• Absolute reduction		3.44	4	-
• Proportional change		3.95	5	-

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	Incremental cost (\$)	Incremental QALY	ICER (\$)	% change from base case
Caregivers per patient (not included in base case, sensitivity analysis = 1.8) <ul style="list-style-type: none"> Absolute reduction plus 1 caregiver per patient Proportional change plus 1 caregiver per patient 		3.00 3.28		
SMR (base case 2.02 based on Duong et al., 2011) <ul style="list-style-type: none"> 3.22 based on Uusitalo et al. (2015) 		2.35		
Max cost of treatment per year (base case \$ based on BSA of m ²) <ul style="list-style-type: none"> \$ (max BSA = m²) \$ (max BSA = m²) \$ (max BSA = m²) \$ (max BSA = m²) 		2.44 2.44 2.44 2.44		

Source: Table 3-21 and Table 3-22 of the resubmission and compiled during evaluation using the Selumetinib Section 3 Workbook
BSA = body surface area; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; SMR = standardised mortality ratio

The redacted values correspond to the following ranges:

¹ \$155,000 to < \$255,000

² \$75,000 to < \$95,000

³ \$135,000 to < \$155,000

⁴ \$115,000 to < \$135,000

⁵ \$95,000 to < \$115,000

6.47 The resubmission also presented a sensitivity analysis that applied a caregiver disutility until the patient reached 18 years of age in the economic model. Two approaches were employed: an absolute reduction to caregiver utility and a proportional change. The submission assumed that caregivers experienced the same relative mean quality of life decrement as patients with NF1. The relative mean difference in utility between patients in the selumetinib and the BSC arms of the model was estimated to be 0.115. It was assumed that the caregivers of patients who received BSC experienced a disutility of 0.23. Therefore, in the absolute reduction approach, the improvement in quality of life for caregivers of patients who received selumetinib, as compared to BSC, was 0.115 (= 0.23 – 0.115). In the proportional change approach, the resubmission calculated the ratio between the QALYs gained for BSC patients and the QALYs gained for selumetinib patients (from the model). The ratio was the applied to the caregiver utility for patients treated with selumetinib to calculate the utility for caregivers of BSC patients.

6.48 The submission estimated that there were on average 1.8 caregivers per patient. Application of the caregiver disutility using the absolute reduction method decreased the ICER by approximately % to \$115,000 to < \$135,000 per QALY gained; using the proportional reduction method decreased the ICER by approximately % to \$95,000 to < \$115,000 per QALY. Due to the heterogeneity of the disease, the number of carers required would vary per patient. If an assumption of one carer per patient was applied, which aligned with the NICE guidance for selumetinib⁸, the ICER decreased by

⁸ <https://www.nice.org.uk/guidance/hst20>

approximately $\frac{1}{2}$ % using the absolute reduction method and $\frac{1}{2}$ % when applying the proportional change.

6.49 Remaining uncertainties with the revised economic model included the:

- extrapolation of immature PFS trial data from the SPRINT trial Stratum I (maximum follow-up of six years) over a time horizon of 50 years;
- assumption that the treatment benefit of selumetinib on health-related quality of life (HRQoL) would continue and maintain throughout the lifetime of patients. Approximately 86% of the QALYs (undiscounted) occurred in the extrapolated period. The PSCR noted that as tumour growth rate slows as patients get older, it was deemed reasonable for patients to maintain the clinical benefits until the end of the time horizon. The ESC considered that the maintenance of clinical benefit was uncertain over the 50 year time horizon; and
- exclusion of patients with asymptomatic PN. The PSCR stated that the asymptomatic PN population was small and therefore the evaluation was considered appropriate to determine the cost-effectiveness of selumetinib for all patients included in the restriction criteria.

Drug cost/patient/year

Table 11: Estimated cost of selumetinib per patient per year (DPMQ)

BSA (m ²)	Dose (mg)	Cost/dose (\$)	Cost/day (\$)	Cost/year (\$)	Cost/year (\$) (Capped at BSA m ²)
0.55–0.69	20 (morning) 10 (evening)				
0.70–0.89	20 BID				
0.90–1.09	25 BID				
1.10–1.29	30 BID				
1.30–1.49	35 BID				
1.50–1.69	40 BID				
1.70–1.89	45 BID				
1.90–1.94	50 BID				

Source: Table 4-19 of the resubmission.

BID = twice daily dosing; BSA = Body Surface Area; DPMQ = dispensed price for maximum quantity.

6.50 In November 2022, the PBAC considered that a fixed cost per patient per year would be preferable for selumetinib as it would reduce the cost effectiveness concerns relating to use in older patients (including adults) and any changes in the average BSA over time (paragraph 7.13, selumetinib PSD, November 2022 PBAC Meeting).

6.51 Data from the NF1 clinic database at the Children’s Hospital at Westmead, which collects patient demographics and disease characteristics was used to compare the Australian population with that in the SPRINT trial. A total of 55% patients from the Westmead database and 32% of patients in the SPRINT trial Stratum I had a BSA greater than or equal to 1.30m², suggesting that Australian patients with NF1 may have a higher BSA. To provide greater financial certainty to the government in the event there are more patients at higher BSA levels in practice compared to the SPRINT

trial Stratum I, the resubmission proposed a fixed maximum cost per patient per year, corresponding to a BSA of 1.73 m^2 (average BSA of a 12 year old).

Estimated PBS usage & financial implications

- 6.52 This resubmission was not considered by DUSC. In November 2022, the DUSC considered that the usage estimates were likely underestimated, and the financial impact estimates were uncertain (paragraph 6.90, selumetinib PSD, November 2022 PBAC meeting).
- 6.53 As in the previous submission, the resubmission used an epidemiological approach to estimate the use and financial implication of listing selumetinib. The resubmission addressed the following issues which were raised by the PBAC in the November 2022 consideration:
- A 10% price reduction in the effective EMP was proposed.
 - A prevalence only based epidemiological approach was applied. This approach was consistent with the previous DUSC advice, which removed incident patients (as incident patients would have been captured in the prevalence estimate).
 - The resubmission removed the time on treatment approach applied to the prevalent patient population. Instead, the submission stated that the uptake rates applied accounted for naïve initiations and continuing patients from previous years. The resubmission assumed 7.76 prescriptions per patient per year for individuals with a BSA of 0.55-0.69 m^2 and 10.35 prescriptions per patient per year for all other BSA categories per year.
 - Proportion of patients with symptomatic, inoperable PN was revised from 74% to 67%.
 - The eligible population was divided into two cohorts: (i) patients aged 2-5 years and (ii) patients aged 6 to 18 years. Different uptake rates were applied to each subgroup to adjust for the ability to swallow whole capsules and to better align with the age distribution observed in the SPRINT trial Stratum I. Previously, the uptake rate was 40% in Year 1, increasing to 95% in Year 6.
 - Dose and number of prescriptions were calculated based on the BSA distribution in the SPRINT trial Stratum I, instead of the mean BSA in the trial, which was the approach used in the previous submission.
 - Inclusion of annual cost of ophthalmological monitoring (MBS item 104) in addition to the previously included two additional magnetic resonance imaging scan (MBS item 63301).
- 6.54 A summary of the data sources and parameter values used to estimate the utilisation and financial impact of listing selumetinib is presented in Table 12.

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Table 12: Key inputs for financial estimates

Data	Value	Source	Comment
Eligible population			
Australian population aged ≥2 years to ≤18 years	Yr 2024: 5,769,249	ABS projection (2024-2029)	-
Prevalence of NF1	1 in 3,000	The Royal Children's Hospital Melbourne; Boulanger & Larbrisseau (2005)	-
Proportion of patients with PN	30% (range: 20%-50%)	Survey of seven Australian clinicians experienced in treating PN and validated at Australian Clinical Advisory Board; Anderson & Gutmann (2015); Copley-Merriman et al. (2021); Gross et al. (2018); Hirbe & Gutmann (2014); Friedrich et al. (2005).	-
Proportion of patient with symptomatic NF1 PN	67% (range: 60%-74%)	Survey of seven Australian clinicians experienced in treating PN and validated at Australian Clinical Advisory Board; Hamoy-Jimenez et al. (2020); Nguyen et al. (2011)	Reduced from 74% in the previous submission.
Proportion of patients with inoperable NF1 PN	90% (range: 87.7%-90%)	Survey of seven Australian clinicians experienced in treating PN and validated at Australian Clinical Advisory Board; Prada et al. (2012); Wolkenstein et al. (2023)	-
Selumetinib share	80%	Survey of seven Australian clinicians experienced in treating PN and validated at Australian Clinical Advisory Board	Although uncertain, this was considered acceptable given the off-label use of trametinib for treating patients with NF1 PN in Australia and the ongoing recruitment of the TiNT trial.
Compliance rate	85%	Submission assumption	Although lower than the compliance rate observed in the SPRINT trial Stratum I, this was considered acceptable.
Treatment utilisation			
Uptake rate for patients aged 2-5 years.	Yr 1: 15% Yr 2: 25% Yr 3: 25% Yr 4: 30% Yr 5: 30% Yr 6: 30%	Submission assumption to account for the initial criteria to include ability to swallow capsules.	The total proportion of eligible patients treated over the 6 years has been revised from 95% (in previous submission) to 64%. The submission stated that the approach accounted for naïve initiations plus continuing patients from previous years. The application of uptake to a prevalent population is not appropriate. Patient numbers were not adjusted to account for initiations in the previous year, which would likely overestimate use. The use of uptake rates to account for continuing patients is also highly uncertain. Overall, the PBAC considered that the revised proportion of eligible patients treated (64%) was reasonable.
Uptake rate for patients aged 6-18 years.	Yr 1: 45% Yr 2: 60% Yr 3: 70% Yr 4: 75% Yr 5: 75% Yr 6: 75%	Submission assumption based on discussions with the PBAC and clinicians at the facilitated resolution workshop.	

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Data	Value	Source	Comment
Dose distribution	0.55-0.69m ² : 4% 0.70-0.89m ² : 32% 0.90-1.09m ² : 18% 1.10-1.29m ² : 14% 1.30-1.49m ² : 16% 1.50-1.69m ² : 10% 1.70-1.89m ² : 4% 1.90-1.94m ² : 2%	Dosing was calculated based on the BSA distribution observed in the SPRINT trial Stratum I and ranged from 30 mg per day to 100 mg per day.	-
Costs			
Selumetinib	10 mg: \$ [REDACTED] 25 mg: \$ [REDACTED] Maximum cost per patient based on a BSA of [REDACTED] m ² .	Requested effective EMP	-
Patient copayment	PBS: \$11.18 RPBS: \$4.09	Derived from nintedanib utilisation data on PBS during 2022 calendar year	-
MBS costs – MRI scans	\$400.85	MBS item number: 63301	-
MBS costs – Ophthalmologists visits	\$95.10	MBS item number: 104	-

Source: Table 4-9 of the resubmission.

ABS = Australian bureau of statistics; AEMP = approved ex-manufacturer price; BSA = body surface area; MBS = Medicare Benefits Scheme; MEK = mitogen-activated protein kinase; MRI = magnetic imaging resonance; NF1 = neurofibromatosis type 1; PBAC = Pharmaceutical Benefits Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PN = plexiform neurofibroma(s).

6.55 The estimated use and financial impacts of listing selumetinib are summarised in Table 13.

Table 13: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients eligible	1	1	1	1	1	1
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed ^a	2	2	2	2	2	2
Estimated financial implications of selumetinib						
Cost to PBS/RPBS less co-payments	3	4	4	4	4	4
Net financial implications						
Net cost to PBS/RPBS	3	4	4	4	4	4
Net cost to MBS	3	3	3	3	3	3
Net cost to PBS/RPBS/MBS	3	4	4	4	4	4
Previous submission, November 2022						
Number of patients treated	1	1	1	1	1	1
Number of scripts dispensed ^b	2	2	2	2	2	2
Net cost to PBS/RPBS	4	5	5	5	6	6
Net cost to PBS/RPBS/MBS	4	5	5	5	6	6

Source: Table 4-13; Table 4-16 and Table 4-24 of the resubmission; Table 14, selumetinib PSD, November 2022 PBAC meeting.

MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme

^a Assuming 7.76 prescription per patient per year for individuals with a BSA of 0.55-0.69m² and 10.35 prescriptions per patient per year for all other BSA category per year as estimated by the resubmission.

^b Assuming 10.35 scripts per year as estimated by the submission

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 \$30 million to < \$40 million

⁶ \$20 million to < \$30 million

- 6.56 The resubmission stated that the total proportion of the eligible patient population treated over the first 6 years of listing has been revised from 95% in November 2022 to 64%. The resubmission estimated a lower number of patients from Year 1 to Year 4, but a higher number from Year 5 to Year 6 compared to the November 2022 submission. This difference was due to removal of the application of time on treatment in the resubmission; instead, the resubmission assumed that continuing patients were included in the uptake rates applied. The number of scripts dispensed was higher for all years in the resubmission. This was because the number of scripts per patient per year was based on the BSA distribution observed in the SPRINT trial Stratum I and adjusted to account for an increase in BSA associated with age, rather than a mean BSA of 1.127m² which was applied in the November 2022 submission.
- 6.57 Based on the revised financial estimates, the total cost to the PBS/RPBS of listing selumetinib was estimated to be \$10 million to < \$20 million in Year 6, and total of \$80 million to < \$90 million over the first 6 years of listing. This was approximately 46% lower than the estimates presented in the November 2022 submission, which totalled \$100 million to < \$200 million in the first 6 years of listing. The cost to the PBS/RPBS incorporated the proposed fixed maximum cost per patient per year corresponding to a BSA of 1 m².
- 6.58 Uncertainties relating to the estimated use of selumetinib in the resubmission include that the:

- application of uptake rates to the prevalent patient population was not appropriate as the number of patients who had initiated treatment the previous year were not removed. The ESC considered that this approach likely overestimated use. Further, the use of uptake rates to account for the number of patients continuing treatment from previous years is highly uncertain; and
- number of patients eligible for treatment with selumetinib did not include patients with PN likely to lead to significant symptoms. The PSCR stated that these patients were excluded from the analysis in the resubmission for simplicity as this patient population was small (2.6% of asymptomatic patients). However, the PSCR provided revised estimates which included these patients, which increased the cost to the Government by \$0 to < 10 million over the first 6 years of listing.

6.59 Using a fixed maximum cost per patient per year based on a BSA of [redacted]-[redacted]m², i.e. a maximum BSA of [redacted]m² (corresponding to the mean BSA of 1.127m² in SPRINT trial), decreased the estimated cost to the PBS/RPBS over the first 6 years of listing by 6% from \$80 million to < \$90 million to \$80 million to < \$90 million.

Quality Use of Medicines

6.60 The resubmission did not update the quality use of medicines information provided in the November 2022 submission. The resubmission stated that implementation of TGA approved label wording and consumer medicine information will ensure quality use of medicines. Additionally, a post-marketing safety study has been planned to characterise the long-term safety profile of selumetinib among paediatric patients; however, no Australian patients were expected to be enrolled.

6.61 In the November 2022 submission, both DUSC and the PBAC considered that large capsule size posed quality use of medicine issues, particularly in paediatric population (paragraph 6.93 and 7.19, selumetinib PSD, November 2022 PBAC meeting). The quality use of medicines issue was discussed at the Facilitated Resolution Pathway workshop; however, the issue remains, and it was determined that it will be at the clinician's discretion as to whether a child can swallow the large capsule (page 2, Facilitated Resolution Pathway Workshop Outcomes).

Financial Management – Risk Sharing Arrangements

6.62 The PBAC previously considered that an RSA would be required given the potential use in adult patients in which efficacy and cost-effectiveness of treatment was uncertain. The PBAC considered that an RSA with expenditure caps based on the revised estimated financial impact of listing selumetinib and a rebate of 100% for use exceeding the caps, would likely be appropriate (paragraph 7.15, selumetinib PSD, November 2022 PBAC meeting).

6.63 The resubmission proposed an RSA with a fixed maximum cost per patient based on a BSA of [redacted]m² and a [redacted]% rebate on expenditure above the estimated cap to provide financial certainty if more patients than forecasted are treated and/or if patients on treatment reach a BSA greater than [redacted]m² (Table 14).

6.64 The ESC stated that a RSA based on more conservative financial estimates could potentially further reduce the risks associated with the uncertain efficacy and costs effectiveness claims.

Table 14: Proposed risk share arrangement – overall expenditure caps

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Proposed overall expenditure caps (\$) ^a	[REDACTED]					

Source: Table 4-26 of the resubmission.

^a Includes maximum cost capped at a BSA of [REDACTED] m²

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

7 PBAC Outcome

- 7.1 The PBAC recommended the General Schedule PBS listing of selumetinib for the treatment of symptomatic inoperable plexiform neurofibroma(s) (PN) in paediatric patients with neurofibromatosis type 1 (NF1). The PBAC noted the high clinical need for treatments for this condition and considered that selumetinib provided a clinical benefit for patients compared to best supportive care (BSC). The PBAC considered that the resubmission had addressed most of the issues raised in the previous submission adequately; however, noted that the incremental cost effectiveness ratio (ICER) remained high. The PBAC considered that a further reduction in cost would be required to achieve an acceptable ICER. The PBAC considered the estimated number of treated patients would form a reasonable basis for a risk-sharing arrangement (RSA) and that a rebate of [REDACTED]% for use beyond the expenditure caps would be appropriate.
- 7.2 The PBAC acknowledged the consumer comments relating to this submission which described the quality of life challenges associated with the disease and highlighted the high unmet clinical need for effective treatments. The PBAC noted the significant impact PN associated with NF1 can have on children, including pain and disfigurement. The PBAC noted the comments related to the importance of access to a treatment other than surgery and the high cost of selumetinib.
- 7.3 The PBAC again considered that the proposed place in therapy of selumetinib as an alternative to BSC was reasonable.
- 7.4 The PBAC noted that for patients with symptomatic, inoperable PN, the resubmission did not present any additional clinical data. The PBAC recalled that the November 2022 submission presented two unanchored indirect treatment comparisons between the single arm, open-label SPRINT trial Stratum I and a matched cohort from the National Cancer Institute Natural History (NH) study and the placebo arm of trial 01-C-0222. The PBAC recalled that selumetinib was associated with a 5.1% (95% CI: -27.3, 19.0) PN volume decrease compared to a 15% (95% CI: -3.7, 126.2) volume increase in the NH study. In addition, 69.7% (95% CI: 50.8, 82.5) of patients in the SPRINT trial Stratum 1 had not progressed after 5 years, compared with 18.2% (95% CI: 10.8, 27.1) in the NH study.
- 7.5 The PBAC noted that for patients with asymptomatic, inoperable PN at risk of

significant clinical PN-related morbidity, the resubmission presented results from the single arm, open-label SPRINT trial Stratum II. The PBAC noted that for these patients, the results in terms of PN volume change and the proportion of patients who were progression free at week 48 were consistent with patients from Stratum I who had symptomatic PNs.

- 7.6 The PBAC noted that for patients who had commenced treatment in the paediatric setting and had progressed into adulthood additional data were presented from a *post hoc* subgroup analysis of the SPRINT trial Stratum I and the ongoing, open-label Study NCT02407405. The PBAC noted selumetinib was likely to be effective in patients who turn 18 years of age after commencing treatment.
- 7.7 The PBAC recalled that it had previously considered the claim that selumetinib was superior in terms of efficacy compared to BSC was adequately supported in patients with symptomatic, inoperable PN, noting that there were uncertainties due to the small sample size of the SPRINT trial, the unanchored indirect treatment comparisons, and the transitivity issues (paragraph 6.47, selumetinib PSD, November 2022 PBAC meeting). The PBAC considered that selumetinib was also likely superior to BSC for patients with asymptomatic PNs and in adult patients who had commenced treatment in the paediatric setting. The PBAC noted that the magnitude of the benefit in all patients was uncertain due to the lack of comparative data.
- 7.8 The PBAC recalled that as no comparative safety data were presented it had previously considered that the claim of non-inferior safety compared to BSC could not be supported (paragraph 7.10, selumetinib PSD, November 2022 PBAC meeting). Noting that no new comparative safety data were presented in the resubmission and that 68% of selumetinib patients experienced Grade ≥ 3 adverse events, the PBAC considered that selumetinib had an inferior, but manageable, safety profile compared to BSC.
- 7.9 The PBAC recalled that it had identified a number of issues with the November 2022 economic model which reduced its reliability for decision making. The PBAC further recalled that in November 2022 it had stated that a price reduction which resulted in an ICER of \$75,000 to $<$ \$95,000 per QALY would be required.
- 7.10 The PBAC noted that the resubmission presented a revised economic model that addressed most of the issues raised in November 2022 (see Table 6). The PBAC also noted that the revised model corrected for an error in the time to treatment discontinuation (TTD) data and that this correction increased the ICER significantly. The PBAC noted that although the resubmission offered a $\%$ price reduction, the revised base case ICER was \$155,000 to $<$ \$255,000 per QALY gained. The PBAC noted that the ICER was further reduced when carer disutilities were included. Although the PBAC noted that the disutility value applied was high and the methods of application were uncertain, the PBAC considered that selumetinib would potentially result in benefits for others beyond the patient. Thus, when considered in conjunction with the high clinical need and the low utilisation estimates, the PBAC considered that selumetinib would be cost effective at an ICER of no more than \$135,000 to

< \$155,000 per QALY gained.

- 7.11 The PBAC noted that the resubmission had proposed a fixed maximum cost per patient of selumetinib based on a body surface area (BSA) of 1m^2 . The PBAC noted that the reduced cost per patient required for selumetinib to be cost-effective could be attained by either reducing the price of selumetinib or lowering the BSA-based maximum cost per patient.
- 7.12 In terms of the utilisation estimates, the PBAC considered that the changes made were reasonable. The PBAC considered that the proportion of eligible patients receiving treatment (38% in Year 1 to 64% in Year 6, reduced from 95%) was reasonable and appropriately accounted for younger patients being unable to swallow the large selumetinib capsule. In addition, the PBAC considered that asymptomatic patients (as proposed in the PSCR and pre-PBAC response) should be included in the utilisation estimates.
- 7.13 The PBAC noted that the resubmission proposed a RSA with a ██████% rebate for use beyond the expenditure caps to mitigate any outstanding risks associated with weight based dosing and substantial use into adulthood. The PBAC considered that the revised expenditure estimates should be based on the reduced cost per patient of selumetinib and incorporate asymptomatic patients.
- 7.14 In terms of the proposed restriction, the PBAC noted that the resubmission incorporated all of the changes suggested by the PBAC in November 2022 and from the Facilitated Resolution Pathway workshop. The PBAC considered that:
- the first and subsequent continuing supply restrictions could be combined into one continuing treatment phase Authority Required (telephone/online), rather than Authority Required (written) restriction.
 - it would be reasonable for the grandfather restriction to allow patients to transfer to selumetinib from other MEK inhibitors, particularly considering the quality of use issues associated with the large selumetinib capsule. Additionally, the PBAC considered that the grandfather restriction remain in place indefinitely beyond the usual 12 months limit to continue to allow patients who are too young to swallow the selumetinib capsule to be treated another MEK inhibitor.
 - It was not necessary for Services Australia to capture the baseline information from the MRI report; rather, retaining this information in the patient's file would be sufficient.
- 7.15 The PBAC advised that selumetinib is not suitable for prescribing by nurse practitioners.
- 7.16 The PBAC advised that selumetinib should not be exempt from the Early Supply rule.
- 7.17 The PBAC advised that selumetinib should not be considered interchangeable on an individual patient basis with any other PBS-listed drugs.
- 7.18 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were met.

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Specifically, the PBAC found that in the circumstances of its recommendation for selumetinib that:

- a) Selumetinib is expected to provide a substantial and clinically relevant improvement in efficacy over BSC;
- b) Selumetinib is expected to address a high and urgent unmet clinical need as there are no alternative therapies available;
- c) It would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A on the basis of the preceding findings.

7.19 The PBAC advised that this submission would not meet the criteria for an Independent Review as received a positive PBAC recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new item and new indication:

MEDICINAL PRODUCT medicinal product pack	PBS item number	Max. qty packs	Max. qty units	No. of Rpts	Available brands
SELUMETINIB					
selumetinib 10 mg capsule, 60	New	1	60	5	Koselugo
selumetinib 25 mg capsule, 60	New	1	60	5	Koselugo

Category / Program: General Schedule	
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners	
Restriction type: <input checked="" type="checkbox"/> Authority Required (in writing via post/HPOS upload or immediate assessment via online PBS authorities system)	
	Administrative Advice: The Karnofsky Performance Score is available at: https://oncologypro.esmo.org/oncology-in-practice/practice-tools/performance-scales www.mdcalc.com/calc/3168/karnofsky-performance-status-scale
	The Lansky Performance Score is available at: www.mdcalc.com/calc/3176/lansky-play-performance-scale-pediatric-functional-status
	Administrative Advice: No increase in the maximum number of repeats may be authorised.
	Administrative Advice: Special Pricing Arrangements apply.
Restriction Summary / Treatment of Concept	
	Indication: Neurofibromatosis type 1
	Treatment Phase: Initial treatment
	Clinical criteria:
	Patient must have plexiform neurofibroma(s) (PN) that is causing/likely to cause at least one of: (i) significant symptoms/morbidity, (ii) disability, (iii) disfigurement, or (iv) impairment of normal body function;
	AND

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	Clinical criteria:
	Patient must have PN for which complete resection cannot be performed.
	AND
	Clinical criteria:
	Patient must have either a (i) Karnofsky, (ii) Lansky Performance Score of at least 70%
	AND
	Treatment criteria:
	Must be treated by a prescriber who is either: (i) a specialist physician with expertise in neurofibromatosis, (ii) a medical practitioner in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
	Population criteria:
	Patient must be aged between 2 to 18 years
	Population criteria:
	Patient must be able to swallow the whole capsule form of this drug.
	Prescriber instructions: At the time of the authority application, medical practitioners must request the appropriate number of packs of appropriate strength(s) to provide sufficient drug, based on the body surface area (BSA) of the patient, adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescriber instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.
	Prescribing instruction: For the purpose of administering this restriction, significant symptoms/morbidity are defined as but not limited to: 1) head and neck PN that can compromise the airway or great vessels, 2) paraspinal PN that can cause myelopathy, 3) brachial or lumbar plexus PN that can cause nerve compression and loss of function, 4) PN that can result in major deformity or significant disfiguring (e.g. orbital PN), 5) PN of the extremity that can cause limb hypertrophy or loss of function, and 6) painful PN.
	Administrative Advice: The authority application must be made in writing and must include: i) A completed authority prescription form; and ii) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).

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	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>
Restriction Summary / Treatment of Concept: [New 2]	
	Indication: Neurofibromatosis type 1
	Treatment Phase: Continuing treatment
	Clinical criteria:
	Patient must have previously received PBS-subsidised treatment with this drug for this condition
AND	
	Clinical criteria:
	Patient must be tolerating treatment
AND	
	Clinical criteria:
	Patient must have achieved either (i) stabilisation of disease, (ii) adequate response to treatment, if have received at least 12 months of treatment with this drug
AND	
	Treatment criteria:
	Must be treated by a prescriber who is either: (i) a specialist physician with expertise in neurofibromatosis, (ii) medical practitioner in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation
	Prescriber instructions:
	At the time of the authority application, medical practitioners must request the appropriate number of packs of appropriate strength(s) to provide sufficient drug, based on the body surface area (BSA) of the patient, adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.
	Prescriber instructions:
	Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records
	Prescribing instructions:
	For the purpose of administering this restriction, adequate response is defined as:
	1. Stability or improvement of the initial baseline measurements prior to initiating treatment with this drug
	2. Relevant imaging has not shown an increase in tumour size of 20% or more

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	<p>Administrative Advice: Applications for authorisation under this restriction may be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/HPOS) or by telephone by contacting the Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday).</p>
<p>Restriction Summary / Treatment of Concept: [New 3]</p>	
	<p>Indication: Neurofibromatosis type 1</p>
	<p>Treatment Phase: Transitioning from non-PBS to PBS-subsidised supply – ‘Grandfather’ arrangements</p>
	<p>Clinical criteria</p>
	<p>Patient must have previously received treatment with this drug for this condition prior to [PBS listing date] OR</p>
	<p>Patient must have previously received treatment with another mitogen-activated protein kinase (MEK) inhibitor for this condition prior to [PBS listing date]</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have met all other PBS eligibility criteria that a non- ‘Grandfather’ patient would ordinarily be required to meet, meaning that at the time non-PBS subsidised supply of a MEK inhibitor (including selumetinib) was commenced, the patient:</p> <p>(I) had PN that caused/was likely to cause at least one of: (i) significant symptoms/morbidity, (ii) disability, (iii) disfigurement, (iv) impairment of normal body function; (II) had PN for which complete PN resection could not be performed either (i) safely, (ii) without causing unacceptable morbidity (III) had either a (i) Karnofsky, (ii) Lansky Performance Score of at least 70% (IV) was aged between 2 and 18 years. (V) was able to swallow the whole capsule form if received non-PBS supply with selumetinib</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be tolerating treatment</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have achieved either (i) stabilisation of disease, (ii) adequate response to treatment, if have received at least 12 months of treatment</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a prescriber who is either: (i) a specialist physician with expertise in neurofibromatosis, or (ii) a medical practitioner in consultation with a specialist physician with expertise in neurofibromatosis if attendance is not possible due to geographic isolation</p>
	<p>Prescriber instructions: At the time of the authority application, medical practitioners must request the appropriate number of packs of appropriate strength(s) to provide sufficient drug, based on the body surface area (BSA) of the patient, adequate for 4 weeks, according to the specified dosage in the approved Product Information (PI). A separate authority prescription form must be completed for each strength requested. Up to a maximum of 5 repeats will be authorised.</p>
	<p>Prescriber instructions: Confirmation of eligibility for treatment with diagnostic reports must be documented in the patient's medical records.</p>

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	<p>Prescribing instruction: For the purpose of administering this restriction, significant symptoms/morbidity are defined as but not limited to:</p> <ol style="list-style-type: none"> 1) head and neck PN that can compromise the airway or great vessels, 2) paraspinal PN that can cause myelopathy, 3) brachial or lumbar plexus PN that can cause nerve compression and loss of function, 4) PN that can result in major deformity or significant disfiguring (e.g. orbital PN), 5) PN of the extremity that can cause limb hypertrophy or loss of function, and 6) painful PN.
	<p>Prescribing instructions: For the purpose of administering this restriction, adequate response is defined as:</p> <ol style="list-style-type: none"> 1. Stability or improvement of the initial baseline measurements prior to initiating treatment with this drug 2. Relevant imaging has not shown an increase in tumour size of 20% or more
	<p>Administrative Advice: Patients may qualify for PBS-subsidised treatment under this restriction once only. For continuing PBS-subsidised treatment, a 'Grandfathered' patient must qualify under the Continuing treatment criteria.</p>
	<p>Administrative Advice: The authority application must be made in writing and must include:</p> <ol style="list-style-type: none"> i) A completed authority prescription form; and ii) A completed authority application form relevant to the indication and treatment phase (the latest version is located on the website specified in the Administrative Advice).
	<p>Administrative Advice: Any queries concerning the arrangements to prescribe may be directed to Services Australia on 1800 700 270 (hours of operation 8 a.m. to 5 p.m. Monday to Friday). Prescribing information (including Authority Application forms and other relevant documentation as applicable) is available on the Services Australia website at www.servicesaustralia.gov.au Applications for authorisation under this restriction should be made in real time using the Online PBS Authorities system (see www.servicesaustralia.gov.au/hpos) Alternatively, applications for authority to prescribe can be submitted online using the form upload facility in Health Professional Online Services (HPOS) at www.servicesaustralia.gov.au/hpos Or mailed to: Services Australia Complex Drugs Reply Paid 9826 HOBART TAS 7001</p>

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

9 Context for Decision

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

10 Sponsor's Comment

Alexion welcomes the PBAC's recommendations for PBS listing of selumetinib for the treatment of symptomatic inoperable plexiform neurofibroma(s) (PN) in paediatric patients with neurofibromatosis type 1 (NF1). Alexion will continue to work closely with the Department on a timely PBS listing so that children who may benefit from this treatment option have access at the earliest opportunity.