SMC2540

selumetinib hard capsules (Koselugo®)

Alexion Pharmaceuticals

07 July 2023

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the orphan medicine process

selumetinib (Koselugo®) is not recommended for use within NHSScotland.

Indication Under Review: as monotherapy for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric patients with neurofibromatosis type 1 (NF1) aged 3 years and above.

In an open-label, single-arm phase II study in paediatric patients with NF1 and symptomatic inoperable PN, selumetinib was associated with a response rate of 66%.

The submitting company's justification of the treatment's cost in relation to its health benefits was not sufficient and in addition the company did not present a sufficiently robust economic analysis to gain acceptance by SMC.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Vice Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Selumetinib is a selective inhibitor of mitogen activated protein kinase kinases 1 and 2 (MEK 1/2) which are components of the RAF-MEK-ERK pathway that is commonly activated in human cancer. MEK inhibition can block the proliferation and survival of tumour cells associated with activation of the RAF-MEK-ERK pathway.[1, 2]

The recommended dose of selumetinib is 25mg/m^2 of body surface area (BSA), taken orally twice daily (approximately every 12 hours). Treatment should continue as long as clinical benefit is observed, or until PN progression or the development of unacceptable toxicity. There are limited data in patients older than 18, therefore continued treatment into adulthood should be based on benefits and risks to the individual patient as assessed by the physician. However, starting treatment with selumetinib in adults is not appropriate.[2]

1.2. Disease background

Neurofibromatosis 1 (NF1) is a genetic neurocutaneous condition with a prevalence in adult and paediatric populations from 20 to 24 cases per 100,000 persons. It is associated with the loss in function of the NF1 tumour suppressor gene. The clinical features of the disease are diverse and include skin conditions, tumour growth (benign and malignant), neurological issues, orthopaedic manifestations and cardiovascular morbidities. Diagnosis is based on the presence of two or more of the following clinical features: six or more café-au-lait macules, two or more neurofibromas or one PN, freckling in axilla or groin, optic glioma, two or more Lisch nodules (iris hamartomas), a distinctive bony lesion or a first-degree relative with NF1. Life expectancy is reduced by 8 to 15 years in persons with the disease (mainly due to malignant neoplasms and cardiovascular causes), with malignancy the most common reason for death in those under 30 years.[1, 3-5]

Plexiform neurofibromas are benign peripheral nerve sheath tumours that typically grow along large nerves and plexuses. They affect between 30% to 50% of patients with NF1 and tend to develop between birth and 18 years of age. The growth rate is variable and unpredictable, with the most rapid during the first decade of life. They can grow into surrounding tissue causing significant morbidity including pain, neurological and motor dysfunction, airway compromise, visual impairment and disfigurement; these symptoms tend to worsen over time and rarely resolve spontaneously. There is also an increased risk of developing malignant peripheral nerve sheath tumours which can arise from PNs; these tumours metastasize widely and are associated with a poor prognosis. Patients may have a single or multiple PNs and severity varies from mild to severe.[1, 3]

1.3. Treatment pathway and relevant comparators

There are no pharmacological treatments licensed to cure, prevent or reduce the volume of PNs. Current treatment options include pain management and surgical intervention when possible for complete or partial tumour removal. Surgical removal can be challenging because of the vascular structure of the tumour and proximity to surrounding nerves and tissues; life-threatening haemorrhage can also occur, particularly with facial PN.[1] The most relevant comparator for the indication under

review is best supportive care (BSC) which typically includes symptom management, pain relief, psychological support, and physiotherapy.

1.4. Category for decision-making process

Selumetinib has a conditional marketing authorisation from the Medicines and Healthcare Products Regulatory Agency.

Selumetinib meets SMC orphan criteria.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of selumetinib for the indication under review is from SPRINT Phase II Stratum I. Details are presented in Table 2.1.[1, 6, 7]

Table 2.1. Overview of relevant studies

Criteria	SPRINT Phase II Stratum I
Study Design	Open-label, single-arm, multicentre (4 sites in the US) phase II study.
Eligible Patients	Patients aged 2 to 18 years with NF1 with ≥1 measurable (≥3cm), inoperable PN (defined as PN that could not be surgically completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity) that caused significant morbidity with ≥1 neurofibroma-related complication. Patients >16 years must have had a Karnofsky performance level of ≥70%, and patients ≤16 years must have had a Lansky performance of ≥70%. All patients had to be able to swallow whole capsules.
Treatments	Oral selumetinib 25mg/m^2 BSA twice daily (approximately 12 hourly) on a continuous 28 day dosing cycle. Patients with progressive disease (increase of ≥20% in volume of PN or ≥13% increase in product of the longest two perpendicular diameters or ≥6% in longest diameter) within 1.5 years prior to study entry continued selumetinib as long as they did not have disease progression during treatment. Patients without disease progression within 1.5 years prior to study entry continued selumetinib for a maximum of 2 years unless a partial response was observed, in which case treatment could continue until criteria for discontinuation were met. Patients could be re-treated if PN had volume increase ≥15% within 2 years of stopping selumetinib, Treatment duration was not limited for patients who showed an imaging response, unless the patient experienced subsequent disease progression or met other off-treatment criteria.
Randomisation	All patients (n=50) received selumetinib.
Primary outcome	ORR, defined as the percentage of patients with a CR or cPR. cPR was defined as a target PN volume decrease of ≥20% compared to baseline, confirmed by volumetric MRI within 3 to 6 months. CR was defined as the disappearance of the target PN. Unblinded assessment by NCI-POB using REiNS criteria.
Secondary outcomes	DOR; TTP; TTR; PFS; clinical outcome measures of symptoms related to PN and health-related quality of life.
Statistical analysis	Efficacy analysis were conducted in the FAS (all patients who had received one dose of selumetinib). Descriptive statistics.
BSA=body surface area; cPR=confirmed partial response; CR=complete response; DOR = duration of response; FAS=full analysis set; MRI=magnetic resonance imaging; NCI-POB=National Cancer Institute–Paediatric Oncology Branch; NF1= neurofibromatosis type 1; ORR=objective response rate; PN=plexiform neurofibroma; REiNS =	

Response Evaluation in Neurofibromatosis and Schwannomatosis; PR=partial response; TTP = time to progression; TTR = time to tumour response; PFS = progression free survival; US=United States;

The first data cut was in June 2018 after a median follow-up of 24-cycles. Results are presented in Table 2.2. A subsequent unplanned second data cut in March 2021 provided a further 2 years and 9 months of data and these results were used to inform the economic analysis.[1, 7]

Table 2.2: Results from SPRINT Phase II Stratum I in the FAS[1, 7, 8]

	Selumetinib n=50
Data cut-off	**29 June 2018**
Median follow-up	24 cycles
Primary outcome: ORR per REiNS criteria[A]	
ORR, % (n)	66% (33)
CR, %	0%
cPR, %[B]	66%
SD, %	22%
Secondary outcomes	
Median DOR	NR
Median TTR[C]	8 cycles
Median PFS	NR
PFS events, n	3
KM estimated PFS at cycle 24	-
KM estimated PFS at cycle 48	-
cPR=confirmed partial response; CR=complete response; DOR=duration of response; ORR=objective response rate; KM=Kaplan-Meier; NCI-POB=National Cancer Institute–Paediatric Oncology Branch; NR=not reached; PFS=progression free survival; PN=plexiform neurofibroma; SD=stable disease; TTR=time to response. [A]Assessed by NCI-POB central analysis by a single reviewer; [B]Response was confirmed within 3 to 6 months after the criteria for first response were met. Partial response was defined as decrease in the volume of the target PN by 20% or more compared with baseline. [C]Measured in 33 responders *The results from the March 2021 data cut-off were considered confidential by the company.	

At the June 2018 data cut, two sensitivity analyses were conducted for the primary outcome using an independent central review (ICR) of volumetric MRIs of the target PN lesion read by radiologists according to modified Response Evaluation in Neurofibromatosis and Schwannomatosis (REiNS) criteria. Both reviewers were blinded to visit date and name but the second was presented images of each patient in sequential order. For the first (pre-planned) ICR analysis ORR was 44% and in the second (post-hoc) it was 40% (no complete responses in either analysis).[1] These are lower than ORR (66%) from the protocol-specified assessment by NCI-POB central analysis by a single unblinded reviewer.

2.2. Health-related quality of life outcomes

Patient-reported outcomes were used to assess Health-Related Quality of Life (HRQoL) and PN associated morbidities including: pain, motor function, airway function, bowel and bladder function, disfigurement and vision function. These clinical outcome assessments were measured as secondary outcomes and were used to demonstrate the clinical relevance of tumour shrinkage. General HRQoL was measured on the Paediatric Quality of Life Inventory (PedsQL), pain intensity was measured using the Numeric Rating Scale-11 (NRS-11), pain interference with daily activities was assessed using the Pain Interference Index (PII) and motor function was assessed using the Patient-Reported Outcome Measurement Information System (PROMIS).[1] The results are detailed in Table 2.3.

Table 2.3: Patient-Reported Outcomes from SPRINT Phase II Stratum I, 29 June 2018 cut-off[1]

	Baseline	Pre-cycle 13
Paediatric Quality of Life Inventory (PedsQL)		
Patient-reported impaired global HRQoL	33% (11/33)	31% (9/29)
Patient-reported clinically meaningful improvement (≥10.33 points)	-	38% (11/29)
Parent-reported impaired global HRQoL	56% (28/50)	36% (16/45)
Parent-reported clinically meaningful improvement (≥11.90)	-	53% (24/45)
Pain Numeric Rating Scale-11 (NRS-11)		
Adjusted mean change	-	-2.07
Clinically meaningful improvement (≥2 points)	-	50% (12/24)
Pain interference index (PII)		
Patient-reported clinically meaningful improvement (≥0.75 points)	-	34% (10/29)
Patient-reported adjusted mean change	-	-0.65
Parent-reported clinically meaningful improvement (≥1.78 points)	-	33% (14/42)
Parent-reported adjusted mean change	-	-0.82
PROMIS physical functioning		
Patient-reported mobility improvement	-	30% (6/20)
Patient-reported upper extremity improvement	-	26% (5/19)
Patient-reported mobility improvement	-	32% (9/28)
Patient-reported upper extremity improvement	-	15% (4/27)

2.3. Indirect evidence to support clinical and cost-effectiveness comparisons

In absence of a control group the company performed two pre-specified naïve comparisons. These compared selumetinib with a Natural History study and placebo arm of study 01-C-0222 which were used as a proxy for BSC.

Table 2.4: Summary of indirect treatment comparison

Criteria	Overview
Design	Naïve indirect comparison
Population	Patients with NF1 with symptomatic, inoperable PN
Comparators	Selumetinib and BSC (defined as no disease-modifying treatment and symptomatic management only)
Studies included	SPRINT Phase II Stratum I[1, 7], National Cancer Institute (NCI) Natural History study (age-matched cohort)[1, 9] and study 01-C-0222 (placebo arm)[1, 10]
Outcomes	PFS (compared with NCI Natural History study age-matched cohort) and PN growth rate
Results	The results of the naïve treatment comparisons are considered confidential by the submitting company.
Company conclusion	The company concluded that treatment with selumetinib was associated with a reduction in the risk of progression and a durable and sustainable PN response when compared with BSC.

3. Summary of Safety Evidence

Selumetinib was associated with adverse drug reactions consistent with the known safety profile of MEK 2 inhibitors and a high proportion of patients experienced a grade ≥3 adverse events (AEs) and drug interruptions due to AEs. Therefore the regulator noted that selumetinib could not be considered a well-tolerated drug.[1]

In SPRINT Stratum I at data cut-off 29 June 2018, the median total duration of treatment with selumetinib was 26.3 months (range: 1 to 35 months). Any AE was reported by 98% (49/50), patients reporting a grade 3 or higher AE were 62% and these were considered causally related to selumetinib in 38%. Patients with a reported serious AE were 24% and these were considered causally related to selumetinib in 12%. The proportion of patients with a dose reduction due to AEs was 24% and with a dose interruption due to AEs was 80%, with 12% of patients discontinuing therapy due to an AE. The most frequently reported treatment-emergent AEs of any grade with an incidence >50% were: vomiting (82%), blood creatinine phosphokinase increased (76%), diarrhoea (70%), nausea (66%), dry skin (60%), fatigue (56%) and pyrexia (56%).[1]

Asymptomatic reduction in ejection fraction was reported in 22% of patients, with a median time to onset of 226 days and there were a small number of serious reports of left ventricular ejection fraction (LVEF) reduction in paediatric patients within an expanded access programme. Further information on monitoring LVEF and managing selumetinib treatment following a reduction in LVEF has been included in the summary of product characteristics (SPC). Other potential safety risks including physeal dysplasia, ocular toxicity, myopathy, hepatotoxicity and lack of long term exposure will be monitored as part of the planned non-interventional post-authorisation safety study (PASS) included in the MHRA specific obligations.[1, 2, 5]

*Other data were also assessed but remain confidential.**

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Selumetinib is the first medicine to be licensed for the treatment of symptomatic, inoperable PN in patients with NF1.

- In SPRINT Phase II Stratum I, treatment with selumetinib was associated with an ORR of 66% after a median follow-up of 24 cycles at the June 2018 data cut off, Median DOR and PFS had not been reached. The results from a subsequent post hoc data cut off in March 2021 were consistent. [1, 7]

4.2. Key uncertainties

- SPRINT was an open-label, single-arm study with a small sample size (n=50) which is associated with a number of limitations.
    - The single-arm uncontrolled design means that there are no direct data comparing selumetinib with a relevant comparator and results from all study outcomes are descriptive only. The submitting company stated that it was not feasible to conduct a placebo controlled study because of the rarity and severity of the condition and in

addition it would have been unethical because of the lack of alternative pharmaceutical treatments and the likelihood of patients in the placebo group discontinuing treatment early to start selumetinib.

- Subjective efficacy (including imaging interpretation), safety and patient-reported outcomes may be prone to bias including the primary outcome that was read by a single reviewer. In two sensitivity analyses conducted by blinded ICR; both reviewers were blinded to visit date and name. ORR reported was similar for each sensitivity analysis and was lower than the primary analysis (44% and 40% per ICR compared with 66% per NCI-POB). This introduces uncertainty regarding the exact magnitude of benefit.[1]

- There was a wide variation in baseline characteristics including age (ranged: 3.5 to 17.4 years), target PN volume (range: 5.6 to 3820mL) and the time from PN diagnosis (range: 0.7 to 16.5 years). There was also variation in target PN location and status (progressive or non-progressive), which is reflective of the small heterogeneous study population. Furthermore, all patients were recruited across four sites in the US.[1] It is uncertain if the study population accurately reflects patients seen in Scottish clinical practice, which is also difficult to generalise due to the rarity of the condition.

- The favourable effects observed for clinical outcome assessments are likely to be affected by subjective self-scoring and the location and size of PN at baseline. The sample size was considerably lowered for most outcomes, which could only be measured in a specific subset of the study population based on the presence of a particular PN morbidity or because of age restrictions and only the NRS-11, PII and PROMIS questionnaires have been validated for use in NF studies.[1] Therefore, the quality of the evidence suggest that correlations between outcomes and tumour shrinkage are not robustly demonstrated.

- In the absence of direct data, the company performed naïve indirect comparisons which were associated with a number of limitations. This included comparing data sources with different study design, small sample sizes and a naïve methodology unadjusted for possible prognostic variables and heterogeneity of baseline characteristics (NCI Natural History study did adjust for age). Missing data meant comparisons could be made for PFS and PN growth rate only and no safety or HRQoL data have been compared. There was a lack of independent assessment in the control studies which mean imaging results could be prone to bias. Due to these limitations, the results are uncertain.

- SPRINT Phase II recruited those aged ≤18 years and therefore evidence in older patients is limited. There is no upper age limit specified in the licensed indication however the SPC notes that treatment beyond 18 years should be based on risks and benefits to the patient and that it is not appropriate to initiate treatment in adults.[2]

- Selumetinib is formulated as a capsule that cannot be crushed or broken which must be taken on an empty stomach 1 hour before or 2 hours after food and with water only.[2] This could limit use

in younger children or those who struggle to swallow capsules and comply with the strict administration regimen. Dosing is limited to increments of 5mg. [1]

- Follow-up is currently limited and longer-term efficacy and safety are uncertain.

4.3. GB/EMA conditional marketing authorisation specific obligations

The company has specific obligations to complete as set out by the MHRA: submit results from longer follow-up of patients from the SPRINT study and submit a non-interventional long term safety study. The outstanding data from the specific obligations are unlikely to address the key uncertainties in the clinical evidence presented.

4.4. Clinical expert input

Clinical experts consulted by SMC considered that selumetinib filled an unmet need for the indication under review because of a lack of alternative pharmacological interventions. They generally considered that it was a therapeutic advance and that it would be used in paediatric patients with symptomatic inoperable plexiform neurofibromas who could safely take the capsule formulation; prescribing decisions may be taken in collaboration with a wider multidisciplinary team.

4.5. Service implications

As selumetinib is a new treatment for this indication additional clinical resource may be required to manage and monitor clinical outcomes and AEs. The numbers are expected to be low.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of selumetinib, as an orphan medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Symptomatic plexiform neurofibromas (PN) are a complication associated with the lifelong genetic condition neurofibromatosis type 1 (NF1) and they tend to develop in childhood. Symptoms can vary depending on the site of the PN, and include debilitating chronic pain, disfigurement, reduced mobility, reduced vision, and risk of airway compromise. Occasionally these tumours can undergo malignant transformation. In addition to the physical manifestations, affected children experience mental health issues such as depression, anxiety, lack of self-esteem and body image problems. Other issues secondary to the condition include low academic achievement due to school avoidance or regular hospital visits, being subject to bullying and social exclusion and dependency on carers. An increased frequency of attention deficit hyperactivity disorder (ADHD) and autistic spectrum disorders has also been observed in patients with NF1.
- There are no licensed medicines for the treatment of symptomatic PN in NF1 and there is therefore a high unmet need. Surgery is an option in a few cases but can be associated with complications such as excessive bleeding and nerve damage, and many PNs are considered inoperable. Selumetinib would be the first disease modifying treatment licensed for this condition.

- Selumetinib offers hope for patients with this devastating condition, and has the potential to considerably improve quality of life. A reduction in PN volume could improve chronic pain, which may reduce pain medication use. It may reduce the disfiguring effects of PN, which would lessen the psychological distress experienced by patients and may help with children participating in school and extracurricular activities. It could also improve mobility and motor function in some cases.
- The availability of selumetinib is likely to have a large positive impact for the patient's family and carers, reducing burden of care, if there is a clinical improvement in their child's condition. There would be a psychological benefit if it meant that family members did not have to witness their child experience distressing symptoms such as pain or breathlessness. There are also practical benefits; if selumetinib were available in Scotland it could reduce the number of long-distance trips to specialist centres, and there could be financial benefits for families if treatment with selumetinib results in fewer hospital visits and less time out of work.
- The side effects associated with selumetinib are considerable, however patients are very willing to take this medicine as it has the potential to reduce pain, shrink tumours, and reduce disfigurement.

Additional Patient and Carer Involvement

We received patient group submissions from Nerve Tumours UK and Tumour Support Scotland. Both organisations are registered charities. Nerve Tumours UK has received 5.8% pharmaceutical company funding in the past two years, including from the submitting company. Tumour Support Scotland has not received any pharmaceutical company funding in the past two years. Representatives from both organisations participated in the PACE meeting. The key points of their submissions have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case, as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis
Time horizon	Lifetime (100 years based on an assumed starting age of 10 years)
Population	Paediatric patients, aged 3 years and above, with NF1 and inoperable PN.
Comparators	Selumetinib was compared with BSC, which was defined as symptom management, pain relief, psychological support, and physiotherapy.
Model description	A standard partitioned survival model with three main health states: progression-free, progressed disease and death. Only patients in the selumetinib arm could occupy the progression-free state. Patients in the BSC arm were assumed to remain in the progressed disease state for the duration of their lives. The definition of progression used in the model was the same as that used in the main clinical study. Within the modelling the company assumed that disease stabilisation occurs at 18 years of age. At that point, patients receiving selumetinib would cease treatment and see their risk of progression fall to zero.
Clinical data	The primary sources of clinical data for selumetinib patients was the second data cut (March 2021) of SPRINT Phase II Stratum I[7]. This source was used to inform PFS, time-to-discontinuation (TTD), and AEs associated with selumetinib. The company also accessed the Natural History study in NF1 patients[9], and combined it with the data from the SPRINT study through a naïve indirect

	comparison. However, the assumptions that BSC patients could not be progression free, would not discontinue treatment and suffered no AEs, meant the data from the Natural History study were not used directly in the modelling, but were used to support modelling assumptions.
Extrapolation	PFS for selumetinib was extrapolated to the model time horizon based on a constant progression rate estimated from SPRINT Phase II Stratum I data. TTD for selumetinib was extrapolated using a Weibull distribution, up to when patients turned 18 and treatment was assumed to discontinue automatically. Overall survival was assumed to be identical for patients receiving selumetinib or BSC. Mortality was estimated by adjusting Scottish general population life expectancy estimates using a standardised mortality ratio (SMR) for NF1 PN patients reported by Duong et al.[11]
Quality of life	HRQoL for patients in the economic model was estimated from a study commissioned by the submitting company. Vignettes, describing the patient experience across treatment with selumetinib and BSC, were created with input from patients, carers and clinicians. These health descriptions were assigned utility values using the time trade-off method with members of the general public in the UK. These estimates suggested that treatment with selumetinib led to significantly higher quality of life than BSC. Selumetinib patients were assumed to maintain that higher HRQoL across their lifetimes, even after discontinuation, unless they experienced disease progression. At disease progression selumetinib patients were assumed to transition to the lower BSC utility value over a 5-year period. The impact of AEs for selumetinib patients on utility was excluded based on the assumption that these would have minimal impact. When applied in the model, utility values were age and sex adjusted using a model by Ara & Brazier.[12] The submitting company has highlighted that due to the nature of the condition, NF1 PN can also have a detrimental impact upon the health and wellbeing of carers. This was not included in the base case results, although was explored in some of the scenarios presented in Section 6.3.
Costs and resource use	Medicine-related costs included in the analysis were acquisition costs for selumetinib and medications comprising BSC as well as medications used to resolve AEs. Other NHS costs accounted for greater disease monitoring in patients receiving selumetinib. No other NHS costs associated with disease management were included under the assumption they would be applied equally across the treatment arms.
PAS	A Patient Access Scheme (PAS) discount was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHSScotland. Under the PAS, a simple discount was offered on the list price. The results presented in this document take account of the PAS for selumetinib.

6.2. Results

The base case incremental cost-effectiveness ratio (ICER), inclusive of the PAS discount on selumetinib, was estimated as £80,521 per quality-adjusted life-year (QALY) gained. A disaggregated analysis of costs indicated that over 99% of incremental costs associated with selumetinib were due to the cost of acquiring selumetinib, which was very marginally offset by a reduction in the cost of pain medication required.

6.3. Sensitivity analyses

A number of sensitivity analyses were provided by the company to help explore areas of uncertainty. Key scenarios are summarised in Table 6.3, where results are inclusive of the PAS discount on selumetinib.

Table 6.3: Selected scenario analyses with PAS

#	Description	Base Case Value	Scenario Value	ICER (£ per QALY)
1	Starting age	10 years old	5 years old	89,969
2			15 years old	46,717

3	Disease stabilisation age	18 years	20 years	85,511
4			25 years	89,807
5	Mortality	No treatment effect on mortality - equal SMR applied to both arms	Selumetinib patients have lower mortality than BSC patients - a 5% improvement in SMR associated with selumetinib.	79,555
6	Caregiver utility impact	Excluded	1 carer per patient	61,833
7			1.4 carers per patient	56,580
8	Scale of caregiver utility loss [1.4 caregivers assumed]	Excluded	Carer utility loss 75% of patient loss from PN	61,124
9			Carer utility loss 50% of patient loss from PN	66,460
10	Duration of caregiver impact [1.4 caregivers assumed]	Excluded	Carer utility loss until patient reaches 24 years	50,165
11			Carer utility loss until caregiver is 64 years	44,796
12			Carer utility loss for duration of carer's lifetime	40,935

Abbreviations: ICER = incremental cost effectiveness ratio; QALY = quality adjusted life year; SMR = standardised mortality ratio; PN = plexiform neurofibromas.

6.4. Key strengths

- The economic modelling matched the licensed indication.
- The comparator of BSC was appropriate, as there are currently no disease-modifying treatments available for NF1 PN patients.

6.5. Key uncertainties

- The company assumed that the starting age of treatment would be 10 years old, which matched the mean age of patients enrolled in SPRINT Phase II Stratum I. However, given the absence of other treatment options, children may receive treatment earlier and the average age of initiation would decrease over time as it becomes part of standard of care. Under the same efficacy and TTD assumption used in the base case, the modelling suggested that earlier initiation would reduce the cost-effectiveness of treatment (see Scenario 1 in Table 6.3).

- The age at which disease stabilisation took place was a key driver of the model and an area of uncertainty. The submitting company assumed that the risk of progression for selumetinib patients would fall to zero at 18 years of age, and correspondingly no patients would be treated past that point. However, data from the Natural History study suggested that while PN growth is highest in younger children, some untreated patients can see volume increases after the age of 18.[9] Increasing the age at which disease stabilisation is assumed to occur led to a reduction in the cost-effectiveness of selumetinib (Scenarios 3 and 4).

- The model did not allow for BSC patients to be progression-free, and this was an area of uncertainty. Results from the age-matched indirect comparison between the SPRINT Phase II Stratum I and the Natural History studies suggested that a non-negligible proportion of BSC patients could be classified as progression-free (based on the progression definition used in the SPRINT study). The company argued that while those patients did not meet the definition of progression, they did experience PN growth, and so classifying them as progression-free in the model was inappropriate. However, conversely, it was unclear how appropriate it was to group those patients in with the cohort who did meet the defined threshold of progression and assign them the same utility value. If BSC patients with lower volume growth had higher HRQoL, the modelling approach may have overestimated the cost-effectiveness of selumetinib, but to an unknown degree.

7. Conclusion

The Committee considered the benefits of selumetinib in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios and agreed that as selumetinib is an orphan medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, the Committee was unable to accept selumetinib for use in NHSScotland.

8. Guidelines and Protocols

UK based guidelines: "Guidelines for the diagnosis and management of individuals with neurofibromatosis 1" were published in 2007.[3] Available here

9. Additional Information

9.1. Product availability date

October 2021

9.2. Summary of product characteristics

Selumetinib (Koselugo®) 10mg hard capsules SPC

Selumetinib (Koselugo®) 25mg hard capsules SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 day cycle (£)
Selumetinib	**25mg/m^2 twice daily, taken orally**	**11,826**

Costs from eMC Dictionary of Medicines and Devices Browser on 26.02.23. Costs calculated based on a 10 year old (median age in SPRINT Phase II Stratum I) assuming a BSA 1.1m^2. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The company estimated there would be 6 patients eligible for treatment with selumetinib each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 15 May 2023**.**

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.