National Institute for Health and Care Excellence

Highly Specialised Technology (HST)

Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over ID1590

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	AstraZeneca	Yes	Comment noted, no action required.
	Genetic alliance	It is appropriate that the treatment be appraised by NICE as there are currently no treatments licensed for treating inoperable plexiform neurofibromas.	Comment noted. The lack of licensed treatments is highlighted in the draft scope. No action required.
Wording	AstraZeneca	The remit does not mention that patients in the SPRINT study had symptomatic plexiform neurofibromas. The expected licence wording will be: [redacted]	The draft scope has been updated to state that the population is symptomatic and inoperable plexiform neurofibromas.

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	Genetic alliance	This is the standard wording	Comment noted, no action required.
Timing Issues	AstraZeneca	No comment	N/A
	Genetic alliance	As there are no treatment licensed for treating inoperable plexiform neurofibromas it is therefore appropriate that the medicine be appraised quickly in order for patients who would benefit from the treatment to gain access as soon as possible.	Comment noted. The lack of licensed treatments is highlighted in the scope. No action required.
Additional comments on the draft remit	AstraZeneca	No comment	N/A
	Genetic alliance	No comment	N/A

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	AstraZeneca	No comment	N/A
	Genetic alliance	The background information appears to be accurate but is worth adding that its effects are variable from person to person	Comment noted. The background section of the scope has been updated to highlight the variability of symptoms

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			in this population. No action required.
The technology/ intervention	AstraZeneca	No comment	N/A
	Genetic alliance	No comment	N/A
Population	AstraZeneca	The SPRINT study defined inoperable tumours as "*plexiform neurofibromas that cannot be surgically completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the PN*".	Comment noted. At the scoping workshop there were concerns regarding the strictness of this definition of inoperable in the SPRINT clinical trial. The draft scope notes that most surgery is not curative, with reducing the tumour volume a key aim.
	Genetic alliance	No comment	N/A
Comparators	AstraZeneca	Established clinical management without selumetinib in this indication is purely symptomatic treatment (e.g. pain relief).	Comment noted. No action required.
	Genetic alliance	No comment	N/A
Outcomes	AstraZeneca	Bone marrow density was part of safety assessment and was assessed only for the patients enrolled at the NCI who had abnormal bone marrow density.	Comments noted. Bone marrow density has been removed from the

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		Therefore, it is not considered as part of the most important health related benefits or harms of the technology. In addition to physical functioning & HRQoL, other patient reported outcomes such as airway function, bowel/bladder function, visual function and global impression of change and improvement of disfigurement in individual patients are important endpoints to be considered.	outcomes section of the scope. Disfigurement, visual function, bowel/bladder function and airway function have been added to the outcomes section of the scope.
	Genetic alliance	No comment	N/A
Economic analysis	AstraZeneca	No comment	N/A
	Genetic alliance	No comment	N/A
Equality and Diversity	AstraZeneca	No comment	N/A
	Genetic alliance	No comment	N/A
Other considerations	AstraZeneca	No comment	N/A
	Genetic alliance	No comment	N/A
Innovation	AstraZeneca	Plexiform neurofibroma is a debilitating, progressive manifestation of NF1, typically diagnosed in childhood, but with a lifelong impact. Currently there are no licensed treatments for patients with inoperable plexiform neurofibromas. Selumetinib is an oral, potent and highly selective MEK 1/2 inhibitor which has shown efficacy in paediatric patients in the Ph1/2 SPRINT study. Therefore, selumetinib has the potential to be a step change in the management of this condition.	Comment noted. Committee will consider if selumetinib is innovative if this topic is referred.

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	Genetic alliance	Clinical trials have indicated that the treatment leads to the shrinkage of tumours and improvements in clinical outcomes. It would therefore represent a step-change	Comment noted. Committee will consider if selumetinib is innovative if this topic is referred.
Questions for consultation	AstraZeneca	Can you provide an estimate of how many children with inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in England do you expect to be treated with selumetinib per year if this treatment was approved? Please see the box below for a breakdown of the expected patient numbers in England. How is it confirmed that plexiform neurofibromas associated with type 1 neurofibromatosis are inoperable in clinical practice? The SPRINT study defined inoperable tumours as “plexiform neurofibromas that cannot be surgically completely removed without risk of substantial morbidity due to encasement of, or close proximity to, vital structures, invasiveness or high vascularity of the plexiform neurofibroma”. Which treatments are considered to be established clinical practice in the NHS for inoperable plexiform neurofibromas? Currently, no licenced treatments for inoperable plexiform neurofibromas exist. Treatment for inoperable tumours currently consists of symptomatic treatment for pain.	Comments noted.

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		Would selumetinib be administered exclusively within specialised centres? It is expected that selumetinib would be initiated in one of the two specialist centres for neurofibromatosis in England. However, treatment consists of administration of oral treatment and can be performed outside of the centres. Are there any subgroups of people in whom selumetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately? No efficacy subgroups were identified in the SPRINT study.	
	Genetic alliance	No comments	N/A
Additional comments on the draft scope	AstraZeneca	Any additional comments on the draft scope The company would like to submit selumetinib in the present indication for consideration under the NICE HST criteria: The target patient group for the technology in its licensed indication is so small that treatment will usually be concentrated in very few centres in the NHS Currently, care for patients with neurofibromatosis type 1 (NF1) is concentrated in two specialist NHS centres in England: • Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) • Manchester University NHS Foundation Trust (St Mary's, Manchester) The anticipated label for selumetinib will be the treatment of paediatric patients aged 3 years and above, with symptomatic and/or progressive NF1	Comments noted. A decision on which process is most appropriate will be made with consultation comments considered in this decision.

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<tr><th>Section</th><th>Consultee/ Commentator</th><th>Comments [sic]</th><th>Action</th></tr>
<tr><td></td><td></td><td>inoperable plexiform neurofibromas (PNs). Please note that the EMA submission for selumetinib in this indication is [redacted]

The prevalence of NF1 has been stated at 1 in 4,560, based on a study from a family genetic register service in northwest England.i This corresponds with a figure of 1 in 4,500 used by NHS England.ii We estimate the total eligible patient population for selumetinib to be 141 in England, based on the breakdown shown in the table below. Further, we have been advised by UK clinicians that the actual number of patients in this population who are actually diagnosed and treated in these centres is far lower in clinical practice.

<table>
<tr><th>Criteria</th><th>Estimate</th><th>Source</th></tr>
<tr><td>Total population of England</td><td>55.98 M</td><td>Mid-2018 country population dataiii</td></tr>
<tr><td>England NF1 prevalence</td><td>1 in 4,560</td><td>English genetic register studyi</td></tr>
<tr><td>Number of patients with NF1</td><td colspan="2">12,276</td></tr>
<tr><td>Proportion of English population aged 3-17</td><td>9.98 M (16.7 %)</td><td>Mid-2018 country population dataiii</td></tr>
<tr><td>Paediatric patients with NF1</td><td colspan="2">2,050</td></tr>
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<tr><td>Paediatric patients with NF1 who have PN</td><td>25%</td><td>Prevalence of PNs taken at 25%: previously reported as 24.7% and 26% in children with NF1.iv, v</td></tr>
<tr><td>Paediatric patients with PN</td><td colspan="2">513</td></tr>
<tr><td>PNs which are symptomatic</td><td>55%</td><td>Upper end of range taken for proportion of symptomatic PNs reported in children: range 37% (in children <11.5 years of age) to 55% (>11.5 years)vi</td></tr>
<tr><td>Symptomatic patients</td><td colspan="2">282</td></tr>
<tr><td>Proportion of PNs which are inoperable</td><td>50%</td><td>Surgical resection of PNs is generally considered challenging and deciding on the operability of patients is done on a case-by-case basis (internal research). Published data are limited, the average of the below has been used:
43% (n=68)vii
57% (n=7)viii</td></tr>
<tr><td>Total eligible patient population</td><td colspan="2">141</td></tr>
</table>

The target patient group is distinct for clinical reasons
NF1 is a genetic disorder and as such is clinically distinct from similar disorders of the nervous system, namely neurofibromatosis type 2 and</td><td></td></tr>
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		schwannomatosis.ix The diagnostic criteria for NF1 differ from those for neurofibromatosis type 2 and schwannomatosis.x A minority of paediatric patients with NF1 will develop PNs, which are clinically distinct from other forms of neurofibroma (i.e. cutaneous and subcutaneous neurofibromas).x A proportion of these PNs will become symptomatic, with onset of symptoms linked to tumour size and location;viii PNs can cause substantial morbidity due to their growth along multiple nerve branches. Common symptoms of PN include:x xii xiv xi substantial pain and discomfort, disfigurement, nerve dysfunction (weakness/numbness), and bone destruction. Patients with inoperable PNs are clinically distinct from those where surgery is an option. Unlike cutaneous and subcutaneous neurofibromas, surgery to remove benign PNs is often complex due to encroachment of tumours on surrounding nerve structures, and life-threatening haemorrhage may occur.x Surgical interventions also commonly result in additional morbidity to patients.xii Therefore, surgery may only be attempted where risks can be minimised.xiii The condition is chronic and severely disabling NF1 is an incurable condition with highly-variable symptoms, including cutaneous, neurological and orthopaedic manifestations. In addition to PN-associated symptoms mentioned above, patients with NF1 may experience a range of secondary complications depending on tumour size and location, including:xiv xv • Learning difficultiesxvi	

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		• Functional impairment: from obstruction of normal growth/function of tissues caused by large tumoursxvii • Visual impairment: caused by tumour growth around the optic nervexviii • Pain: large tumours may pull on nerves, or compress internal organsxii • Disfigurementxii • Twisting and curvature of the spinexix • Cardiovascular complicationsxv Regular evaluations are required for the early identification and effective management of clinical manifestations of NF1 PN.xx As a result of these complications, patients with NF1 PN experience severely impaired QoL.xxi NF1 has a major adverse effect on patients' lives through severe complications, adverse effects on cosmetic features, and the uncertainty arising from future effects of the disorder. Although the morbidity and the mortality caused by NF1 are dictated by the occurrence of these complications, which may involve any of the body systems, patients have been reported to perceive cosmetic disfigurement as the major clinical problem.xxii Therefore, the ability to reduce tumour size may further improve patient outcomes beyond restored physical function. PNs are a neurological manifestation of NF1 and arise from nerve fascicles that tend to grow along the length of the nerve. PNs occur in a minority of paediatric patients, causing further pain, motor dysfunction and disfigurement.xii Furthermore, there exists a risk that plexiform tumours can progress into malignant peripheral nerve sheath tumours (MPNSTs). Patients with NF1 MPNSTs have a 5-year survival rate of approximately 21%,xxiii confirming progression as a major cause of death in patients with NF1.xxiv	

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		The technology is expected to be used exclusively in the context of a highly specialised service Selumetinib would be expected to provide a new treatment modality for patients with inoperable NF1 with PN, as part of a complex package of care delivered from two specialist UK centres: • Guy's and St Thomas' NHS Foundation Trust (Evelina London Children's Hospital) • Manchester University NHS Foundation Trust (St Mary's, Manchester) Selumetinib inhibits the MEK enzyme in the RAS/MEK/ERK pathway, potentially leading to the inhibition of tumour growth which arises in the absence of functional neurofibramin.xi In the phase II clinical trial (SPRINT; NCT01362803) patients 2-18 years old with NF1, inoperable PN and ≥1 PN-related morbidity received selumetinib at the recommended dose (25 mg/m2 PO BID) every 12 hours with continuous dosing (1 cycle = 28 days) until unacceptable toxicity, patient withdrawal or pharmacodynamics. The technology has the potential for life long use Currently, the intended label for selumetinib will be for children aged 3-17. Size of PNs is generally linked with the incidence of complications.iv It has been shown that PNs grow most rapidly in early age, with the fastest PN growth observed in children under the age of 15.**Error! Bookmark not defined.** xxv xxvi Therefore, paediatric therapy represents the optimal window for prolonged therapeutic effect. Use of selumetinib in this setting offers the potential to prevent the growth of PNs and avoid complicated surgery (see below).xxv Therefore, while selumetinib is not currently intended	

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		for life-long use, the benefits of paediatric treatment would be expected to continue into adulthood. The need for national commissioning of the technology is significant Currently there is no cure for NF1, and there are no licensed therapies in the UK for patients with NF1 with inoperable PN.xxv Surgery is the only option for resection of PNs. However, surgery carries the risk of nerve damage and severe blood loss,xviii increased risk of augmented regrowth after surgery,xxvii and an overall risk of permanent sequelae.xii Most cases of PN require repeat surgical procedures as complete excision is generally not possible due to the infiltrating nature of these tumours.xxviii Infiltration of multiple tissue planes by the tumour is common, making surgery more difficult, or even impossible in some cases.xiii Therefore, there exists substantial need for a therapy for the treatment of NF1 PNs. If licensed, selumetinib will provide the first pharmacological treatment option for patients with symptomatic NF1 with inoperable PN. Selumetinib has recently been granted US Breakthrough Therapy Designation in the US for the treatment.xxix	
	Genetic Alliance	No comment	N/A
	Nerve Tumours UK	Research carried out by our colleagues in the USA has shown Selumetinib reduces the size of plexiform neurofibromas in about 70% of children with NF1. The results of a recent study of fifty children taking Selumetinib twice a day in tablet form, show some clinical benefit as well as some shrinkage of	Comments noted. No action required.

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		the plexiform neurofibroma. Children and their parents noted that symptoms of pain, disfigurement, quality life and muscle strength improved. The side effects of the drug continue to be skin rashes and infection, and nausea, vomiting and diarrhoea. Further research is needed to find out which plexiform neurofibromas will benefit most from Selumetinib treatment. In the UK, Selumetinib is currently available for children and adults on compassionate basis only via the national centres in London and Manchester. A clinical trial is underway at GOSH to investigate the best dosing schedule for children on Selumetinib.	

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

[i] Evans DG et al. 2010. Birth incidence and prevalence of tumor-prone syndromes: Estimates from a UK family genetic register service. Am J Med Genet Part A 152A:327–332.
[ii] B13/S(HSS)/a. 2013/14 NHS Standard Contract For Complex Neurofibromatosis Type 1 Service (All Ages). Available at: https://www.england.nhs.uk/wp-content/uploads/2013/06/b13-comp-neurofib-1.pdf
[iii] Office for National Statistics. 2018 Population estimates. Available at: https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwalesscotlandandnorthernireland
[iv] Nguyen R et al. Plexiform neurofibromas in children with neurofibromatosis type 1: frequency and associated clinical deficits. J Pediatr. 2011 Oct;159(4):652-5.e2.
[v] Boulanger JM & Larbrisseau A. Neurofibromatosis type 1 in a pediatric population: Ste-Justine's experience. Can J Neurol Sci. 2005 May;32(2):225-31.
[vi] Nguyen R et al. Growth dynamics of plexiform neurofibromas: a retrospective cohort study of 201 patients with neurofibromatosis 1. Orphanet Journal of Rare Diseases 2012, 7:75)
[vii] Waggoner DJ et al. Clinic-based study of plexiform neurofibromas in neurofibromatosis 1. Am J Med Genet. 2000 May 15;92(2):132-5.
[viii] Serletis D et al. Massive plexiform neurofibromas in childhood: natural history and management issues. J Neurosurg. 2007 May;106(5 Suppl):363-7.
[ix] NHS Overview - Neurofibromatosis type 1: available at: https://www.nhs.uk/conditions/neurofibromatosis-type-1/
[x] Ferner RE et al. Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet. 2007 Feb; 44(2): 81–88.

[xi] Blakeley JO & Plotkin SR. Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis. Neuro Oncol. 2016 May;18(5):624-38.
[xii] Prada CE et al. Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr. 2012 Mar;160(3):461-7.
[xiii] Needle MN et al. Prognostic signs in the surgical management of plexiform neurofibroma: The Children's Hospital of Philadelphia experience, 1974-1994. J Pediatr 1997;131:678-82
[xiv] Ferner RE. Neurofibromatosis 1 and neurofibromatosis 2: a twenty first century perspective. Lancet Neurol. 2007 Apr;6(4):340-51.
[xv] Tedesco MA et al. The heart in neurofibromatosis type 1: an echocardiographic study. Am Heart J. 2002 May;143(5):883-8.
[xvi] Cutting LE, Levine TM. Cognitive Profile of Children with Neurofibromatosis and Reading Disabilities. Child Neuropsychol. 2010 Sep; 16(5): 417–432.
[xvii] Boyd K et al. Neurofibromatosis type 1. J Am Acad Dermatol. 2009 Jul;61(1):1-14
[xviii] Tonsgard J. Semin Pediatr Neurol 2006;13:2-7.
[xix] Crawford A et al. Neurofibromatosis: Etiology, Commonly Encountered Spinal Deformities, Common Complications and Pitfalls of Surgical Treatment. Spine Deformity. 2012; 85-94.
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[xxi] Wolkenstein P et al. Quality-of-Life Impairment in Neurofibromatosis Type 1A Cross-sectional Study of 128 Cases. Archives of Dermatology. 2001; 137(11): 1421-1425.
[xxii] Wolkenstein P et al. Cost evaluation of the medical management of neurofibromatosis 1: a prospective study on 201 patients. Br J Dermatol. 2000 Jun;142(6):1166-70.
[xxiii] Malignant peripheral nerve sheath tumours in neurofibromatosis 1. J Med Genet. 2002 May;39(5):311-4.
[xxiv] Evans DG, et al. Reduced Life Expectancy Seen in Hereditary Diseases Which Predispose to Early-Onset Tumors. Appl Clin Genet. 2013; 6:53–61
[xxv] Dombi E et al. NF1 plexiform neurofibroma growth rate by volumetric MRI: relationship to age and body weight. Neurology. 2007; 68:643–7.
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[xxviii] Friedrich RE et al. Resection of small plexiform neurofibromas in neurofibromatosis type 1 children; World J Surg Oncol 2005;3:3-6.
[xxix] https://www.astrazeneca.com/media-centre/press-releases/2019/selumetinib-granted-us-breakthrough-therapy-designation-in-neurofibromatosis-type-1-01042019.html