NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Evaluation consultation document

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using selumetinib in the context of national commissioning by NHS England. The highly specialised technologies evaluation committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts, patient experts and NHS England.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from the consultees and commentators for this evaluation and the public. This document should be read along with the evidence (see the committee papers).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of the criteria considered by the committee, and the clinical and economic considerations reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance on the use of selumetinib in the context of national commissioning by NHS England?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: December 2021

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final evaluation document.
- Subject to any appeal by consultees, the final evaluation document may be used as the basis for NICE's guidance on using selumetinib in the context of national commissioning by NHS England.

For further details, see the interim process and methods of the highly specialised technologies programme.

The key dates for this evaluation are:

Closing date for comments: [Day month year]

Second evaluation committee meeting: [Day month year]

Details of membership of the evaluation committee are given in section X.

1 Recommendations

1.1 The committee was minded not to recommend selumetinib as an option for treating symptomatic and inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children aged 3 and over.

1.2 The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second evaluation committee meeting, and should include:

- a patient-level model, including:
  - a progression-free state for the best supportive care arm
  - allows progression to happen after the age of 18
  - accounts for the progressive nature of the condition, age and location of PN
  - clinical outcomes that are important to people with PN, carers and clinicians
- the possibility for selumetinib treatment to continue beyond the age of 18
- utility values obtained from patients in the trial in the analysis by using a mapping algorithm or validation of the time trade off utilities by the mapped utilities
- carer disutility values that are:
  - dependent on PN location and morbidity experienced
  - applied to 1 carer
  - in both selumetinib and best support care arms
- the length of utility benefit waning after stopping treatment to be 1 year
- a breakdown of full resource use costs for selumetinib and best supportive care arms, with comparison between the 2 arms
- inclusion of 2 additional MRIs in the selumetinib arm.

Why the committee made these recommendations

NF1 is a genetic disease that affects multiple organ systems. Around 25% of people with NF1 develop non-malignant peripheral nerve sheath tumours called PN. PN can affect multiple body regions and reach extremely large sizes. Most PNs associated with NF1 are symptomatic, and can cause pain, disfigurement and difficulties with physical functioning. If a PN is inoperable, people have best supportive care, including pain management, physiotherapy, psychological support and sometimes procedures such as a tracheostomy to alleviate severe airway morbidities.

Clinical trial evidence suggests that selumetinib is effective at reducing the volume and size of PN compared with best supportive care.

However, the company uses a simplistic model structure based on the volume of PN. It does not account for the heterogeneity of the disease or include clinical outcomes, such as pain, which are important to people with PN and their parents or carers. The committee acknowledged that selumetinib may be an effective treatment option for people with inoperable PN, however the economic model was not appropriate to estimate the costs and benefits of selumetinib. Further information is needed before a recommendation can be made.

2 Information about selumetinib

Marketing authorisation indication

2.1 Selumetinib (Koselugo, AstraZeneca) has a marketing authorisation in the UK for the 'treatment of symptomatic, inoperable plexiform neurofibromas in paediatric patients with neurofibromatosis type 1 aged 3 years and above'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics.

Price

2.3 The price for selumetinib is £4,223.59 for a 10 mg 60-capsule pack and £10,560.00 for a 25 mg 60-capsule pack (excluding VAT; company submission). The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, the views of people with the condition, those who represent them and clinical experts, NHS England and a review by the evidence review group (ERG). See the committee papers for full details of the evidence. In forming the recommendations, the committee took into account the full range of factors that might affect its decision, including in particular the nature of the condition, the clinical effectiveness, value for money and the impact beyond direct health benefits.

Nature of the condition

Type 1 neurofibromatosis

3.1 Type 1 neurofibromatosis (NF1) is a rare genetic disease in which symptoms arise in early childhood and are lifelong. It is caused by mutations in the NF1 tumour suppressor gene. Because the condition is genetic, it is possible for multiple members of the same family to be affected. Clinical symptoms associated with NF1 commonly begin in early childhood and continue in adulthood. NF1 is a highly heterogeneous disease that can express differently between patients. It can present with a wide range of symptoms and can affect the nervous system, skin, bones and eyes. People with NF1 also have an increased risk of neurological comorbidities such as autism, attention deficit hyperactivity disorder and mental health disorders and an increased risk of certain forms of cancer. For most NF1 patients, the clinical course of the disease is uncertain. This can be a source of anxiety for people and their parents or carers.

Plexiform neurofibromas

3.2 Around 25% of people with NF1 can develop plexiform neurofibromas (PN). The gene mutation in NF1 causes increased cell proliferation and cell survival, which causes PN. PN are usually non-malignant peripheral nerve sheath tumours which can happen anywhere in the body and may reach large volumes. The clinical experts advised that PN commonly develop during early childhood and grow rapidly in size. The rate of growth is much higher during early childhood, slowing as the child reaches adolescence. PN rarely decrease in volume spontaneously and PN growth is associated with morbidity and mortality. The patient expert stated that although growth of PN may slow during adolescence, there can be significant growth in PN in adult life for some people and there is a higher chance of malignancy in disease progression after 18 years of age.

Effect of the condition on people with plexiform neurofibromas

3.3 PN can affect multiple body regions and reach extremely large sizes. Most PN associated with NF1 are symptomatic and associated with morbidities such as pain, disfigurement and difficulties with physical functioning. People with symptomatic NF1 PN experience the morbidities associated with their PN in addition to the clinical manifestations associated with NF1, such as attention deficit hyperactivity disorder, autism and anxiety and depression. The clinical expert explained that the growth of PN progresses quickly in childhood and then usually stabilises into adulthood. In the most serious cases, PN can lead to significant disability or life-threatening organ impairment, for example by placing pressure on spinal nerves or obstructing airways. Pain associated with PN growth is a significant feature for many people with PN and the pain can often become unresponsive to medication, with nerve pain particularly difficult to manage. People with PN may experience generalised pain as well as pain localised to their PN. These PN-associated morbidities can have a substantial negative effect on the persons physical and mental health and daily functioning. The patient experts explained that PN affects everyone

differently and can be unpredictable, which makes living with the condition difficult. The patient experts explained that PN associated with NF1 can affect every aspect of an individual's life, including education, social activities, seeking employment, starting a family and long-term life goals. School can be particularly hard for children with PN, both from a learning perspective and the ability to make and maintain friendships. The committee concluded that PN associated with NF1 is a highly heterogenous condition that can affect the body across multiple organ systems and is associated with significant morbidities.

Effect of the condition on parents and carers

3.4 The patient experts also highlighted the effect of the condition on parents and carers of people with PN. They explained that because of the type of genetic condition, approximately half of families with a child with NF1 will have a parent with the condition also, and sometimes families have multiple children with it too, therefore the burden can be very large on a family. The unpredictable nature of the condition can lead to anxiety or worry for parents and carers, and many are unable to work because of the effect of the condition on their children. Many parents and carers feel unsupported by the NHS, schools, and other services because of difficulties in getting a diagnosis and little understanding of PN. The patient experts explained that the burden on carers varies depending on where on the body the PN is, and the symptoms experienced. Location and symptoms which may significantly affect physical function, such as PNs around the spinal cord, bladder or bowel, may have a significant additional physical burden for carers compared with other locations. However, the emotional burden on carers exists for all PN. The clinical and patient experts advised that pain associated with PN is one of the most important factors on the carer burden, with people experiencing high levels of pain needing a higher level of care. The patient expert stated if treatment can reduce pain, then the burden on carers would be substantially improved. The patient expert also highlighted that NF1 is

associated with other serious morbidities (see section 3.3) which, irrespective of the presence of PN, would still need carer support. The committee concluded that PN associated with NF1 has a substantial effect on parents and carers.

Clinical management

Current treatment options

3.5 Children with PN associated with NF1 are managed within 2 nationally commissioned services in Manchester and London. Currently, surgery is the only available treatment to reduce or remove PN tumours. The clinical experts explained that many children benefit from staged surgery because clinical decisions change over time but that it was rare to remove or resect a whole PN because they tend to be large or invasive. Approximately half of all people with NF1 PN have PN that are considered inoperable (defined as PN which cannot be completely resected without risk of substantial morbidity because of encasement of, or close proximity to, vital structures, invasiveness, or high vascularity). The primary aim of current treatment of inoperable PN is symptomatic management of morbidities that develop because of PN size and location. This may include pain management, physiotherapy, psychological support and sometimes procedures such as a tracheostomy to alleviate severe airway morbidities. The patient experts advised that current treatment options are very limited, involving invasive therapies and often surgery is not able to fully remove the PN. They highlighted that there is lack of knowledge about the condition and many children with NF1 are not known to or attending one of the specialist centres and therefore are not having the correct treatment.

Treatments are needed for inoperable plexiform neurofibromas

3.6 There is no treatment currently available in routine practice to cure, prevent or reduce the volume of inoperable PN. People may be in

considerable pain because of PNs. The patient expert advised that pain associated with PNs is difficult to manage and there is a lack of effective treatments, with nerve pain particularly difficult to manage. Pain relief often takes a considerable amount of time to get right and is especially challenging in children and young people. The availability of pain management clinics for children and young people is very limited, meaning that pain management can be very poor. This affects quality of life and all aspects of daily living. The clinical experts advised that within the nationally commissioned services in Manchester and London, they currently use mitogen-activated protein kinase inhibitors (MEKi), selumetinib and trametinib, through clinical trials and on a compassionate use basis. These treatments are used for patients selected through a MEKi multidisciplinary team (MDT), to prevent further growth or reduce the volume of inoperable PN. The committee concluded that there is a need to provide an effective, non-invasive pharmacological option for people with symptomatic, inoperable PN associated with NF1.

Selumetinib

3.7 Selumetinib is a potent and selective inhibitor of mitogen-activated protein kinase, which is a key component of a cell signalling cascade. This therefore prevents PN growth and promotes PN shrinkage by reducing cell proliferation and preventing abnormal cell survival. Clinical experts explained that selumetinib is currently being used in trials and for compassionate use. Selumetinib is being used mainly in children aged between 8 and 17 years of age, because of the fact that it is only available in capsule form and younger children, and those with learning difficulties and sensory issues are unable to swallow capsules. The experts explained that some children will present with a PN which is unsuitable for surgery early and these children, usually between the ages of 4 and 9 years, have been given trametinib, which is not currently licensed for this condition, because it is available in a paediatric liquid formulation. The clinical experts explained that for those few patients on a MEK inhibitor,

discussions with the patient and their families happen after 2 years to see if treatment should be continued or not, considering clinical benefit, tolerance and toxicity of the drug and if there is any significant progression on imaging. When symptoms are stable but imaging shows worsening of PN clinical experts said they may offer a treatment break. However clinical experts stated that there was no correlation between volumetric data from MRIs and clinical outcomes. Experience of long-term usage is limited but 1 expert stated that they have a patient who has continued trametinib for 5 years. The clinical experts explained, if recommended for use in the NHS, all people for whom selumetinib may be suitable, including those currently taking trametinib but now able to swallow capsules, would be discussed at an MDT meeting to determine eligibility. It was noted that the marketing authorisation for selumetinib specifies the PN must be inoperable. The clinical experts explained that complete surgical resection is often not possible and PN may only be completely surgically resected if there is no risk of damage to the surrounding structures or substantial morbidity. Therefore, PN for which only partial resection can be achieved would be considered inoperable, and therefore selumetinib treatment would be suitable. The clinical experts advised that if selumetinib was recommended, those children currently taking trametinib would only switch to selumetinib once they could swallow capsules. The experts also highlighted that some adolescents in their centres had chosen not to have treatment, or stopped treatment with selumetinib for skin toxicity reasons or the need for more frequent monitoring which may interfere with their school work. The committee recognised that there is a thorough and robust process in place within the specialist centres to determine individual suitability of selumetinib treatment.

Clinical effectiveness

Data sources

3.8 The committee considered the various sources of clinical-effectiveness data. The company submitted clinical-effectiveness evidence for selumetinib from the SPRINT Phase 2 Stratum 1 trial done by the National Cancer Institute and supported by the company. SPRINT is an ongoing, single arm, open label study of children aged 2 to 18 years with symptomatic, inoperable PN associated with NF1 who had selumetinib. The clinical experts advised that in clinical practice, the definition of inoperable, symptomatic PN is broader than in the trial (see section 3.5). Because of the single arm nature of SPRINT, to determine the comparative effectiveness of selumetinib against standard care, the company provided non-randomised comparisons with 2 external control studies:

- The National Cancer Institute Natural History Study
- The placebo arm of tipifarnib study

Both external control studies were done by the National Cancer Institute Paediatric Oncology Branch, which was the same group who did SPRINT. Therefore, the methodologies used are similar and comparable. The committee acknowledged that PN associated with NF1 is rare and the data from clinical trials is limited.

Results of SPRINT Phase 2 Stratum 1

3.9 The aim of SPRINT is to evaluate the objective response rate to selumetinib in NF1 PN. This was defined as the rate of confirmed partial response and complete response using centrally read volumetric MRI (partial response defined as PN volume decrease of at least 20% compared with baseline; complete response defined as the disappearance of the target PN). The primary outcome, objective response rate was achieved in 68% of people in SPRINT compared with

0% in the Natural History Study. Median progression-free survival has not been reached in SPRINT, compared with 1.3 years for the Natural History Study. The probability of progression-free survival at 3 years is 84% in SPRINT, compared with 15% in the Natural History Study and 0% of people in SPRINT experienced PN growth rate of more than 20%, compared with 43% in the Natural History Study. SPRINT also showed a median change in PN volume from baseline to most recent MRI of -23% compared with 77% in the Natural History Study. Other outcomes measured in SPRINT included health-related quality of life, measured using the Paediatric Quality of Life Inventory (PedsQL) and clinical outcome measures such as pain, motor function, airway function, visual function and physical functioning. However, these outcomes were not analysed statistically against a comparator arm and only trends were reported by the company. The clinical and patient experts confirmed that these clinical outcome measures, in particular pain, are the most important outcomes to people with PN and their carers. The clinical experts outlined that reducing the volume of PN by 20% may not result in a clinically meaningful improvement both for individuals with PN and in terms of carer burden, although it was recognised that pain could be reduced by a shrinkage of PN and therefore this would affect both patient and carer burden. The experts highlighted specific clinical outcomes are more important to individuals with PN and their carers than PN volume reduction. The committee understood that although these other measures were captured in the clinical trial, they were not included in the company model. The committee concluded that these secondary clinical outcome measures are important to people with PN and their carers, and therefore would have liked to see them and their effect on quality of life included in the modelling.

SPRINT Phase 2 Stratum 1 is generalisable to the UK population

3.10 SPRINT was done in the US. The ERG was concerned that this may limit the generalisability of SPRINT to the eligible UK population. The company

advised that on assessing the baseline characteristics, people included in SPRINT are broadly representative of the eligible UK population. The clinical experts advised that the population in SPRINT is broadly aligned with those who would have treatment with selumetinib in the UK. The committee concluded that SPRINT is generalisable to the UK population.

The company's economic model

The company's model structure was not suitable for decision making

3.11 The company developed an area under the curve model structure, also known as a partitioned survival model, to assess the cost effectiveness of selumetinib in NF1 PN. The model consists of 3 health states; stable/non-progressive disease; progressive disease; or death. The model assumes that everyone enters in a progressive disease health state. Those in the selumetinib arm experience disease stabilisation within the first year of treatment and stay in the progression-free state until disease progression. Disease progression can happen up to the age of 18, after which treatment is stopped and no progression is assumed to happen. Those in the best supportive care arm stay in the progressed health state for the duration of the model. At clarification, the ERG had concerns about the type of model used. It recognised the heterogeneity of PN associated with NF1 and outlined that the current model structure does not capture disease heterogeneity, progression in the best supportive care arm or the effect of various treatment effect modifiers such as age, PN size and location and number of PN. It suggested that a patient-level model may be more useful for decision making. In response, the company stated that a patient-level model was not feasible because of insufficient data. During original model scoping, the company considered a regression-based patient-level model, with the intention to include PN location, baseline PN volume, PN growth rate and age as potential covariates. However, the data was limited to 50 patients from SPRINT Phase 2 Stratum 1 therefore there was an insufficient number of patients to power any meaningful

subgrouping analysis. The company explained a patient-level model would need a substantial number of assumptions with a high degree of uncertainty and therefore preferred a more pragmatic approach that focused on a limited number of broad assumptions. The committee recognised the challenges in modelling NF1 PN and understood the complexities associated with a patient-level model. It appreciated that a patient-level model may be more difficult and have high levels of uncertainty, but it preferred a model structure that represents the disease and includes outcomes that clinical and patient experts advised were important (see sections 3.3 and 3.4). An assumption in the company's model related to everyone in the best supportive care arm staying in the progressive health state. In its submission, the company presented the probability of progression-free survival from SPRINT and the Natural History Study. At clarification, the ERG highlighted that in the Natural History Study age-matched cohort, 15% of people had progression-free survival at 3 years. It felt this supports the assumption that progression-free survival should also be included in the best supportive care arm of the model. In response, the company outlined that most people in the Natural History Study had some degree of PN growth and the 15% reported to be progression free at 3 years meant that they had not experienced a PN volume increase of at least 20%. The committee agreed with the ERG and requested a progression-free health state for the best supportive care arm. The committee concluded that the company model is not suitable for decision making and it would prefer to see a patient-level model that included outcomes that may have a direct effect on the quality of life of people with PN and their carers and includes the possibility for transition from the initial progressed disease state to progression free in best supportive care arm, which would better reflect the natural history of the disease.

Modelling of progression and selumetinib treatment should continue beyond the age of 18

3.12 The company's model assumes that once people reach the age of 18, PN size stabilises and therefore no progression events happen after this age. The ERG had concerns about this, based on data from the Natural History Study which suggested some progression events would happen after the age of 18. The ERG felt that if some progression events would happen after the age of 18 in clinical practice, the assumption of no progression in the model beyond this point would favour selumetinib. The clinical and patient experts advised that there may still be progression events that happen after the age of 18. The committee noted that progression may happen after the age of 18 and this is not included in the company model. The company's model also assumes that the maximum duration of treatment was until children reach the age of 18 years. The clinical expert advised that the duration of treatment is uncertain and that when progression is determined by volumetric imaging, it can be subjective. Therefore, treatment decisions would be made by the MDT and based on important clinical outcomes. The clinical expert envisaged that if there was an ongoing perceived clinical benefit and selumetinib was well tolerated, then treatment may continue beyond the age of 18 years. The committee concluded it would prefer to see the inclusion of progression beyond the age of 18 in the modelling and that selumetinib treatment may continue beyond the age of 18 and this should also be included in the modelling

All resource use costs for selumetinib and best supportive care should be included

3.13 The company's model only includes costs for selumetinib, adverse event costs, pain medication costs and MRI costs. It assumes all other costs in relation to disease management and monitoring would be the same in both arms. It felt excluding costs for management of PN associated morbidities is conservative, because it is anticipated a reduction in PN volume may lead to reduced PN associated morbidity costs in the

selumetinib arm. The ERG highlighted that the limited costs included in the model does not provide a representative overview of all relevant costs for the selumetinib and best supportive care arms. The clinical experts advised that people eligible for treatment with selumetinib would need additional investigations before starting and during treatment. The investigations needed would vary depending on the location of the PN but the clinical experts advised these investigations would be more frequent than those needed with best supportive care. The committee agreed that all relevant costs should be included in the analysis and that the current costs included were insufficient. The committee concluded it would prefer to see analyses with full resource use included for both best supportive care and selumetinib arms, as this would allow a comparison of all the costs associated with selumetinib treatment compared with best supportive care.

People having selumetinib would have 2 additional MRIs per year

3.14 In its base case, the company assume that selumetinib treatment would be associated with an additional 2 MRI scans per year compared with best supportive care. The ERG preferred to include 4 additional MRI scans. The clinical expert advised that people on best supportive care normally have 1 MRI scan per year and further MRI scans may be done during any acute changes. People having MEKi as part of a clinical trial currently have 4 MRI scans per year, however because of the need for general anaesthetic, the clinical expert envisaged in NHS clinical practice, 2 additional MRI scans per year would be the most needed by people having selumetinib unless any acute changes happened. Therefore, the committee concluded that the company assumption of 2 additional MRI scans per year was reasonable.

Utility values

The time trade off utility estimates are not appropriate for decision making

3.15 In its base case, the company used time trade off interviews with 100 members of the general public, using different health state vignettes, to estimate health state utility values for on and off selumetinib treatment (the actual utility values are academic in confidence and cannot be reported here). The ERG had concerns about the time trade off vignette study because it fails to meet the NICE reference case that health-related quality of life must be measured or reported directly. The committee was concerned that the time trade off study was not based on the experience of people with PN and the vignettes did not reflect what is important to people with PN and their carers. The committee noted the vignettes for stable disease included a definition that the PN was reducing in size and for progressed disease the PN was increasing in size, yet the derived utilities were applied throughout the model even at ages when for most people disease will have stabilised. However, feedback from the clinical expert and trial data suggested that there is no correlation between PN volume and clinical outcomes. The committee also noted that the vignettes did not account for the heterogeneity of the disease based on PN location and the effect on the clinical outcomes important to people with PN and their carers. The committee concluded it would have preferred to see direct utility data from the trial included in the analysis.

Direct utility data from SPRINT Phase 2 Stratum 1 is preferred

3.16 The company provided Paediatric Quality of Life Inventory (PedsQL) data, that was collected in the SPRINT trial. They chose not to map PedsQL to EQ-5D because it felt the mapping function from Khan et.al (2014), was inappropriate. It concluded that Khan et.al, was not applicable to younger children recruited in SPRINT and the sample from Khan et.al, were not recruited based on having health conditions. In its clarification response, the company provided utility values from NICE's highly specialised

technology appraisal on burosumab for treating X-linked hypophosphataemia in children and young people, stating the values were relatively similar to the utility results from their time trade off vignette study. The ERG noted that the company provided direct PedsQL data from the trial, however the ERG explained that it is not possible to determine the appropriateness of the size of the difference in utilities from the vignette study using the PedsQL data presented. It explained that PedsQL is a widely used measure of youth health-related quality of life for which a value set is available to estimate utilities. Therefore, the ERG would have preferred to see PedsQL data mapped to EQ-5D or PedsQL data from the trial used to validate the time trade off vignette utilities. The committee understood that PedsQL is a specific paediatric measure of quality of life and was disappointed that direct utility values from the trial were not used in the modelling or to validate the utility values derived from the time trade off study. It recognised that when mapping utility values, it is difficult to extrapolate from healthy individuals in the mapping study to people with PN but acknowledged there are other mapping algorithms available; the company could have mapped the PedsQL onto the Child Health Utility 9D to get utility values. The committee concluded it would have preferred to see an attempt at mapping and use of direct utility data from the trial included in the analysis or at the very least use the mapped values to validate the time trade off values.

The company's preferred carer disutility value is too high

3.17 The clinical and patient experts advised that PN associated with NF1 has a substantial effect on the quality of life of parents and carers. This may be because of emotional distress, social isolation, the mental burden of providing a range of support and disrupted social activities or time off work. The company did not identify utility data specific to parents and carers and therefore in its base case, assumed the same relative utility decrement for carers as people with the condition and applied this to the best supportive care arm only (the exact utility decrement is academic in

confidence and cannot be reported here). The ERG considered the utility decrement applied to parents and carers in the company base case was unjustifiable and higher than values reported in the literature and previous NICE appraisals. The ERG preferred to use a utility decrement for parents and carers of 0.07, which is based on carers of children with activity limitations in NICE's highly specialised technology appraisal guidance on burosumab for treating X-linked hypophosphataemia in children and young people and NICE's technology appraisal guidance on abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis. The patient experts explained that it is common for parents to also have NF1, and therefore the company carer disutility value was appropriate. The committee recognised that there would be a disutility associated with caring for people with PN, however, because the care needs vary based on PN location (see section 3.4) the committee would have preferred to see disutility values dependent on PN location and the associated morbidity. The committee also noted that selumetinib may relieve pain and increase the utility of individuals with PN, therefore increasing the carers utility. However, the other comorbidities associated with NF1, especially those not responsive to selumetinib, means it cannot be assumed there would be no carer disutility in the selumetinib arm. The committee concluded the company carer disutility value is unjustifiably high, a carer disutility should be applied to the selumetinib arm as well as the best support care arm and it would prefer to see carer disutility values dependent on PN location and morbidity experienced.

The number of carers the disutility should apply to is 1

3.18 The company assumes that the carer utility decrement would apply to 1.4 carers. This was based on the average UK household size of 2.4 and the assumption that everyone in the household is a carer. The ERG considered that an assumption of 1 carer is more appropriate and that not everyone in the household would be a carer, for example, other children. The committee concluded there was not enough evidence to assume

everyone in the household is a carer, and therefore preferred the ERG assumption of 1 carer.

Utility waning over 1 year after progression is appropriate

3.19 In the company's model, the utility for people in the selumetinib arm is assumed to improve from baseline up to the treatment specific utility value within 1 year of starting treatment. For people whose disease maintains a partial response or stays stable while on selumetinib treatment, the utility value remains constant. If people in the selumetinib arm experience disease progression, the model assumes the utility value declines back to baseline over a period of 5 years. The company assume a linear waning of utility over a 5-year period. The ERG considers that there is no supporting evidence to assume a waning period of 5 years and that this represents a substantial period of benefit relative to the treatment period. The ERG preferred a linear decline in utility over 1-year post-progression as this equals the period assumed to obtain full on-treatment utility after treatment initiation. The clinical experts felt it was difficult to comment on the waning of utility after stopping treatment because of the limited experience of using selumetinib, however they assumed there would be no ongoing treatment benefit when selumetinib is stopped. The company highlighted that 5-year follow-up data suggests not all people who stopped treatment experienced disease progression. The committee recognised that it may be reasonable to assume some period of progression-free survival after stopping treatment, however the clinical experts advised that decisions on stopping treatment would be based on clinical outcomes rather than radiological volume increases. Therefore, the committee recognised selumetinib treatment is likely to be stopped because of worsening symptoms and therefore preferred a more rapid decline in utility. It concluded that the ERG assumption of waning of utility 1 year after progression was reasonable.

Applying quality-adjusted life year (QALY) weighing

3.20 The interim process and methods of the highly specialised technologies programme specifies that a most plausible incremental cost-effectiveness ratio (ICER) of below £100,000 per QALY gained for a highly specialised technology is normally considered an effective use of NHS resources. For a most plausible ICER above £100,000 per QALY gained, judgements about the acceptability of the highly specialised technology as an effective use of NHS resources must take account of the size of the incremental therapeutic improvement. This is revealed through the number of additional unadjusted QALYs gained and by applying a 'QALY weight'. It understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 unadjusted QALYs. Because no robust comparison of selumetinib with best supportive care was provided, the committee was unable to conclude if it was appropriate to apply a QALY weight for that comparison.

Cost-effectiveness results

3.21 Because the committee did not accept the company's model for decision making, it concluded that it could not establish if selumetinib could be considered an effective use of NHS resources without further information.

Other factors

Innovation

3.22 The company highlighted that selumetinib is the first licensed disease-modifying treatment for NF1 PN. However the committee noted that the clinical experts advised there is currently 1 other MEKi, which is licensed for some cancers but unlicensed for this condition, being used to treat some people with NF1 PN.

Equalities

3.23 Patient and professional groups noted that not all people with NF1 PN have access to the specialist services in London and Manchester. The

committee recognised the difficulty in ensuring equal provision of services to everyone, however, it noted this is not an equalities issue with relation to the protected characteristics outlined in the Equality Act.

Conclusion

3.24 The committee recognised that PNs associated with NF1 are rare and can substantially affect the lives of people with the condition, their families and carers. It understood that the only alternative to selumetinib is standard care which provides limited symptom relief, while most PNs continue to progress with standard care. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that selumetinib could be a promising technology for certain people and is likely to be associated with long-term benefits. However, it was not presented with an appropriate economic model to allow a valuation of the costs and benefits for evaluation. Further information is needed before a recommendation can be made.

Recommendation

3.25 The committee considered the clinical evidence and recognised that selumetinib may be a promising treatment option for those who would be eligible for it. However, the committee was not provided with an economic model that allows it to determine the benefit and costs of selumetinib treatment compared to best supportive care. Therefore, the committee was minded not to recommend selumetinib as an option for treating symptomatic and inoperable PN associated with type 1 neurofibromatosis in children aged 3 and over. The committee recommends that NICE requests further clarification and analyses from the company, which should be made available for the second evaluation committee meeting, and should include:

- a patient-level model, including:
  - a progression-free state for the best supportive care arm

  - allows progression to happen after the age of 18
  - accounts for the progressive nature of the condition, age and location of PN
  - clinical outcomes that are important to people with PN, carers and clinicians
- the possibility for selumetinib treatment to continue beyond the age of 18
- utility values obtained from patients in the trial in the analysis by using a mapping algorithm or validation of the time trade off utilities by the mapped utilities
- carer disutility values that are:
  - dependent on PN location and morbidity experienced
  - applied to 1 carer
  - in both selumetinib and best support care arms
- the length of utility benefit waning after stopping treatment to be 1 year
- a breakdown of full resource use costs for selumetinib and best supportive care arms, with comparison between the 2 arms
- inclusion of 2 additional MRIs in the selumetinib arm

Peter Jackson
Chair, highly specialised technologies evaluation committee
November 2021

4 Evaluation committee members and NICE project team

Evaluation committee members

The highly specialised technologies evaluation committee is a standing advisory committee of NICE.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each highly specialised technology evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

Nigel Gumbleton
Technical lead

Joanna Richardson
Technical adviser

Daniel Davies
Project manager

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