NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final evaluation document

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

1 Recommendations

1.1 Selumetinib is recommended, within its marketing authorisation, for treating symptomatic and inoperable plexiform neurofibromas (PN) associated with type 1 neurofibromatosis (NF1) in children aged 3 and over, only if the company provides selumetinib according to the commercial arrangement (see section 3).

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.

Issue date: March 2022

Because of limited available evidence, 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. But, the committee acknowledged that selumetinib may be an effective treatment option for people with inoperable PN, even when considering the uncertainty in the economic modelling and the benefits not captured by the model. Based on the same considerations, it also provides value for money within the context of a highly specialised service. Selumetinib is therefore recommended for use in the NHS.

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 for selumetinib.

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 (simple discount patient access scheme). This makes selumetinib available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

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 people with NF1, the clinical course of the disease is uncertain. This can be a source of anxiety for people with NF1 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 PN

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 NF1, such as attention deficit hyperactivity disorder, autism and anxiety and depression, as well as the clinical manifestations associated with their PN. 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 negatively affect a person's 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 heterogeneous 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 approximately half of families with a child with NF1 will have a parent with the condition also, and sometimes families have more than 1 child with the condition. 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 have felt unsupported by the NHS, schools, and other services because of difficulties in getting a diagnosis and limited 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 considerably affect physical function, such as PNs around the spinal cord, bladder or bowel, may have a considerable additional physical burden for carers compared with other locations. However, the emotional burden on carers exists for all affected by 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 have their condition managed within 2 nationally commissioned services in Manchester and London. Currently, surgery is the only available treatment within routine care to reduce or remove PN tumours. The clinical experts explained that many children benefit from staged surgery and 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 either not known to or are not attending one of the specialist centres and therefore are not having the optimal support and care including access to therapies as part of clinical trials or for compassionate use.

Treatments are needed for inoperable PN

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 or 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 only available in capsule form. As younger children, and those with learning difficulties and sensory issues may be unable to swallow capsules, selumetinib is being used mainly in children aged between 8 and 17 years. The clinical 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 MEKi, 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 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 growth by 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. In response to consultation, the company explored including clinical outcomes in the model but considered it is not feasible to correlate changes in quality of life with specific morbidities. This is because very few people in SPRINT had each type of morbidity and because of the heterogeneity in size and location of PN and the associated morbidities (see section 3.1 and section 3.2). The ERG commented that it would prefer clinical outcomes included in the model but acknowledged the limitations of the data. The committee recognised the difficulty of including clinical outcomes in the model because of the heterogeneity of NF1 PN and this would need many assumptions. A clinical expert also explained that 20% of people with PN have PN growth that is potentially life-threatening. It therefore also would have liked to have seen sub-group analysis for these people, because this may be where selumetinib offers the greatest benefit. It concluded that 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 is suitable for decision making

3.11 The company originally 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. The committee had concerns about the type of model used. They recognised the heterogeneity of PN associated with NF1 and outlined that the model structure does not capture this heterogeneity, or the effect of various treatment effect modifiers such as age, PN size and location and number of PN. They suggested that a patient-level model may be more useful for decision making. In response to consultation, 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 were too few patients to allow a

meaningful subgrouping analysis with sufficient statistical power. The company explained a patient-level model would need a substantial number of assumptions,adding further to the 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. Although it would have preferred a model structure that represents the disease and includes outcomes that clinical and patient experts advised were important (see section 3.3 and section 3.4), the committee appreciated that a patient-level model presents difficulties and may have high levels of uncertainty. The committee noted that the company had revised its model to include the possibility for disease progression to happen up to the age of 24 (see section 3.13), treatment to continue after the age of 18 (see section 3.14) and the inclusion of a progression-free health state in the best supportive care arm (see section 3.12) as per the committee's preferences at the first committee meeting. On balance it decided the revised area under the curve model structure submitted by the company in response to consultation was suitable for decision making.

Utility values for health states defined by the presence or absence of disease progression, should be consistent between the selumetinib and best supportive care arms

3.12 An assumption in the company's original 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. The committee therefore requested that progression-free survival should also be included in the best supportive care arm of the model. In response to consultation, the company revised its model to include a progression-free state in the

best supportive care arm. It noted that people in the best supportive care arm do not experience the symptom improvement seen in the selumetinib arm and should not have an equivalent utility. In its revised base case, it therefore applied a different utility score for the progression-free state in the best supportive care arm based on the midpoint between the baseline utility and the utility for progression-free state in selumetinib arm. The ERG commented that when health states are defined in terms of progression, it is inappropriate to assume different utilities for the same progression-free state in different treatments arms. It also noted in the company model, people in the selumetinib arm stay progression-free longer than the best supportive care arm. The committee welcomed the addition of a progression-free state in the best supportive care arm. The committee noted however, that the time trade off vignettes provided by the company did not include utility values for people progression-free off treatment, that is, the progression-free state in the best supportive care arm. Therefore, in the absence of specific utilities, it concluded the ERG's approach in which utility values for health states defined by the presence or absence of disease progression, are consistent between the selumetinib and best supportive care arms.

Modelling of progression should continue beyond the age of 18

3.13 The company's original model assumed 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 requested the model be revised to allow for this possibility. In response to consultation, the

company revised its model to include the possibility of progression after the age of 18. It applied an annual progression rate for both arms after the age of 18 up to a maximum of 24. After the age of 24, it assumed any further PN progression would stop. The annual progression rate was derived from the ratio of tumour growth rate in children and adults (the exact annual progression rate is commercial in confidence and cannot be reported here). The committee recognised that there would be progression after the age of 18 but were uncertain about what percentage of people would progress after the age of 18. Based on clinical expert testimony that the rate of PN growth slows as people reach adolescence (see section 3.2), the committee concluded that PN progression up to the age of 24 was reasonable although noted some uncertainty in the assumption of stopping at exactly at the age of 24.

Selumetinib treatment could continue beyond the age of 18 for some patients

3.14 The company's original model assumed that the maximum duration of treatment was until children reach the age of 18. The clinical expert advised that the duration of treatment is uncertain and that when progression is determined by volumetric imaging, decisions on whether to continue treatment or not 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. In response to consultation, the company revised its model to include the possibility of treatment continuing beyond the age of 18. The company reiterated that it would expect most people, if not all, to stop treatment once they reach 18. In its revised model, the company estimated the percentage of people who would continue treatment into adulthood and included this in its revised base case (the exact percentage is commercial in confidence and cannot be reported here). The clinical expert advised that people continuing treatment beyond the age of 18 would usually be those with PN

growth that is potentially life-threatening and estimated that this would be around 20% of the eligible population. The committee noted the clinical expert's estimate and concluded that the percentage of people continuing selumetinib treatment beyond the age of 18 provided by the company was reasonable.

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

3.15 The company's original model only included costs for selumetinib, adverse event costs, pain medication costs and MRI costs. The committee agreed that the costs included in the original model were insufficient and that 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. In response to consultation, the company provided resource use costs for both arms. The types and frequency of monitoring were collected from a clinical expert and the company calculated the corresponding costs and included these in its revised base case. The company did not assume a potential cost saving from symptom improvement because of treatment with selumetinib, which it suggested was a conservative approach. The ERG noted that the details of the communication between the expert and the company were not provided, and neither were sources for the unit costs. The committee heard from the clinical expert that most monitoring costs would be associated with selumetinib treatment and there may be some monitoring costs that would be done by individual specialties depending on the location of the PN, for example respiratory teams, which are not included. The committee welcomed the additional resource use costs provided by the company although recognised the uncertainty in the estimates. However, it concluded the resource use costs associated with selumetinib treatment compared with best supportive care provided in the company revised model were suitable for decision making.

People having selumetinib would have 2 additional MRIs per year

3.16 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 a 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

In the absence of plausible mapped utilities, the time trade off utility estimates are used in decision making

3.17 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 (see section 3.1 and section 3.2). The company also 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. 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 NF1 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. In response to consultation, the company mapped the PedsQL onto the Child Health Utility 9D using 3 validated mapping algorithms; Lambe et al (2018)., Mpundu-Kaambwa et al (2017)., and Sweeney et al (2020). When the algorithms were applied to baseline

PedsQL data from SPRINT, they believed the resulting utility values to be unrealistically high. The company explained that all 3 mapping algorithms were not suitable for people with severe conditions because they overestimate utility scores, therefore it maintained the use of time trade off interviews to estimate health state utility values for on treatment, progression-free and off treatment, progressed disease. It explained the vignettes incorporated various aspects important to patients and their carers including physical, social and emotional parameters. The committee reiterated that it would have preferred to see direct utility data from the trial included in the analysis, however it acknowledged the issues with the mapping algorithms. It recognised that there remains considerable uncertainty relating to the utility values estimated from the time trade off interviews but concluded in the absence of any plausible mapped utilities they would have to use them for decision making.

The company's preferred carer disutility value is too high

3.18 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 original 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 committee 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 committee preferred the ERG's suggested value, 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's carer disutility value was appropriate. The committee recognised that there would be a disutility associated with caring for people with NF1 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. In response to consultation, the company could not derive the specific impact of single locations and morbidities and account for likely interplay of different combinations of morbidities when estimating carer disutility. It maintained that a utility decrement of 0.07 does not reflect the significant negative impact of NF1 PN on carers and it did not change its original carer disutility for the best supportive care arm. It acknowledged the committee preference to include carer disutility in the selumetinib arm but explained this should reflect the impact of effective disease control with selumetinib compared with best supportive care. Therefore, the company revised its assumption to include a carer disutility in the selumetinib arm, however the disutility value used, according to the company, represents a reasonable point between the disutility applied in the best supportive care arm and the ERG preferred disutility. The ERG considered there is no supporting evidence for using the company's original carer disutility value in the best supportive care arm and still preferred the disutility value of 0.07. The ERG acknowledged that improvement in disease control with selumetinib compared with best supportive care should be considered in the model and agreed applying a lower carer disutility value in the selumetinib arm is reasonable. It therefore applied a carer disutility value of 0.035, half the best supportive

care carer disutility value, to the selumetinib arm. The committee noted it had not been presented with supportive evidence for the company's carer disutility value. It also recalled that this value is unjustifiably higher than carer disutility values used in previous NICE appraisals. It concluded a carer disutility value of 0.07 applied to the best supportive care arm and a carer disutility value of 0.035 applied to the selumetinib arm is preferred.

The number of carers the disutility should apply to is 1

3.19 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 not everyone in the household would be a carer, for example, other children. In response to consultation, the company maintained that the utility decrement should apply to 1.4 carers. The committee recalled that care needs vary based on PN location (see section 3.4 and section 3.18). It accepted that some people with serious morbidity caused by NF1 PN may need more than 1 carer, however, some people with less serious morbidity may need less than 1 carer. Therefore, on average, applying the utility decrement to 1 carer is reasonable. It concluded there was not enough evidence to assume everyone in the household is a carer and the heterogeneity of the condition means some people with NF1 PN will have higher care needs while others will have lower care needs. It therefore preferred the ERG assumption of 1 carer.

Utility waning over 1 year after progression is appropriate

3.20 In the company's original 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 assumed the utility value

declines back to baseline over a period of 5 years. The company assumed a linear waning of utility over a 5-year 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, but they assumed there would be no ongoing treatment benefit when selumetinib is stopped. 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 and therefore the committee were persuaded to prefer the ERG's assumption of a linear decline in utility over 1-year post-progression. In response to consultation, the company updated its model to assume a linear waning of utility over a 3-year period after progression. The company considered it is important to account for the preventative nature of treatment with selumetinib when considering decline in utility after stopping. Meaning, in people having selumetinib who experience PN growth after stopping, PN would be smaller and less of a burden and this residual benefit would continue long term. The committee noted there were only 2 time trade off vignettes; people having treatment whose disease was not progressing, and people not having treatment with progressed disease. Therefore, when people stop selumetinib they are assumed to have their disease progressing and the utility experienced should match the utility from the off treatment, progressed disease vignette. The committee recognised that selumetinib treatment is likely to be stopped because of worsening symptoms and preferred a more rapid decline in utility that matches the time to obtain on-treatment utility after starting selumetinib and concluded that the ERG assumption of waning of utility 1 year after progression was preferred.

Cost-effectiveness results

3.21 The company and NHS England have agreed a confidential commercial discount for selumetinib. All cost-effectiveness results of the economic analysis incorporate this discount.

3.22 The company's revised base-case analysis included the following assumptions:

- inclusion of a progression-free state in the best supportive care arm, with a utility which is a midpoint between the baseline utility and the utility for people treated with selumetinib in the progression-free state
- the possibility for PN progression to happen after the age of 18 up to a maximum age of 24 when PN progression is assumed to stop
- the possibility for some people to continue treatment beyond the age of 18
- full resource use costs provided by the company included in both the best supportive care arm and selumetinib arm
- costs associated with 2 additional MRI scans per year included in the selumetinib arm
- utility values from the time trade off vignette study
- carer utility decrement in the best supportive care arm that is the same utility decrement as people with the condition and a carer utility decrement in the selumetinib arm that the company considered to be a reasonable point between the disutility applied in the best supportive care arm and the ERG preferred disutility
- carer disutility applied to 1.4 carers
- linear decline in utility over 3 years after progression in the selumetinib arm

These assumptions resulted in an incremental cost-effectiveness ratio (ICER) of £78,696 per quality-adjusted life year (QALY) gained.

The committee preferred the assumptions used by the ERG in their revised base case. Some of these assumptions were the same as the company's: the possibility for PN progression to occur after the age of 18 up to a maximum age of 24 when PN progression is assumed to stop; the possibility for some people to continue treatment beyond the age of 18; full resource use costs provided by the company included in both the best supportive care arm and selumetinib arm; costs associated with 2 additional MRI scans per year included in the selumetinib arm; and the use of the utility values from the time trade off vignette study. However, some of the assumptions in the ERG's revised base case differed from the company's in relation to:

- inclusion of a progression-free state in the best supportive care arm, with the same utility as those applied to the progression-free state in the selumetinib arm (see section 3.12)
- a carer disutility value of 0.07 applied to carers of people in the best supportive care arm and a carer disutility value of 0.035 applied to carers of people in the selumetinib arm (see section 3.18)
- carer disutility values applied to 1 carer (see section 3.19)
- linear decline in utility over 1 year after progression in the selumetinib arm (see section 3.20).

The committee noted that applying all their preferred assumptions resulted in an ICER of £99,770 per QALY gained.

Applying QALY weighing

3.23 The interim process and methods of the highly specialised technologies programme specifies that a most plausible 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'. The committee understood that a weight between 1 and 3 can be applied when the QALY gain is between 10 and 30 unadjusted QALYs. The committee discussed the undiscounted QALY gains associated with selumetinib and highlighted that these were below 10 in the scenario that was considered most plausible by committee (the exact QALY gains are commercial in confidence so cannot be reported here). The committee concluded that the undiscounted QALY gains for the scenario incorporating its preferred assumptions did not meet the criteria for applying a QALY weight.

Impact of the technology beyond direct health benefits and on the delivery of the specialised service

3.24 The committee discussed the effects of selumetinib beyond its direct health benefits and the evidence of the patient experts. It was aware NF1 PN is a highly heterogeneous condition that has a very large effect on people with NF1 PN and their families, including the emotional effect on carers, family relationships and siblings with the disease (see sections 3.1, 3.2, 3.3 and 3.4). NF1 PN affects everyone differently and can be unpredictable, meaning the future health of an individual with NF1 PN can be uncertain and may be highly distressing for people with NF1 PN and their carers. The patient experts emphasised that NF1 PN can affect every aspect of an individual's life including their education, employment, and physical and mental health (see section 3.3). The patient experts considered the mental health impact on people with NF1 PN and their carers, sometimes resulting in anxiety and depression, may not be fully captured. The clinical expert explained there is a high unmet need within NF1 PN and emphasised the benefit of selumetinib being an oral treatment and therefore some people may avoid the negative impacts of surgery. Overall, the committee concluded that selumetinib may affect people beyond its direct health benefits, but it noted that the full effect of

these benefits had not been fully quantified. The committee considered these benefits in its decision making however any net benefits were offset by the uncertainties associated with the model structure and some of the assumptions in the committee's preferred base case.

Delivery of specialist services

3.25 The company and clinical experts confirmed that treatment with selumetinib would be started and supervised by clinicians experienced in managing NF1 PN. The committee noted that NF1 PN is currently managed in 2 specialist centres in England. Selumetinib would be started at the specialist centres, with the potential for treatment to continue with local healthcare providers if this is safe and useful. The committee concluded that selumetinib would be administered at specialist centres under the existing arrangements for people with NF1 PN.

Other factors

Innovation

3.26 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, trametinib, which is licensed for some cancers but unlicensed for this condition, being used to treat some people with NF1 PN.

Equalities

3.27 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

3.28 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. The committee considered that selumetinib is a high-cost technology and uncertainties remained with parameters used in the model, such as the effect of selumetinib on outcomes important to people with NF1 PN and their carers, utility values, what age PN progression stops, when treatment with selumetinib would stop and the model structure. However, it concluded that using its preferred assumptions, the most plausible ICER was likely to be below the threshold considered to provide value for money in the context of a highly specialised service when the company's confidential discount was applied. So, selumetinib is recommended for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over.

4 Implementation

4.1 Section 8(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE highly specialised technologies guidance. When a NICE highly specialised technologies guidance recommends the use of a

drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final evaluation document.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraph above. This means that, if a patient has NF1 PN and the doctor responsible for their care thinks that selumetinib is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Review of guidance

5.1 The guidance on this technology will be considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Peter Jackson,
Chair, highly specialist technology evaluation committee
March 2022

6 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

ISBN: [to be added at publication]