NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Health Technology Appraisal

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

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of selumetinib within its marketing authorisation for treating inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 years and over.

Background

Neurofibromatosis (NF) refers to a group of genetic disorders that primarily affect the cell growth of neural tissues. There are two forms of NF: type 1 (NF1) and type 2 (NF2). NF1 is the more common form and caused by a defect in the gene, NF1, situated at chromosome 17q11.2[1].

NF1 is an incurable condition with highly-variable symptoms, including cutaneous (skin), neurological (nervous system) and orthopaedic (skeletal) manifestations. While most children with NF1 only experience mild symptoms, it can cause secondary complications including learning difficulties, visual impairment, pain, disfigurement, twisting and curvature of the spine, high blood pressure and epilepsy[2,3]. Although the morbidity and the mortality caused by NF1 are dictated by the occurrence of these complications, which may involve any of the body systems, patients were found to perceive cosmetic disfigurement as the major clinical problem[4].

Plexiform neurofibromas (PNs) are a neurological manifestation of NF1 and arise from nerve fascicles that tend to grow along the length of the nerve. PNs occur in approximately 20-50% of NF1 patients causing pain, motor dysfunction and disfigurement[5]. PNs can also develop into malignant peripheral nerve sheath tumours (MPNST), which are associated with poor survival[1]. Most PNs are diagnosed in early childhood and grow most rapidly during this period. Complete surgical resection of these tumours is often not feasible, and regrowth of the tumour after incomplete surgical resection has been observed. Surgery is often complicated as tumours can be intertwined with healthy tissue.

Treatment for NF1 may include physiotherapy, psychological support and pain management[5]. Effective medical therapies are lacking for the treatment of NF1 related PNs and there are currently no treatments with a marketing authorisation for this group.

The technology

Selumetinib (AZD6244) is an orally active, adenosine triphosphate (ATP) independent inhibitor of the mitogen-activated kinase (MEK). The NF1 gene provides instructions for making a protein called neurofibromin, which negatively regulates the RAS/MAPK pathway, helping to control cell growth, differentiation, and survival. Mutations in the NF1 gene may result in dysregulations in RAS/RAF/MEK/ERK signalling, which can cause cells to grow, divide and copy themselves in an uncontrolled manner and may result in tumour growth. Selumetinib inhibits the MEK enzyme in this pathway, potentially leading to inhibition of tumour growth.

Selumetinib currently does not have a marketing authorisation for inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over. It has been studied in clinical trials in children who were between 2-18 years old with NF1 and had inoperable PN.

Intervention(s)	Selumetinib
Population(s)	Children aged 3 and over with inoperable plexiform neurofibromas associated with type 1 neurofibromatosis.
Comparators	Established clinical management without selumetinib
Outcomes	The outcome measures to be considered include: • complete and partial response rate • growth rate of PN • bone mineral density • physical functioning • pain • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Appraisals in development (including suspended appraisals): Selumetinib for treating differentiated thyroid cancer NICE technology appraisal guidance [GID-TA10207]. Publication date to be confirmed.
Related National Policy	NHS England (2018) Highly specialised services 2017 NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' NHS England (2018) Manual for prescribed specialised services 2018/19 chapter 39 NHS England (2017) Next steps on the five year forward view NHS England (2019) NHS Long Term Plan NHS England. 2013/14 NHS Standard Contract For Complex Neurofibromatosis Type 1 Service (All Ages – B13/S(HSS)/a). Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domain 2.

Questions for consultation

Can you provide an estimate of how many children with inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in England do you expect to be treated with selumetinib per year if this treatment was approved?

How is it confirmed that plexiform neurofibromas associated with type 1 neurofibromatosis are inoperable in clinical practice?

Which treatments are considered to be established clinical practice in the NHS for inoperable plexiform neurofibromas?

How common are malignant peripheral nerve sheath tumours (MPNST) in Children aged 3 and over with inoperable plexiform neurofibromas associated with type 1 neurofibromatosis?

Please describe the current clinical pathway for children with inoperable plexiform neurofibromas associated with type 1 neurofibromatosis.

How would selumetinib fit into the clinical pathway for inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children 3 years and over?

Would selumetinib be administered exclusively within specialised centres?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom selumetinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which selumetinib will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.

Do you consider selumetinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a ‘step-change’ in the management of the condition)?

Do you consider that the use of selumetinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the appraisal committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

References

1. Patient: Neurofibromatosis. Available from https://patient.info/doctor/neurofibromatosis-pro

2. NHS. Symptoms: Neurofibromatosis type 1 https://www.nhs.uk/conditions/neurofibromatosis-type-1/symptoms/

3. Varni JW, Nutakki K, Swigonski NL. Speech difficulties and patient health communication mediating effects on worry and health-related quality of life in children, adolescents, and young adults with Neurofibromatosis Type 1. Am J Med Genet A. 2019 May 13.

4. Wolkenstein P, Zeller J, Revuz J et al. Quality-of-Life Impairment in Neurofibromatosis Type 1A Cross-sectional Study of 128 Cases. *Archives of Dermatology*. 2001; 137(11): 1421-1425. Available from: http://dx.doi.org/10.1001/archderm.137.11.1421

5. Dombi E,Baldwin A, Marcus L, et al. Activity of Selumetinib in Neurofibromatosis Type 1–Related Plexiform Neurofibromas N Engl J Med 2016; 375:2550-2560

6. NHS. Treatment – Neurofibromatosis type 1. Available from: https://www.nhs.uk/conditions/neurofibromatosis-type-1/treatment/ [Accessed 2 July 2019]