NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Highly Specialised Technologies Evaluation

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

Final scope

Final remit/appraisal objective

To appraise the clinical and cost effectiveness of selumetinib within its marketing authorisation for treating symptomatic and 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, cosmetic disfigurement is perceived by many children with the condition 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]. The location of the PN on the body can impact the severity of the symptoms experienced and the complexity of the condition. 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 inoperable PNs, other treatments are aimed at reducing the symptoms. There are currently no treatments with a marketing authorisation for people who cannot have surgery.

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 aged 2-18 years old with NF1 and inoperable PN.

Intervention(s)	Selumetinib
Population(s)	Children aged 3 and over with symptomatic and 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 • disfigurement • physical functioning • visual function • airway functioning • bowel and bladder continence • pain • adverse effects of treatment • health-related quality of life (children).

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.

References

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