Appendix B

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Mirdametinib for treating symptomatic inoperable plexiform neurofibromas in people 2 years and over with neurofibromatosis type 1

Final scope

Draft remit/evaluation objective

To appraise the clinical and cost effectiveness of mirdametinib within its marketing authorisation for treating symptomatic inoperable plexiform neurofibromas in people 2 years and over with neurofibromatosis type 1.

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, also known as NF2-related Schwannomatosis). 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. There are approximately 25,000 people in the UK diagnosed with NF1[2]. While most people with NF1 may only have 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[3,4].

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 30 to 50% of people with NF1[5]. It can cause symptoms including pain, motor dysfunction and disfigurement[4]. 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. But they can continue to grow in adolescence and early adulthood[6]. Approximately 30% to 50% of all people with NF1 PN have inoperable PN[7] (that is PN which cannot be completely resected without a risk of substantial morbidity because of close proximity to vital structures, invasiveness, or high vascularity). Other estimates suggest this proportion may be lower. Surgery is often complicated as tumours can be intertwined with healthy tissue.

NICE highly specialised technology guidance 20 recommends targeted systemic therapy with a mitogen-activated protein kinase 1 and 2 (MEK1/2) inhibitor selumetinib for treating symptomatic and inoperable PN in children aged 3 years and over.

The technology

Mirdametinib (Ezmekly, SpringWorks Therapeutics) is a highly selective small-molecule inhibitor of mitogen-activated kinase (MEK1 and MEK2). It blocks MEK activity in the RAS-mitogen-activated protein kinase (RAS MAPK) signalling cascade, blocking the proliferation and survival of tumour cells.

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Mirdametinib has a marketing authorisationin the UK for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

Intervention(s)	Mirdametinib
Population(s)	People aged 2 years and over with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas
Subgroups	If the evidence allows the following subgroups will be considered: • Children and young people aged 2 to 17 years with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas • Adults aged 18 years and over with neurofibromatosis type 1 and symptomatic inoperable plexiform neurofibromas • People with neurofibromatosis type 1 according to site of symptomatic inoperable plexiform neurofibromas
Comparators	In children aged 3 years and over • Selumetinib • Established clinical management without mirdametinib In children who are 2 years old and people aged 18 years and over • Established clinical management without mirdametininib
Outcomes	• 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

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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	**Related highly specialised technology appraisals:** Selumetinib for treating symptomatic and inoperable plexiform neurofibromas associated with type 1 neurofibromatosis in children aged 3 and over (2022) NICE Highly specialised technologies guidance HST20

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