NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Diroximel fumarate for treating relapsing-remitting multiple sclerosis

Draft scope (pre-referral)

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of diroximel fumarate within its marketing authorisation for relapsing–remitting multiple sclerosis.

Background

Multiple sclerosis is a chronic neurological condition which affects the brain, optic nerves, and spinal cord. It often results in progressive neurological impairment and severe disability. Multiple sclerosis has an unpredictable course which varies in severity and rate of progression. Symptoms can include pain, disturbance to muscle tone including weakness or spasticity, chronic fatigue, unsteady gait, speech problems, incontinence, visual disturbance and cognitive impairment. Relapsing-remitting multiple sclerosis is the most common clinical form of multiple sclerosis. It is characterised by periods of remission (where people may have no symptoms, or they may be relatively stable) followed by relapses (which may or may not result in residual disability). Relapsing–remitting multiple sclerosis can progress to secondary progressive multiple sclerosis, which is characterised by more persistent or gradually increasing disability; some people with secondary progressive disease continue to have relapses.

Approximately 131,000 people in the UK have multiple sclerosis, and about 7,000 people are diagnosed each year.[1] Approximately 85% of people are diagnosed with relapsing–remitting multiple sclerosis and around 50% of those people transition to secondary progressive multiple sclerosis within 20 years of diagnosis.[2] A small number of people are diagnosed with secondary progressive multiple sclerosis without a previous diagnosis of relapsing–remitting multiple sclerosis.

Current pharmacological management of relapsing–remitting multiple sclerosis includes disease-modifying agents to reduce the frequency and severity of relapses and the rate of disease progression.

NICE recommends the following treatment options for relapsing–remitting multiple sclerosis:

- peginterferon beta-1a for relapsing–remitting multiple sclerosis (NICE TA624)
- ocrelizumab for active relapsing–remitting multiple sclerosis only if alemtuzumab is contraindicated or otherwise unsuitable (NICE TA533)
- interferon beta-1a and glatiramer acetate for relapsing–remitting multiple sclerosis and interferon beta-1b for relapsing–remitting multiple sclerosis with 2 or more relapses within the last 2 years (NICE TA527)

- teriflunomide and dimethyl fumarate for active relapsing–remitting multiple sclerosis, only if people do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis (NICE TA303 and TA320 respectively)

- alemtuzumab for active relapsing–remitting multiple sclerosis (NICE TA312). Note: this guidance will be updated to reflect the European Medicines Agency (EMA) restriction of the use of alemtuzumab to treat relapsing–remitting multiple sclerosis if the disease is highly active despite treatment with at least one disease-modifying therapy or if the disease is worsening rapidly

- fingolimod for highly active relapsing–remitting multiple sclerosis in adults who have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon (NICE TA254)

- natalizumab for rapidly-evolving severe relapsing–remitting multiple sclerosis (NICE TA127)

- cladribine tablets for treating highly active multiple sclerosis only if the person has rapidly evolving severe relapsing–remitting disease or disease that has responded inadequately to treatment with disease-modifying therapy (NICE TA616).

Treatments for relapsing–remitting multiple sclerosis are also used for people with active secondary progressive multiple sclerosis, as evidenced by relapses. NICE TA527 recommends interferon beta-1b for treating secondary progressive multiple sclerosis in people with continuing relapses.

The technology

Diroximel fumarate (ALK 8700, Biogen Idec) is a derivative of fumaric acid that helps prevent the degeneration of the myelin sheath of nerve fibers, without leading to systemic immune suppression. It is administered orally.

Diroximel fumarate does not currently have marketing authorisation in the UK for treating relapsing–remitting multiple sclerosis. It has been studied in clinical trials as a monotherapy compared to dimethyl fumarate and in a single arm study in people with relapsing–remitting multiple sclerosis.

Intervention(s)	Diroximel fumarate
Population(s)	People with relapsing–remitting multiple sclerosis

Comparators	For people with active relapsing–remitting multiple sclerosis: • beta interferon • dimethyl fumarate • glatiramer acetate • ocrelizumab • ozanimod (subject to ongoing NICE appraisal) • peginterferon beta-1a • teriflunomide. For people with highly active relapsing–remitting multiple sclerosis despite previous treatment: • alemtuzumab (subject to EMA restriction) • cladribine • fingolimod • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal). For people with rapidly-evolving severe relapsing–remitting multiple sclerosis: • alemtuzumab (subject to EMA restriction) • cladribine • natalizumab • ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • ozanimod (subject to ongoing NICE appraisal). For people with active secondary progressive multiple sclerosis (evidenced by continuing relapses): • established clinical management, including interferon beta-1b or other disease modifying therapies used outside their marketing authorisations • siponimod (subject to ongoing NICE appraisal).

Outcomes	The outcome measures to be considered include: • relapse rate • severity of relapse • disability (for example, expanded disability status scale [EDSS]) • disease progression • symptoms of multiple sclerosis (such as fatigue, cognition and visual disturbance) • freedom of disease activity • mortality • 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. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. 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. The availability of any patient access schemes for the intervention or comparator technologies should be taken into account. This includes the arrangements within the risk-sharing scheme, which was agreed for the supply of disease modifying treatments for Multiple Sclerosis in the NHS (see Health Service Circular 2002/004).

Other considerations	Guidance will only be issued in accordance with the marketing authorisation. If the evidence allows, the following subgroups of patients will be considered: • patients with relapsing–remitting multiple sclerosis whose disease has inadequately responded to treatment with disease-modifying therapy • patients with relapsing–remitting multiple sclerosis whose disease is intolerant to treatment with disease-modifying therapy • patients with highly active relapsing–remitting multiple sclerosis • patients with rapidly evolving severe relapsing–remitting multiple sclerosis • patients with active secondary progressive multiple sclerosis.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Peginterferon beta-1a for treating relapsing–remitting multiple sclerosis (2020). NICE technology appraisal guidance 624. Review date July 2023. Cladribine tablets for treating relapsing–remitting multiple sclerosis (2017). NICE technology appraisal guidance 616. Review date 2022. Ocrelizumab for treating relapsing–remitting multiple sclerosis (2018). NICE technology appraisal guidance 533. Review date July 2021. Beta interferons and glatiramer acetate for treating multiple sclerosis (2018). NICE technology appraisal guidance 527. Review date June 2021. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis (2014). NICE technology appraisal guidance 320. Review date to be confirmed. Alemtuzumab for treating relapsing–remitting multiple sclerosis (2014). NICE technology appraisal guidance 312. Review date to be confirmed. Guidance will be updated to reflect EMA license restriction. Teriflunomide for treating relapsing–remitting multiple sclerosis (2014). NICE technology appraisal guidance 303. Review date to be confirmed. Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (2012). NICE technology appraisal guidance 254. Review date to be confirmed. Natalizumab for the treatment of adults with highly active relapsing–remitting multiple sclerosis (2007). NICE

	technology appraisal guidance 127. Review date to be confirmed. **Appraisals in development (including suspended appraisals)** Autologous haematopoietic stem cell transplantation for treating multiple sclerosis. NICE technology appraisals guidance [ID1111]. (suspended) Laquinimod for treating relapsing-remitting multiple sclerosis. NICE technology appraisals guidance [ID560]. (suspended) Ozanimod for treating relapsing multiple sclerosis. NICE technology appraisals guidance [ID1294]. Expected publication date TBC. Siponimod for treating secondary progressive multiple sclerosis. NICE technology appraisals guidance [ID1304]. Expected publication date TBC. **Related Guidelines:** Multiple sclerosis in adults (2014). NICE guideline 186. Review date to be confirmed **Related Interventional Procedures:** Percutaneous venoplasty for chronic cerebrospinal venous insufficiency for multiple sclerosis (2012). NICE interventional procedure guidance 420. **Related Quality Standards:** Multiple sclerosis (2016) NICE quality standard QS108. **Related NICE Pathways:** Multiple sclerosis (2014) NICE pathway.
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2017) Manual for Prescribed Specialised Services 2017/18. Chapter 11. Adult specialist neurosciences services https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf NHS England (May 2014) Clinical commissioning policy: Disease Modifying Therapies for Patients with multiple sclerosis (MS) Department of Health and Social Care, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1-4. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

Have all relevant comparators for diroximel fumarate been included in the scope? Which treatments are considered to be established clinical practice in the NHS for relapsing–remitting multiple sclerosis?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom diroximel fumarate is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider diroximel fumarate will fit into the existing NICE pathway on Multiple sclerosis?

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 diroximel fumarate is 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 diroximel fumarate 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 diroximel fumarate 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).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1. Public Health England (2020) Multiple sclerosis: prevalence, incidence and smoking status - data briefing. Accessed July 2020.

2. Multiple Sclerosis Trust (2017) Secondary progressive multiple sclerosis. Accessed May 2020.