NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final appraisal document

Diroximel fumarate for treating relapsing-remitting multiple sclerosis

1 Recommendations

1.1 Diroximel fumarate is recommended as an option for treating active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years) in adults, only if:

- they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis and
- the company provides diroximel fumarate according to the commercial arrangement (see section 2).

1.2 If patients and their clinicians consider diroximel fumarate to be one of a range of suitable treatments (including dimethyl fumarate), choose the least expensive treatment, taking into account administration costs, dosage, price per dose and commercial arrangements.

1.3 These recommendations are not intended to affect treatment with diroximel fumarate that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

The summary of product characteristics states that diroximel fumarate is expected to be as clinically effective as dimethyl fumarate, which NICE already recommends for

Issue date: April 2022

active relapsing–remitting multiple sclerosis. Clinical trial evidence suggests that diroximel fumarate causes fewer gastrointestinal side effects than dimethyl fumarate.

Comparing the costs of diroximel fumarate and dimethyl fumarate is appropriate because the 2 treatments work in the same way and are likely be used in the same population. The total costs associated with diroximel fumarate are similar to or lower than those associated with dimethyl fumarate. So diroximel fumarate is recommended.

2 Information about diroximel fumarate

Marketing authorisation indication

2.1 Diroximel fumarate (Vumerity, Biogen) has a marketing authorisation 'for the treatment of adult patients with relapsing–remitting multiple sclerosis'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for diroximel fumarate.

Price

2.3 The list price of diroximel fumarate is £1,471.07 per pack (231 mg, 120 capsules; excluding VAT; price as quoted in company's submission).

The company has a commercial arrangement (simple discount patient access scheme). This makes diroximel fumarate 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 appraisal committee considered evidence submitted by Biogen, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

People with relapsing–remitting multiple sclerosis would welcome an additional oral treatment

3.1 Multiple sclerosis is a chronic, lifelong disease with no cure, resulting in progressive, irreversible disability. It has a wide range of distressing and debilitating symptoms including loss of balance, stiffness, spasms, speech problems, fatigue, pain, incontinence and vision problems. Most people have the relapsing–remitting form of the disease, characterised by periods of new or worsened symptoms. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Statements from patient experts highlighted that multiple sclerosis has a significant impact on all aspects of life. Current treatments are associated with side effects, and people commonly switch treatments multiple times to balance effectiveness and safety risks. Oral treatments for relapsing–remitting multiple sclerosis are limited, but people generally prefer them because they are easier to use. The committee agreed that a range of treatments provides options for different responses and personal preferences and that there was an unmet need for oral treatments with fewer side effects. It concluded that people would welcome additional oral treatment options for relapsing–remitting multiple sclerosis.

Decision problem

The company's proposed population is consistent with NICE's recommendations for active relapsing–remitting multiple sclerosis

3.2 The company proposed that diroximel fumarate should be considered as an alternative to other first-line disease-modifying treatments for active relapsing–remitting multiple sclerosis, and for the population in the NICE technology appraisal on dimethyl fumarate for treating relapsing-remitting multiple sclerosis (TA320). The committee noted that in TA320, dimethyl fumarate was not recommended for people with highly active or rapidly evolving severe multiple sclerosis because of a lack of evidence. It also

noted that active relapsing–remitting multiple sclerosis was normally defined as 2 clinically significant relapses in the previous 2 years when dimethyl fumarate was recommended in 2014. The committee was aware that in current practice clinicians sometimes offer disease-modifying treatments to people considered to have 'active' disease with a single recent relapse or the presence of radiological activity, such as new MRI lesions, without a clinical relapse, as the guidance allows for this interpretation. The committee concluded that the company's proposed population was consistent with previous NICE recommendations for active relapsing–remitting multiple sclerosis.

Dimethyl fumarate is an appropriate comparator for cost comparison

3.3 The company presented a comparison with a NICE-recommended treatment, dimethyl fumarate (TA320). The company, which is the marketing authorisation holder for both treatments, chose dimethyl fumarate as the comparator because it is one of the most widely prescribed disease-modifying treatments for active relapsing–remitting multiple sclerosis in England. The committee recalled that TA320 recommended dimethyl fumarate for active relapsing–remitting multiple sclerosis and excluded highly active or rapidly evolving severe multiple sclerosis, aligned with the relevant population for diroximel fumarate. So, if recommended, diroximel fumarate would likely be used as an alternative treatment for people who would currently have dimethyl fumarate. The committee concluded that dimethyl fumarate is a relevant comparator for diroximel fumarate and a cost comparison is appropriate.

Clinical effectiveness

Diroximel fumarate and dimethyl fumarate are expected to be equally effective

3.4 Regulatory approval for diroximel fumarate was granted because it has the same active metabolite as dimethyl fumarate and pharmacokinetic analyses have demonstrated bioequivalence. This meant that evidence on

the clinical efficacy of dimethyl fumarate was accepted by the regulators to reflect the clinical efficacy of diroximel fumarate. The ERG also considered the clinical effectiveness of diroximel fumarate and dimethyl fumarate to be similar because of the established bioequivalence. The committee concluded that diroximel fumarate and dimethyl fumarate are expected to be equally effective.

Diroximel fumarate has fewer gastrointestinal side effects and overall has a similar safety profile to dimethyl fumarate

3.5 The safety of diroximel fumarate was compared with that of dimethyl fumarate in a phase 3, randomised, double-blind trial, EVOLVE-MS-2. This trial included 504 patients with relapsing–remitting multiple sclerosis who were neurologically stable and had 5 weeks of treatment with diroximel fumarate or dimethyl fumarate. Gastrointestinal side effects were assessed using 2 patient self-reported scales developed by the company, ranging from 0 (no gastrointestinal side effects) to 10 (extreme gastrointestinal side effects). The results suggested that diroximel fumarate was associated with fewer gastrointestinal side effects than dimethyl fumarate, regardless of the severity scale threshold used to define the presence of side effects. The patient expert submissions stated that gastrointestinal side effects are less likely to interfere with regular daily activities and work productivity with diroximel fumarate than with dimethyl fumarate. The ERG also noted that other non-gastrointestinal side effects assessed in EVOLVE-MS-2 for diroximel fumarate were aligned with those of dimethyl fumarate, and overall the safety profile of diroximel fumarate was better. The committee noted that some side effects, for example flushing, which the patient experts' submission described as bothersome, continued with diroximel fumarate. However, the patient expert submissions suggested that flushing is mostly mild to moderate, reduces after the first month of treatment and is less likely to result in treatment discontinuation than gastrointestinal side effects. The committee concluded that treatment with diroximel fumarate has fewer

gastrointestinal side effects and overall may be associated with a better safety profile than dimethyl fumarate.

Cost comparison

The total costs associated with diroximel fumarate are similar to or lower than those associated with dimethyl fumarate

3.6 The company presented a cost-comparison analysis that compared the acquisition costs of diroximel fumarate and dimethyl fumarate. The company stated that, because diroximel fumarate is an oral treatment and can be self-administered at home, similar to other oral disease-modifying treatments, no changes in service provision or management will be needed. The base case assumed equal treatment effect, monitoring, safety profile and subsequent therapies for diroximel fumarate and dimethyl fumarate. The ERG considered the cost comparison appropriate. Considering the confidential patient access schemes for diroximel fumarate and dimethyl fumarate, the committee concluded that the total costs associated with diroximel fumarate were similar to or lower than those associated with dimethyl fumarate (the exact results cannot be reported here because the discounts are confidential).

Conclusion

Diroximel fumarate is recommended as an option for treating relapsing–remitting multiple sclerosis in adults

3.7 The committee concluded that the criteria for a positive cost comparison were met because:

- diroximel fumarate is expected to provide similar or greater overall health benefits compared with dimethyl fumarate
- the total costs associated with diroximel fumarate were similar to or lower than the total costs associated with dimethyl fumarate.

The committee noted that the ERG had no concerns with the company

submission. The committee therefore recommended diroximel fumarate as an option for treating relapsing–remitting multiple sclerosis in adults. It concluded that the population included in the recommendation for diroximel fumarate should be consistent with that in the company's proposal and in TA320, that is, people who:

- have active relapsing-remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years)
- do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis.

If patients and their clinicians consider diroximel fumarate to be 1 of a range of suitable treatments, including dimethyl fumarate, the least expensive should be chosen (taking into account administration costs, dosage, price per dose and commercial arrangements).

4 Implementation

4.1 Section 7 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 appraisal within 3 months of its date of publication. Because diroximel fumarate has been recommended through the fast track appraisal process, NHS England and commissioning groups have agreed to provide funding to implement this guidance 30 days after publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal 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 appraisal 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 paragraphs above. This means that, if a patient has relapsing–remitting multiple sclerosis and the doctor responsible for their care thinks that diroximel fumarate 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 3 years after publication. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Charles Crawley
Chair, appraisal committee
April 2022

6 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal 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 technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Rebecca Thomas and Emma Douch
Technical leads

Yelan Guo
Technical adviser

Daniel Davies
Project manager

ISBN: [to be added at publication]