NICE appraisal consultation document for dimethyl fumarate [ID585]

Response from the Multiple Sclerosis Trust and UK Multiple Sclerosis Specialist Nurse Association

12th March 2014

Please find below comments from the MS Trust and UKMSSNA in relation to the Appraisal Consultation Document (ACD) for dimethyl fumarate, published in February 2014. The ACD states that the Appraisal Committee is minded not to recommend dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis (MS).

Our submission will address the following areas, as set out in the ACD, namely:

a) Has all of the relevant evidence been taken into account?
b) Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
c) Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
d) Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

We do not believe that there are any points relating to item D. All our points relate to the first three items for consideration.

The MS Trust and UKMSSNA are extremely disappointed that the Committee is minded not to recommend dimethyl fumarate for adults with relapsing-remitting multiple sclerosis.

Our comments focus on the following major issues.

1. **Exclusion of highly active despite treatment subgroup (HA)**

   The MS Trust and UKMSSNA are particularly concerned that the Committee is unable to support a recommendation for dimethyl fumarate in highly active despite treatment (HA) sub-group.

We have noted in previous technology appraisal submissions to NICE that 'rapidly evolving severe (RES)' and 'highly active despite previous treatment (HA)' are de-facto sub-groups created during the licensing of natalizumab and fingolimod which do not reflect clinical reality or the true complexity of prescribing. In clinical practise, these sub-groups overlap and represent the upper end of a spectrum of disease activity in relapsing-remitting MS, characterised by more frequent and more disabling relapses which may not be controlled by initial treatment with beta interferon drugs or glatiramer acetate. Failure to reduce the number and severity of relapses has a devastating impact both in the short and long term.

The committee heard from clinical experts that dimethyl fumarate would be considered as a first-line treatment option alongside beta interferons or glatiramer acetate (4.3). We would agree that this is a target population for dimethyl fumarate.

Clinical specialists also considered that dimethyl fumarate may provide a treatment option for people with relapsing-remitting MS previously treated with beta interferons or glatiramer acetate (and now teriflunomide) whose disease had failed to respond or who had experienced adverse reactions (4.3). We would also agree that this is a target population for dimethyl fumarate. We would argue that, in clinical practice, this sub-group is equivalent to the HA sub-group defined for fingolimod in NICE TA guidance 254 (ie people who have an unchanged or increased relapse rate or ongoing severe relapses, compared with the previous year, despite treatment with beta interferon).

Both DEFINE and CONFIRM included participants who had previously received disease modifying treatments. Eligibility criteria included at least one clinically documented relapse in the previous 12 months. The manufacturer presented results for pre-specified sub-groups which found that dimethyl fumarate was equally effective in both treatment-naïve and treatment-experienced patients (3.6). We would interpret these results as demonstrating that dimethyl fumarate is effective in patients who continue to have relapses despite treatment with beta interferon or glatiramer acetate (ie HA sub-group), contrary to the Committee's views (4.10). We trust that the manufacturer will be able to provide further data to support the use of dimethyl fumarate in the HA sub-group.

The consequence of explicitly excluding the HA sub-group could have the effect of preventing people from switching to dimethyl fumarate if initial treatment is ineffective. As the range of disease modifying treatments increases there needs to be a pragmatic acknowledgement that switching treatment may be right for some patients for a variety of clinically legitimate reasons. If in consultation with their MS neurologist, a patient opts to switch, relevant Technology Appraisals should not have introduced roadblocks or perversions in a treatment pathway that make this difficult or impossible. Excluding the HA sub-group is a potential case in point and NICE should ensure that its TAs support and facilitate shared decision making and best fit of treatment to patient needs and preferences.

We would not anticipate that dimethyl fumarate would be considered routinely as a treatment option for the rapidly evolving severe sub-group, for whom natalizumab would be recommended.

2. Economic model

While the ERG and Committee were satisfied with the manufacturer's economic model (4.12, 4.13), the Committee has requested further analyses. We trust that the manufacturer will provide these. The difficulty in calculating cost effectiveness of MS drugs is well recognised.

The innovative nature of oral route of administration is acknowledged in the ACD, in fact the Committee considered that additional QoL benefits were not fully captured in the QALY, and that the ICER may decrease when the benefits of oral treatment are taken into consideration (4.22).

In reviewing the innovative nature of dimethyl fumarate, the Committee observed that a twice daily administration schedule may lower adherence compared with once daily options (4.22). The factors influencing adherence are complex. We anticipate that MS nurses will retain an important role working with people to help them choose a treatment that is right for them, monitoring and motivating them to support adherence. The manufacturer is also planning adherence programmes to avoid early discontinuation of treatment.

3. Extending the range of treatment options

The committee heard from both clinical and patient experts about the importance of access to a range of medicines, particularly for those who are unable to tolerate current treatments which are associated with significant side effects and injection site reactions.

Despite the overall efficacy of current treatments for reducing frequency and severity of MS relapses, any one of them can simply fail to work in a particular patient, or cause debilitating side effects. Clinicians lack tools to predict who would respond well to a specific therapy.

Four of the current first line treatments (Avonex, Betaferon, Extavia and Rebif) have the same mechanism of action. If a patient fails to respond to one of these there are limited alternative treatments with a different mechanism of action.

All but one of the current first line treatments are self-injected. Through supporting people who are taking the current first line treatments, we are aware that the requirement for long-term injections places a burden on them and in some cases leads to a decision not to start treatment, delays initiating treatment or results in reduced adherence. Self-injecting is painful, results in anxiety and stress; can lead to skin reactions and complications at injection sites; may be difficult for people whose manual dexterity is limited, requiring help from carers and families; and imposes restrictions on a number of aspects of general living.

Dimethyl fumarate offers greater efficacy at reducing relapse rates compared to current disease modifying treatments and consequent avoidance of residual disability and reduction in asymptomatic lesions; beta interferons, glatiramer acetate and teriflunomide reduce relapse rates by approximately 30%, dimethyl fumarate by approximately 50%. It is taken as tablets, acts in

a different way to the current disease modifying drug therapies, and has a different profile of side effects. It will significantly enhance the range of treatments available to people with relapsing-remitting MS, providing a genuine alternative to the current therapies.

Conclusion

MS remains a cause of severe disability for many young adults. Current first line treatments have demonstrated effectiveness at reducing relapses but the greater efficacy of dimethyl fumarate would undoubtedly be beneficial.

Research evidence demonstrates the importance of active, early treatment of relapsing-remitting MS to prevent axonal damage and avoid irreversible disability. The European Commission has licensed dimethyl fumarate for the treatment of adults with relapsing-remitting MS.

The MS Trust and UKMSSNA encourage the Committee to recognise that dimethyl fumarate would be an important addition to the small range of available disease modifying therapies for MS.

As with other disease modifying therapies, dimethyl fumarate should be prescribed by neurologists, with commencement of therapy and ongoing monitoring provided by specialist MS nurses.

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