NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation
John Radcliffe Hospital, Oxford University Hospitals Trust, Oxford,

Are you (tick all that apply):

- ✓
  a specialist in the treatment of people with the condition for which NICE is considering this technology?

- ✓
  a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?

- ✓ consultant neurologist
  an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)?

- ✓ clinical lead for the DOH Risk sharing scheme for disease modifying therapies.
  other? (please specify)

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I agree with the content of the statement submitted by Biogen Idec and would also like to add the following information:

What is the expected place of the technology in current practice?
How is the condition currently treated in the NHS? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?
Current first line therapies are injectable treatments (beta-interferon and glatiramer acetate) which require either weekly intramuscular injections or 3-7 times per week sub-cutaneous injections, depending on the product. This requires training of the patient or their family and a lot of on-going nurse support and monitoring because of injection technique issues and the often significant injection site reactions. Some patients are so anxious about this route of administration that they decline treatment. Second line agents include intravenous natalizumab which requires day case admission monthly to hospital, or oral fingolimod therapy where beta-interferon fails. There aren't any major differences of practice relevant to this new therapy, and this probably relates to the existing national criteria for MS disease modifying therapies that limit variations in practice

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
It is difficult to predict outcome in individual patients with relapsing remitting MS. However the results of the clinical trials analyses shows that dimethyl fumarate appears effective within the sub-groups analysed suggesting its efficacy isn't focussed on a specific sub-group of patients we can select out in clinical practice. Thus it appears that this treatment is effective across a broad range of patients and thus as long as the treatment is cost–effective, patients should have option of selecting this therapy if it is appropriate for their type/stage of MS and their life style needs.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
The treatment would be administered through already set up specialist MS clinics across the UK (as all other disease modifying therapies are). Compared to other available treatments it won't require injection training and support (beta-interferon and glatiramer acetate) day case admission (natalizumab) or first dose day case monitoring or a retinal assessment (fingolimod). Blood test monitoring and urine analysis can be done in primary care with specialist MS nurse liaison (who already exists in the specialist MS clinic services).

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If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Not already available.

Please tell us about any relevant clinical guidelines and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.
There are Association of British Neurologist Guidelines which were previously used (1) and a new Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (2) currently being assessed via the neurology clinical reference group (CRG) for beta-interferons, glatiramer acetate, fingolimod and natalizumab. The guidelines were based on the NICE appraisals and subsequent data from clinical trials. The new draft guidelines although based on NICE appraisals have led to some 'illogical' pathways (such as limitations because of the enrolment criteria within the clinical trials) which will be reviewed via the neurology CRG.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?
An oral twice daily therapy will have obvious benefits to the current injectable first line treatments, will be easier to start and manage and will be more acceptable to most patients. In addition, whereas current first line therapies are generally accepted to reduce relapses in the region of 30%, dimethyl fumarate reduced relapse rate by around 50% in the clinical trials. This relapse effect appears to be similar to fingolimod (a once daily oral treatment) which is only available as a second line therapy but less than intravenous natalizumab (another second line therapy). I'm not aware of any extra monitoring required for this therapy other than blood tests, urine analysis, and follow up within the current MS services.
Thus this new treatment represents a step-change in treatment for MS patients i.e. an <u>oral first line therapy and with a greater relapse effect</u>.

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.
I assume that, as the treatment is effective in all clinical subgroups of relapsing remitting MS, then the rules for starting therapy will be based on their relapse activity (as enrolled within the clinical trials) or for those who have fulfilled the criteria prior to starting other treatments and who wish to switch for lifestyle reasons or because of intolerance or greater risks of other treatments.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects

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that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?
My opinion is that the clinical trial conditions were appropriate to extrapolate the findings to UK practice. The most important outcomes are the clinical ones i.e. relapses and disability outcomes. Relapse rates are easier to interpret and their length and impact on patients are often underestimated. Disability outcomes are more controversial although a conventional outcome used in clinical trials is the confirmed outcome at three months (and sometimes at six months) as presented in appendix I. This is likely to represent a mix of permanent disability, long relapses and biological noise (the latter controlled for by the placebo groups). Long-term effects on disability cannot be determined within a 2-3 year study because of the natural history of MS and thus has to be modelled. The MRI outcomes are supportive but there is not the data to show whether short-term imaging outcomes can predict long-term treatment effects (mainly because of the difficultly in measuring long-term treatment effects).

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Dimethyl fumarate is not being used currently in routine clinical practice and so the side effects are from the clinical trials (appendix I). Clearly flushing is quite common and GI side effects but these appear to settle over the first few months. Mild skin and blood abnormalities may occur. Side effects were troublesome enough to discontinue drug in 12-13~~6~~% of patients overall, ~~but this was~~ compared to 6% in~~able to~~ placebo and improvement in quality of life outcomes might suggest the side effects in those remaining on treatment were mild.

Equality and Diversity

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 this appraisal:

- **Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be 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;**

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- Could lead to recommendations that 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
I cannot see any way this would occur unless NICE restricted use based upon age or gender.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

None I'm aware of

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
I don't think there would be any real difficulties or hurdles in starting to deliver this treatment to patients within 3 months as MS disease modifying services are already set up for other available treatments.

References:

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1. Association of British Neurologists: Revised (2009) Association of British Neurologists' guidelines for prescribing in MS 2. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS), April 2013, Reference: NHSCB/D04/P/a, NHS Commissioning Board