NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Dimethyl fumarate for treating 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: United Kingdom Clinical Pharmacy Association
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)?

√ 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)? **Member**

- other? (please specify)

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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?

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?

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)?

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?

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.

Current disease-modifying therapy for relapsing-remitting multiple sclerosis (RRMS) includes beta-interferon and glatiramer (self-injected), natalizumab (monthly infusions) and fingolimod (tablet). Access to DMTs on the NHS is mainly guided by Association of British Neurologist (ABN) guidelines and NICE Technology Appraisals (TA). Geographical variation exists as MS treatment was commissioned locally until April 2013 and different funding agreements may have been reached historically between Primary Care Trusts (PCT) and providers. Interferons and glatiramer are widely regarded as equally effective first-line treatments; the decision which one to start is shared between the clinician and the patient. It may be influenced by patient preference (frequency of administration) as well as patients' past medical history (eg history of mental health problems). Natalizumab is reserved for patients with rapidly evolving severe (RES) RRMS who are either treatment naïve or are failing on first-line treatment. Patients can only be considered for fingolimod if they have highly active RRMS and have failed on interferon beta. Natalizumab and fingolimod can therefore be considered as 2nd line treatment options after interferon beta/glatiramer.
NICE TAs / ABN guidelines and more recently the Specialist Commissioning Policy are setting out the starting and stopping criteria for each drug.
We anticipate that the new technology will be positioned as 2nd line treatment after interferon/glatiramer. It will be particularly an option for patients who made the decision to start glatiramer as 1st line treatment and are therefore not eligible for fingolimod. This is a positive development for patients otherwise excluded from oral therapy.
Other patient groups who should be considered are: Patients who are needle-phobic, and patients on natalizumab who experience problems with monthly infusions, non-responders to all existing therapies.
The technology is being administered at least twice daily; this may pose a problem for patients with cognitive impairment as they are at risk of poor compliance.
The technology should be initiated under the care of a specialist in the treatment of multiple sclerosis and can be managed within the clinic setting by specialist MS nurses. Pre-screening would be required within the specialist setting to inform baseline data (mainly full blood count, liver function tests, renal function, cholesterol); ongoing monitoring in terms of safety (including PML) and efficacy would be expected to occur within the specialist setting.
The technology is currently not available in the clinical setting which the author is familiar with.

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Relevant clinical guidelines are the ABN guidelines 2001 and NICE TA 127/254 which have informed the current commissioning policy NHSCB/D04/P/a - April 13.

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?

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.

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 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?

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?

The technology will increase the number of oral treatments from one to two. As this technology has been trialled in direct comparison to glatiramer, a different group of patients may eventually gain access to oral therapy – which eliminates (or at least reduces) the current inequality for patients who do not qualify for fingolimod.

Oral treatment has the obvious advantage of being less invasive as injectables. This has an impact on patients' quality of life and on the wider health economy (fewer days off work for regular infusion appointments, day unit attendance reduced). However this has to be balanced against the risk of poor compliance especially in patients with cognitive impairment. Measures need to be put in place to support patients accordingly.

Fumaric acid esters are established treatment in Germany for adults with moderate to severe plaque psoriasis and are available on named-patient basis in the UK. Although robust trial data is lacking, the treatment is being used since 1959 which provides a wealth of safety data. By comparing data from dermatological experience with the 2 pivotal trials (DEFINE and CONFIRM), it is evident that occurrence and frequency of adverse drug reactions are comparable and data may be extrapolated beyond trial periods. This is particularly an advantage as the usage of the technology will eventually exceed MS trial periods.

The most common side effects are gastrointestinal symptoms, leading to a considerable discontinuation rate in dermatological patients (30 – 40%). In general, the technology seems to be well tolerated but monitoring of FBC (severe lymphopenia, leucopenia, eosinophilia), LFTs, renal function and cholesterol will be a requirement. Recent reports (n=5) of PML after long-term treatment of several years (albeit not within the MS trial cohort and not with the BG-12 formulation) must not go unnoticed and stringent monitoring/surveillance is recommended. JC virus testing prior to commencing treatment would be beneficial.

In general, the evidence is promising and hints towards greater efficacy as current treatments. Compliance within a clinical trial setting is obviously much easier to achieve than in real life. It remains to be seen if the outcomes are therefore replicable in real life settings, particularly with a multiple daily dosing regime. Relevant outcomes (as per scope) have been measured in the clinical trials and are therefore applicable.

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.

No access to additional information.

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)?

Additional resources (staff, facilities) should not be necessary in order to implement the technology. Dimethyl fumarate should provide a further disease modifying treatment option for multiple sclerosis but not necessarily increase the number of patients receiving disease-modifying therapy overall. The extent of clinic and laboratory monitoring required by the licencing authorities will also determine the resource requirement. However we do not envisage that monitoring requirements would be more extensive than currently available treatments.

If testing for JC virus is to be recommended, then the test should be made available free of charge from the manufacturer Biogen (as this is currently the case for patients on natalizumab).

Although it is expected that the prescribing of the technology will be restricted to specialists only, additional training/education for respective staff (specialist nurses, clinicians, specialist pharmacists) will still be necessary.

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The NICE TA will be instrumental in providing guidance regarding start/stop criteria as well as eligibility for the technology. It will also inform the development of local treatment pathways (although it is hoped that NICE Multiple Sclerosis Guidelines will be updated with all new drugs included as with the number of available treatments, the pathway becomes increasingly complex).

Currently available self-administrable therapies i.e. beta-interferons, glatiramer acetate and fingolimod are offered available through homecare supply. We would expect dimethyl fumarate to be offered similarly, ideally through a range of homecare providers to suit local arrangements and contracts.

Equality

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;
- 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.

Experience from the Fingolimod NICE TA shows that there is a risk that patients on interferons will be excluded based on available trial data and economic analysis.