Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Dimethyl-fumarate for treating relapsing forms of 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: **Association of British Neurologists**

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)? ☑

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What is the expected place of the technology in current practice?

How is the condition currently being treated in the NHS?
There are three main categories of medical treatment for people with relapsing remitting MS (pwRRMS), (i) treatment of relapses, (ii) symptomatic treatment, and (iii) disease modifying treatment (DMT). The drug discussed here (Dimethyl-fumarate, DMF) belongs to the latter category. Current standard 1st line DMT for pwRRMS who fulfil the criteria issued by the ABN 2001 (updated 2009) consist of β-interferons and glatiramer acetate. pwRRMS who despite treatment with one of the β-interferons have ongoing disease activity (either indicated by relapses and/or gadolinium-enhancing (Gd^+) lesions on brain magnetic resonance imaging (MRI), may switch to (2nd line) treatment with either natalizumab or fingolimod. Both natalizumab and fingolimod are considered by NICE as cost-effective treatments. Natalizumab also has a NICE recommendation as a 1st line DMT in pwRRMS with a rapidly evolving severe (RES) course of their disease.

Is there significant geographical variation in current practice?
DMT is guided by national and rather strict criteria (ABN 2001/2009 and NICE guidance, see below). Therefore, geographic variation in treatment practice should be minimal. Nevertheless, significant variation appears to exist across the UK in the interpretation of certain aspects of the mentioned guidelines, for example about the time point when to initiate treatment. A recent study by the UK MS Society revealed that pwRRMS who live in Northern Ireland are more than twice as likely to be taking DMT than if they live in Wales. Across Europe, only Poland and Romania have a smaller proportion of pwRRMS taking DMT.

Are there differences of opinion between professionals as to what current practice should be?
Differences in prescribing practises are based on (i) whether the 2001 or 2009* version of the ABN guidelines is being used and (ii) how strict the criteria are being applied. There is now a general tendency among colleagues to treat earlier in the course of the disease in order to try and delay development of disability.

*The main difference between the two versions of the ABN guideline is the inclusion in the 2009 version of (i) patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of MS), and (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity.

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What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

1st line DMT are currently all injectable drugs. These drugs (β-interferons and glatiramer acetate) reduce the frequency of relapses by about 35%. Whilst they are generally safe and well tolerated the side effects of β-interferons can be unpleasant, at least during the first 6-8 weeks of treatment (mainly flu-like symptoms & injection site reactions). There is currently no oral drug licensed as 1st line DMT for pwRRMS. Assuming efficacy is at least equal to current 1st line DMT an oral drug would provide significant benefit for pwRRMS (ease of use and drug adherence). Negative effects of the new technology over and above those reported in the clinical studies are not expected.

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?

There is good evidence that high disease activity during the first few years (≥3 relapses during the first 2 years, high lesion load on MRI at onset, Gd^+ lesions) predicts poor outcome, ie. more rapid accrual of disability and early conversion to secondary progressive MS.

DMF has been efficacious in pwRRMS across subgroups of patients. The risks (e.g. decreased lymphocyte count, elevation of hepatic enzymes) are manageable with adequate risk minimisation measures. Specific efficacy data are lacking for pwRRMS with high disease activity.

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)?

Eligibility for the drug should be evaluated by a consultant neurologist with experience in the treatment of pwRRMS, and follow-up provided as per standard care, ie. every 6-12 months.

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?

The technology is not yet available in the NHS.

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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.
The key documents to guide decisions regarding DMT in the UK are currently:
- NICE clinical guideline 8 (2003). Multiple sclerosis: management of multiple sclerosis in primary and secondary care.
- Revised (2009) ABN guidelines for prescribing in multiple sclerosis
- NICE technology appraisal guidance 32 (2002). Beta interferon and glatiramer acetate for the treatment of multiple sclerosis.
- NICE technology appraisal guidance 127 (2007). Natalizumab for the treatment of adults with with highly active relapsing–remitting MS.
- NICE technology appraisal guidance (2012). Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis.

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?
The efficacy of DMF over placebo on disease activity (relapses and MRI indices) has been demonstrated. Efficacy on progression of disability has not clearly been established as the effect lacked consistency across the two studies that led to submission for licensing. Though only historical comparison can be made across products in the absence of head to head comparative data, the efficacy of DMF is comparable, perhaps even superior, to that of β-interferons.

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.
Whilst the starting and stopping rules of the current ABN 2009 guideline for 1st line DMT should be followed at this point in time, we are aware of discussions to modify treatment strategies in the near future to systematically include MRI (and potentially other disease biomarkers) to tailor treatment more individually to achieve freedom of disease activity.

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?

Two, 2-year, randomised, double-blind, placebo controlled studies in pwRRMS were performed (study 1 [DEFINE] with 1234 subjects, and study 2 [CONFIRM] with 1417 subjects). Efficacy and safety was demonstrated in pwRRMS with EDSS scores between 0 and 5 inclusive, who had experienced at least one relapse during the year prior to randomisation, or who had a brain MRI within 6 weeks of randomisation that demonstrated at least one Gd^+ lesion. Study 2 contained a rater-blinded comparator (glatiramer acetate).

Compared to placebo, subjects treated with DMF had a clinically meaningful and statistically significant reduction on the primary endpoint in studies 1 (proportion of subjects relapsed at 2 years), and 2 (annualised relapse rate at 2 years). In both studies, the efficacy of DMF given either as a 240 mg twice daily or 240 mg three times daily dose was comparable. The annualised relapse rate for glatiramer acetate versus placebo was 0.286 and 0.401 in study 2, corresponding to a reduction of 29%, which is consistent with prior knowledge.

Analysis of treatment effect on disability progression of DMF versus placebo revealed the following: The estimated proportion of subjects with 12-week confirmed disability progression at 2 years was 0.146 for DMF twice daily and 0.222 for placebo [hazard ratio 0.68 (95% CI 0.52, 0.88)]; the estimated proportion of subjects with 24-week confirmed disability progression at 2 years was 0.105 for DMF twice daily and 0.148 for placebo [hazard ratio 0.71 (95% CI 0.52, 0.96)].

In summary, whilst there is unequivocal evidence for a significant effect of DMF on relapses, efficacy on disability endpoints is less clear as the 6 month outcome did not confirm the 3 month outcome. However, looking at the data as a whole, there is compelling evidence of clinically meaningful efficacy: DMF has a significant effect on relapses and MRI predictors of disability such as the number of Gd^+ lesions and of T_1 hypo-intense lesions ("black holes"), suggesting pwRRMS may benefit in the long term in terms of clinical disability.

The population enrolled in the clinical trials of DMF is reflective of pwRRMS seen on a regular basis in the UK. Therefore, the trial results should clearly be applicable to the UK population.

What is the relative significance of any side effects or adverse reactions?

Exposure to DMF has identified flushing, gastro-intestinal (GI) disorders, skin events, infections and several laboratory parameters as the most common adverse events. Especially flushing and GI events are likely to be manageable by dose

titration during the first week or so of treatment and by temporary dose reduction during the course of treatment. Cardiovascular events have been reported for Fumaderm, a product very similar to DMF, but only in a few pwRRMS on DMF. Though renal toxicity would be expected from preclinical studies, renal & urinary events in pwRRMS were only slightly more frequent compared to placebo in the studies. Two renal malignancies were reported in the clinical program, supported by findings from the Fumaderm postmarketing experience (four cases of renal malignancies). Laboratory abnormalities include WBC, lymphocytes, and liver enzymes (ALT and AST). This seems manageable through primary and secondary care. Though no case of progressive multifocal leucencephalopathy (PML) occurred in pwRRMS during the clinical trials, four cases have been reported in patients taking Fumaderm for other indications.

Overall the risk-benefit balance is in favour of treatment with DMF.

In what ways do these affect the management of the condition and the patient's quality of life?
As stated above, management of common side effects should straightforward in primary & secondary care.

Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
The technology is not yet available through the NHS, therefore post marketing experience in the UK is limited. PML has been reported in four patients taking a drug very similar to DMF (Fumaderm) for other indications. The two renal malignancies reported in the clinical program of DMF for pwRRMS are supported by findings from the Fumaderm postmarketing experience (four cases of renal malignancies).

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.

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.

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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?
The delivery of care for would be simplified as treatment with DMF would not require pwRRMS to learn a specific technique (subcutaneous of intramuscular injection) under the supervision and guidance of a specialist nurse.

Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?
It is unlikely any significant additional education would be required.

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;
We are unaware of any evidence to that effect.

- 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;
We are unaware of any evidence to that effect.

- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.
We are unaware of any evidence to that effect.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.