Appendix G – Patient/carer organisation statement template

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 your views on the technology and the way it should be used in the NHS.

Patients and patient advocates can provide a unique perspective on the technology, which is not typically available from the published literature.

To help you give your views, we have provided a template. The questions are there as prompts to guide you. You do not have to answer every question. Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: Multiple Sclerosis Trust

Are you (tick all that apply):

- a patient with the condition for which NICE is considering this technology?
- a carer of a patient with the condition for which NICE is considering this technology?
- ✓ an employee of a patient organisation that represents patients with the condition for which NICE is considering the technology? If so, give your position in the organisation where appropriate (e.g. policy officer, trustee, member, etc)

Director of Service Development

- other? (please specify)

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What do patients and/or carers consider to be the advantages and disadvantages of the technology for the condition?

1. Advantages

(a) Please list the specific aspect(s) of the condition that you expect the technology to help with. For each aspect you list please describe, if possible, what difference you expect the technology to make.

The MS Trust is in contact with over 40,000 people affected by MS; that's people with MS, their families, friends and the health care professionals who help manage MS. A major component of our work is supporting people with health-related issues and enabling informed decision making with their health professionals.

MS is commonly diagnosed between the ages of 20 and 40, at a time when people are developing careers, starting families, taking on financial obligations. Approximately 80% will have relapsing remitting MS (RRMS). Through our enquiry service we are only too aware of the devastating impact MS relapses can have both in the short and long term. We speak daily to people who are dealing with issues relating to relapsing remitting MS: coping with the impact of diagnosis, choosing which treatment to take, understanding and balancing risk/benefit profiles, dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses.

MS relapses are unpredictable in onset, severity, type of symptoms, and duration. Recovery is often incomplete, leading to accumulation of disability with each successive relapse. Residual disability may be apparent, such as impaired mobility, but may also be less overt, such as depression, fatigue, cognitive problems or sexual dysfunction. The more invisible consequences of a relapse can often be overlooked by health professionals, family and work colleagues yet impact on quality of life and capacity to remain in employment as profoundly as more apparent symptoms.

Relapses have a significant impact on the ability to work, leading to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in considerable direct and indirect financial burden, both for the individual, their family and the state. They can have a profound effect on a person's daily activities, social life and relationships and present considerable psychosocial and emotional challenges for both the individual and for family and friends.

In a cash-strapped NHS, the reality is that services to support people coping with a relapse, such as physiotherapy or the provision of equipment or carers, are often limited or non-existent. The quality of and access to care is highly dependent on where someone lives. Individuals contacting the MS Trust frequently report that the urgent access to physiotherapists or occupational therapists necessitated by a rapid onset of symptoms is rarely possible. A recent caller to our enquiry service reported a 10 week waiting list to see a physiotherapist for treatment of walking problems following a relapse. As well as prolonging the effect of the relapse on someone's life, these delays risk compounding problems, introducing further distress to the individual and cost to the NHS.

Research evidence supports the treatment of people with relapsing remitting MS early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that even if people with MS continue to have relapses while on therapy, they may still be deriving benefit from the treatment. State of

the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; reducing relapse rates is an essential component of this aim.

A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing remitting MS.

Dimethyl fumarate offers

- greater efficacy at reducing relapse rates compared to current disease modifying treatments
- consequent avoidance of residual disability
- reduction in asymptomatic lesions
- practical/convenient route of administration

(b) Please list any short-term and/or long-term benefits that patients expect to gain from using the technology. These might include the effect of the technology on:
- the course and/or outcome of the condition
- physical symptoms
- pain
- level of disability
- mental health
- quality of life (lifestyle, work, social functioning etc.)
- other quality of life issues not listed above
- other people (for example family, friends, employers)
- other issues not listed above

1. Relapse reduction
In the two pivotal phase III clinical trials, DEFINE and CONFIRM, twice daily dimethyl fumarate reduced relapses by 53% and 44% compared to placebo. Current first line disease modifying treatments (beta interferon and glatiramer acetate) reduce relapses by approximately 30%.

2. Reduction in disability progression
In DEFINE, twice daily dimethyl fumarate significantly reduced the risk of sustained disease progression by 38% compared to placebo; in CONFIRM reductions in disability progression were not significant. Two year trial may not be a sufficiently long time-frame to give an accurate measure of disability progression.

3. Reduced administration of steroids and fewer hospital admissions
Combining data from DEFINE and CONFIRM, at 2 years twice daily dimethyl fumarate reduced the annualized rate of relapses requiring IV steroids by 48% and reduced the annualized rate of MS-related hospitalizations by 34%. Reducing the use of steroids decreases the long-term effects of their usage and subsequent complications such as osteoporosis. Reducing hospitalizations has economic benefits as well as minimising the psychological and practical impact of relapses on the individual and family. Reducing relapse rates might also be expected to reduce A&E attendance.
Giovannoni G et al. Relapses requiring intravenous steroid use and multiple sclerosis (MS)-related hospitalizations: an integrated analysis of the BG-12 (dimethyl fumarate) phase 3 studies (P07.121). Neurology 2013; 80(Meeting Abstracts 1): P07.121
http://www.neurology.org/cgi/content/meeting_abstract/80/1_MeetingAbstracts/P07.121

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4. Quality of life and symptom control
A common theme from our contacts with people affected by MS is the strain of living with the unpredictability of MS. People with MS have a significantly higher rate of depression than the normal population with in excess of 50% having an episode of depression during the course of their disease. Active management with dimethyl fumarate and the consequent reduced rate of relapses is likely to help people feel in control of their condition and reduce the level of depression.

Combining data from DEFINE and CONFIRM, dimethyl fumarate resulted in significant improvements in physical and mental aspects of health and functioning, general well-being, and overall health status compared with placebo in patients with relapsing remitting MS.
Kita M et al. Effects of BG-12 (dimethyl fumarate) on quality of life in patients with relapsing–remitting multiple sclerosis (RRMS): an integrated analysis of the phase 3 DEFINE and CONFIRM Studies (P07.092). Neurology 2013; 80(Meeting Abstracts 1): P07.092.
http://www.neurology.org/cgi/content/meeting_abstract/80/1_MeetingAbstracts/P07.092

5. Oral route of administration
Overwhelmingly, an oral route of administration is seen as a real benefit by people with MS. Through supporting people who are taking one of 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 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.

2. Disadvantages

Please list any problems with or concerns you have about the technology. Disadvantages might include:
- aspects of the condition that the technology cannot help with or might make worse
- difficulties in taking or using the technology
- side effects (please describe which side effects patients might be willing to accept or tolerate and which would be difficult to accept or tolerate)
- impact on others (for example family, friends, employers)
- financial impact on the patient and/or thier family (for example cost of travel needed to access the technology, or the cost of paying a carer)

1. Side effect profile
In clinical trials, dimethyl fumarate's main side effects included flushing and gastrointestinal events (diarrhoea, nausea, abdominal pain) which improved or resolved after the first month. In DEFINE and CONFIRM the drop out rates from GI events were 2-6% and from flushing 1-4%. It is not clear if these side effects will have an impact on adherence in clinical use.

Reduced lymphocyte counts and raised liver enzyme levels have also been reported in clinical trials and may require monitoring in general use.

2. Twice daily administration
SmPC not published yet, so details of recommended dosing are not available. We are assuming one tablet taken 2 times a day. Twice daily administration may lead to reduced adherence compared to once daily treatments.

The factors influencing adherence are complex but 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.

3. Are there differences in opinion between patients about the usefulness or otherwise of this technology? If so, please describe them.

We are not aware of any. From discussions with people who are newly diagnosed, the majority with relapsing remitting MS expect to start treatment early. There will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines.

4. Are there any groups of patients who might benefit **more** from the technology than others? Are there any groups of patients who might benefit **less** from the technology than others?

We are submitting this response in advance of the EMA licensing decision and without in depth knowledge of any subgroup analysis that may have taken place on the clinical data.

We anticipate that dimethyl fumarate will be licensed as a first line treatment for relapsing remitting MS. In clinical trials, dimethyl fumarate has been well-tolerated. Following FDA approval in the States, there have been no safety concerns and specific sub-groups who might benefit more or less from the drug have not been identified

A common topic of our discussions with people with RRMS relates to difficulties associated with self-injection. People who are currently using one of the injectable DMTs should not be excluded from switching to dimethyl fumarate if, following discussions with their neurologist, this is considered appropriate. This would allow them to benefit from greater clinical efficacy and a more practical route of administration.

Comparing the technology with alternative available treatments or technologies

NICE is interested in your views on how the technology compares with existing treatments for this condition in the UK.

(i) Please list any current standard practice (alternatives if any) used in the UK.

The current drug therapies that are available as first line treatments are:
Avonex - interferon beta 1a
Betaferon and Extavia - interferon beta 1b
Rebif - interferon beta 1a
Copaxone - glatiramer acetate
Tysabri - natalizumab
Gilenya - fingolimod. Approved by NICE as a second line treatment when relapse rates remain unchanged or increase despite at least 12 months beta interferon treatment.

(ii) If you think that the new technology has any **advantages** for patients over other current standard practice, please describe them. Advantages might include:

- improvement of the condition overall
- improvement in certain aspects of the condition
- ease of use (for example tablets rather than injection)
- where the technology has to be used (for example at home rather than in hospital)
- side effects (please describe nature and number of problems, frequency, duration, severity etc)

Beta interferons and glatiramer acetate reduce relapse rates by approximately 30%, dimethyl fumarate by approximately 50%. We know from regular conversations with people with MS that some choose not to start or continue treatment with current disease modifying treatments because of injection anxiety or side effects. From their perspective, the greater efficacy, oral route of administration of dimethyl fumarate and freedom from flu-like side effects will be significant advantages.

Natalizumab is approved by NICE for people with rapidly evolving severe MS; it appears to have a greater efficacy than dimethyl fumarate although the two drugs have not been compared in head-to-head clinical trials. We would expect this group to continue to be treated with natalizumab; while the majority of people taking natalizumab do not have concerns about monthly visits to hospital out-patient clinics for infusions, many do talk to us about their concerns about the risk profile of natalizumab.

Fingolimod is approved by NICE as a second line treatment only after 12 months of beta interferon treatment. This has created a roadblock in the treatment pathway for people who continue to relapse with glatiramer acetate, as they will only be eligible for fingolimod if they switch to one of the beta interferons for a further 12 months, which are unlikely to be more efficacious. For patients the most important issue is getting access to the right drug at the right time and not experiencing needless, avoidable and burdensome delay. The same problem will arise for those who continue to relapse while taking dimethyl fumarate or one of the other new disease modifying treatments currently going through licensing and appraisal. While we recognise that this situation results from the wording of the EMA licence for fingolimod, we wish to flag up the clinical issues it has created and urge NICE to consider how this could be resolved in the best interest of patients and the NHS.

(iii) If you think that the new technology has any **disadvantages** for patients compared with current standard practice, please describe them. Disadvantages might include:
- worsening of the condition overall
- worsening of specific aspects of the condition
- difficulty in use (for example injection rather than tablets)
- where the technology has to be used (for example in hospital rather than at home)
- side effects (for example nature or number of problems, how often, for how long, how severe).

None, although as noted above it is unclear how people will tolerate side effects of dimethyl fumarate (GI events and flushing) in routine use.

Research evidence on patient or carer views of the technology
If you are familiar with the evidence base for the technology, please comment on whether patients' experience of using the technology as part of their routine NHS care reflects that observed under clinical trial conditions.

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Taking any drug in the context of a clinical trial, with greater attention from health professionals, will be different from taking it in routine NHS care. Given the ease of oral administration of dimethyl fumarate, there are two main risks: a risk of lower levels of adherence (intentional or unintentional) and a risk that people may become disconnected from MS services. MS nurses and other MS professionals will have a key role in promoting adherence, and continue to have a key role in managing other symptoms that individuals may experience as part of their MS. People will need to be informed about side effects and closely supported to avoid early discontinuation of treatment.

Are there any adverse effects that were not apparent in the clinical trials but have come to light since, during routine NHS care?

None that we are aware of. Dimethyl fumarate has not been used in routine NHS care.

Are you aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to an appraisal of this technology? If yes, please provide references to the relevant studies.

Bevan S, et al. Ready to Work? Meeting the Employment and Career Aspirations of People with Multiple Sclerosis. Work Foundation: London; 2011
http://www.theworkfoundation.com/DownloadPublication/Report/289_289_MS3.pdf

- This report highlighted the problems faced by people of working age in the UK and showed that people with MS lose an average of 18 working years, with many dropping out of employment very rapidly after diagnosis.

MS Society. A lottery of treatment and care – MS services across England and the UK. MS Society: London; 2013
http://mslottery.mssociety.org.uk/wp-content/uploads/2013/04/England-ms-lottery.pdf

- Across the UK, only 40% of those that are eligible are taking a disease modifying treatment.

Multiple Sclerosis International Federation. MSIF survey on employment and MS. MSIF: London; 2010
http://www.msif.org/about-ms/day-to-day-living-with-ms/employment-education-and-ms/employment-and-ms-survey.aspx

- Having stable MS was rated as the most important factor enabling people with MS to remain in work. Disease modifying treatments were listed as one of the top five factors enabling people to remain employed.

Availability of this technology to patients in the NHS

What key differences, if any, would it make to patients and/or carers if this technology was made available on the NHS?

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.

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An oral route of administration would have a major impact on the quality of life of the person with MS and their families and friends; reduced relapses and less disability have profound personal benefits for quality of life, employment and active participation in society

What implications would it have for patients and/or carers if the technology was **not** made available to patients on the NHS?

There is potential for greatly increased costs to the NHS and state if the technology is not made available. Oral route of administration is preferred by the majority of people with MS, so we anticipate greater uptake of this treatment, leading to better quality of life for people with MS and their families and friends.

If the technology is not made available, there is potential for a greater burden on the NHS, to the economy and to carers in the short term to support relapses, since these require steroid treatment, time off work, and can require significant care to be provided to the individual in relapse. In the long term, since relapses can result in individuals accumulating disability, there are significant NHS-related costs in caring for more severe MS, including the potential for increased A&E attendance, hospital admissions and treatment – sometimes in ITU; provision of expensive equipment such as wheelchairs; as well as the potential loss of economic activity of family members caring for people with MS.

Are there groups of patients that have difficulties using the technology?

None that we are aware of.

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.

None.

Other Issues

Please consider here any other issues you would like the Appraisal Committee to consider when appraising this technology.

None.