NICE National Institute for Health and Care Excellence

Fast Track Appraisal

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

Committee Papers

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FAST TRACK APPRAISAL

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** **and** **final stakeholder list** are available on the NICE website.

1. **Company submission summary** from **Biogen**
2. **Patient group, professional group and NHS organisation submissions from:**
   a. **Multiple Sclerosis Society**
   b. **Multiple Sclerosis Trust**
   c. **Association of British Neurologists**
3. **Evidence Review Group report** prepared by **School of Health and Related Research (ScHARR)**
4. **Evidence Review Group – factual accuracy check**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Fast track appraisal: cost-comparison case

Diroximel fumarate for treating relapsing–remitting multiple sclerosis [ID1673]

Document A

Company evidence submission summary for committee

Biogen confirm that all information in the submission summary is an accurate summary or replication of evidence in the main submission and accompanying appendices and that wherever possible a cross reference to the original source is provided.

November 2021

File name	Version	Contains confidential information	Date
ID1673_Diroximel fumarate RRMS_NICE FTA Document A [redacted].docx	**V2.0**	**No**	**09 February 2022**

Contents

Tables and figures

Submission summary

A.1. The technology

Table 1: Technology being appraised – B.1.2 (page 9)

UK approved name and brand name	Diroximel fumarate (DRF; Vumerity®)
Mechanism of action	DRF, a pro-drug of monomethyl fumarate (MMF), is indicated for the treatment of relapsing forms of MS. Similar to dimethyl fumarate (DMF), DRF undergoes rapid pre-systemic hydrolysis by esterases and is converted to the active metabolite, MMF. The mechanism by which MMF exerts its therapeutic effect in multiple sclerosis is not known. Following oral administration, DRF undergoes rapid hydrolysis pre-systemically to the active metabolite MMF. Preclinical studies indicate that DRF and DMF pharmacodynamic responses appear to be mediated through activation of the nuclear factor (erythroid derived 2)-like 2 (Nrf2) transcriptional pathway. DMF has been shown to upregulate Nrf2-dependent antioxidant genes in patients (e.g. *NQO1*). On initial metabolism, DMF generates stoichiometric quantities of MMF and methanol (a known irritant) in a 1:1 ratio, which may cause localised GI effects of the gut endothelium. In comparison, owing to the distinct chemical structure of DRF, MMF and methanol are generated in a 9:1 ratio. DRF is therefore hypothesised to elicit less localised irritation in the GI tract than DMF. On initial metabolism, DMF generates stoichiometric quantities of MMF and methanol (a known gastric irritant) in a 1:1 ratio, which may cause localised GI effects of the gut endothelium. DRF, compared with DMF, is hypothesised to elicit less localised irritation in the GI tract on account of its distinct chemical structure and corresponding metabolites, generating MMF and methanol in a 9:1 ratio. The MAA for DRF was submitted to the European Medicines Agency (EMA) in November 2020 under the legal basis of Article 8(3) of Directive 2001/83, as a full stand-alone application for a medicinal product containing a known active substance. In accordance with Article 10.2.b of Directive 2001/83, DRF will be considered part of the same Global Marketing Authorisation as DMF and should be treated as containing the same active substance as patients are exposed to the same therapeutic moiety i.e. MMF.(1)
Marketing authorisation/CE mark status	DRF received a Medicines Health Regulatory Agency (MHRA) marketing authorisation for the treatment of adult patients with RRMS' on 8 November 2021. The MHRA followed the ECDRP (reliance route) for the initial marketing authorisation application. Positive CHMP opinion was received on 16 September 2021. Subsequent EMA approval is expected in November 2021.

Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The MHRA approved indication is: 'Vumerity is indicated for the treatment of adult patients with relapsing remitting multiple sclerosis' DRF is not indicated in any other populations. Patients with hypersensitivity to the active substance, any excipients listed in the SmPC or other fumaric acid esters. Patients with suspected or confirmed PML. The summary of product characteristics (SmPC) is presented in Appendix C.
Method of administration and dosage	The starting dose is 231 mg twice a day. After 7 days, the dose should be increased to the recommended maintenance dose of 462 mg twice a day. Temporary dose reductions to 231 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 462 mg twice a day should be resumed. If a patient misses a dose, a double dose should not be taken. The patient may take the missed dose only if they leave 4 hours between doses. Otherwise, the patient should wait until the next scheduled dose.
Additional tests or investigations	No additional tests or investigations are anticipated beyond those that are currently required for all patients with MS.
List price and average cost of a course of treatment	Proposed List price per pack (231 mg, 120 capsules): £1,471.07 Acquisition cost per year: £17,849
Patient access scheme/commercial arrangement (if applicable)	[redacted]

Key: CHMP, Committee for Medicinal Products for Human Use; DMF, dimethyl fumarate; DRF, diroximel fumarate; EMA, European Medicines Agency; GI, gastrointestinal; MA, marketing authorisation; MMF, monomethyl fumarate; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; RRMS, relapsing–remitting multiple sclerosis; SmPC, summary of product characteristics.
Source: CHMP Positive Opinion(2); Vumerity SmPC.(3); MHRA marketing authorisation(4)

A.2. Clinical pathway of care

Multiple sclerosis (MS) is a progressive, lifelong disease that requires lifelong management. Relapsing–remitting multiple sclerosis (RRMS) reflects disease where periods of remission are followed by relapses, which can significantly contribute to disability progression.(5-7) In the absence of a cure, alongside the heterogeneity of the patient population, it is important to have multiple treatment options available to help physicians and patients manage RRMS over their lifetime.

Diroximel fumarate (DRF) offers an additional oral treatment option for adult patients with RRMS who do not have highly active (HA) or rapidly evolving severe (RES) RRMS. DRF is the intended as an alternative treatment option to dimethyl fumarate (DMF), the most widely prescribed disease modifying treatment (DMF) for MS. A cost-comparison fast track appraisal (FTA) has been undertaken for DRF due to its established bioequivalence to DMF, appraised and reimbursed by NICE in 2014.(8) Additionally, DRF offers the potential for improved GI tolerability and associated positive impacts on health-related quality of life (HRQL) (see Section A.6).

Due to it's potential for improved GI tolerability, DRF is expected to be offered to eligible patients who would otherwise receive DMF.

In preparation for the NICE submission for DRF, UK clinical input was sought through teleconferences with five clinical experts (clinicians and nurses) with extensive experience of treating patients with MS.

The healthcare professionals considered the patient baseline characteristics from EVOLVE-MS 1 to be representative of the clinical cohort seen in their practice and agreed that DRF would be used in the same line of treatment as DMF. Furthermore, experts provided insights to the resources used to treat AEs and agreed that if DMF cannot be tolerated, or if patients had pre-existing GI problems then DRF could be used as an alternative treatment.(9)

A.3. Key drivers of the cost effectiveness of the comparator(s)

The sole comparator considered in this appraisal is DMF, which was appraised by NICE in 2014 for the treatment of patients with RRMS [TA320].(8) Evidence informing the appraisal for DMF was taken from the DEFINE, CONFIRM and ENDORSE trials. Of note, since TA320, longer term data on DMF has been published from a 13 year phase III, randomised extension study of DEFINE and CONFIRM to evaluate long-term safety and efficacy of DMF in patients with RRMS (ENDORSE).(10) Evidence considered in the DMF appraisal is not presented here, with the focus of this submission based on the bioequivalence exposure to MMF and, [redacted]use in clinical practice due to improved tolerability profile and [redacted].

A.4. Decision problem and NICE reference case

The submission focuses on people with RRMS who do not have HA or RES RRMS.

The evidence base on DRF is limited to this population, and this population aligns with the reimbursed population for the selected comparator for fast-track appraisal (FTA): DMF. DMF is the selected comparator due to the following rationale:

- DRF has demonstrated bioequivalence to DMF
- DMF is the most widely prescribed DMT for RRMS in NHS England with a significant active RRMS market share of [redacted] and market share of [redacted]% of the total market in all forms of MS combined (IQVIA HQA monthly hospital prescribing data, data on file)
- DMF is the predominant treatment DRF would displace if approved for use on the NHS

The decision problem addressed within this submission is presented in Table 2.

Table 2: The decision problem – B.1.1 (pages 7−8)

	Final scope issued by NICE/reference case	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with RRMS	People with RRMS who do not have HA or RES RRMS	NA (detail added for clarity)
Intervention	DRF	DRF	NA
Comparator(s)	• Beta interferon • DMF • Glatiramer acetate • Ocrelizumab (only if alemtuzumab is contraindicated or otherwise unsuitable) • Ofatumumab (subject to ongoing NICE appraisal) • Ozanimod (subject to ongoing NICE appraisal) • Peginterferon beta-1a • Ponesimod (subject to ongoing NICE appraisal) • Teriflunomide	• DMF	DMF provides an appropriate single comparator for cost-comparison as: • DMF is the most widely prescribed DMT for RRMS in NHS England • DMF is the predominant treatment DRF would displace, validated in a medical advisory board (section B1.3.5) • DMF is recommended for the population of relevance to this appraisal in TA320
Outcomes	• Relapse rate • Severity of relapse • Disability (for example, EDSS) • Disease progression • Symptoms of MS (such as fatigue, cognition and visual disturbance) • Subclinical disease activity (for example, MRI outcomes)	• Proportion with relapse • Annualised relapse rate • Disability (EDSS and T25FW) • Disease progression (CDW3M) • Freedom from disease activity (NEDA-3 and NEDA-4) • Subclinical disease activity (MRI outcomes)	Outcomes aligned to the EVOLVE clinical trial programme that provides pivotal trial evidence for DRF.

	• Mortality • Adverse effects of treatment • Health-related quality of life	• Adverse effects of treatment • Health-related quality of life (EQ-5D and SF-12)	
Economic analysis	NICE guidelines state that: *"A technology will be appraised through the fast-track appraisal process if a cost comparison case can be made that shows it is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance for the same indication."*	As efficacy is the same for DRF and DMF, a cost-comparison analysis was conducted, considering treatment-related costs only.	N/A
Subgroups to be considered	If the evidence allows, the following subgroups of patients will be considered: People who could not tolerate previous treatment		In line with most clinical trials in MS, which generally have this as part of the exclusion criteria, the EVOLVE programme did not generate evidence for this subgroup of patients. While these patients do comprise a relevant subgroup in clinical practice, this subgroup is therefore excluded due to a lack of evidence.
Key: CDW3M, confirmed disability worsening at 3 month; DMF, dimethyl fumarate; DMT, disease-modifying therapy; DRF, diroximel fumarate; EDSS, Expanded Disability Status Scale; EQ-5D, EuroQol-5 Dimension 5-level Questionnaire; HA, highly active; MRI, magnetic resonance imaging; NA, not applicable; NEDA-3, No Evidence of Disease Activity-3; NEDA-4, No Evidence of Disease Activity-4; RES, rapidly evolving severe; RRMS; relapsing–remitting multiple sclerosis; SF-12, Short Form Survey – 12 Item; T25FW, Timed 25-Foot Walk.			

A.5. Clinical effectiveness evidence

The trial programme supporting registration of DRF consists of:

1. Pre-clinical pharmacokinetic studies establishing bioequivalence of DRF to DMF (see Appendix I)
2. Clinical studies investigating the comparative short-term safety of DRF versus DMF and long-term safety and efficacy of DRF (EVOLVE-MS-1 and 2)
3. Clinical studies investigating the comparative safety and efficacy of DMF versus placebo and glatiramer acetate (GA) (CONFIRM, DEFINE, ENDORSE). DMF was appraised in 2014 by NICE,(8) and as such clinical evidence has not been presented in this submission

Clinical studies supporting registration are summarised in Table 3.

Table 3: Clinical effectiveness evidence – B.3.2 (pages 22-23)

	DRF studies	
Study title	EVOLVE-MS-1 (NCT02634307)(11)	EVOLVE-MS-2 (NCT03093324)(12)
Study design	Phase III, open-label, single-arm study	Phase III, randomised, double-blind, head-to-head, 5-week study
Population	Adults aged 18–65 years with a confirmed diagnosis of RRMS and who were neurologically stable with no evidence of relapse in the 30 days before screening.	Adults aged 18–65 years with a confirmed diagnosis of RRMS and who were neurologically stable with no evidence of relapse in the 30 days before screening.
Intervention(s)	De novo patients: • DRF 231 mg BID (Week 1) • DRF 462 mg BID (Weeks 2–96) Rollover patients from EVOLVE-MS-2: • DRF 462 mg BID over 96 weeks	• DRF 231 mg BID (Week 1) • DRF 462 mg BID (Weeks 2–5)
Comparator(s)	N/A	• DMF 120 mg BID (Week 1) • DMF 240 mg BID (Weeks 2–5)
Outcomes specified in the decision problem	• Relapse (ARR, MR relapse) • Disability (EDSS, T25FW) • Disease progression (CDW3M) • Freedom from disease activity (NEDA-3, NEDA-4) • Subclinical disease activity (MRI) • Adverse effects of treatment • Health-related quality of life (EQ-5D, SF-12)	• Adverse effects of treatment • Health-related quality of life (IGISIS, GGISIS)
Superiority, equivalence or non-inferiority trial?	Non-comparative	Superiority

Reference to section in submission	B.3.6.2 (pages 50-55) B.3.10.2 (pages 60-65) B3.10.3 (page 65-67) Appendix L.3	B.3.6.1 (pages 46-50) B.3.10.1 (pages 57-60)
Key: ARR, annualised relapse rate; BID, twice a day; CDW3M, confirmed disability worsening at 3 months; DMF, dimethyl fumarate; DRF, diroximel fumarate; EDSS, Expanded Disability Status Scale; EQ-5D-5L, EuroQol-5 Dimension 5-level Questionnaire; GGISIS, Global Gastrointestinal Symptom and Impact Scale; GI, gastrointestinal; IGISIS, Individual Gastrointestinal Symptom and Impact Scale; MS, multiple sclerosis; NA, not applicable; NEDA-3, No Evidence of Disease Activity-3; QoL, quality of life; RRMS, relapsing–remitting multiple sclerosis; T25FW, Timed 25-Foot Walk.		

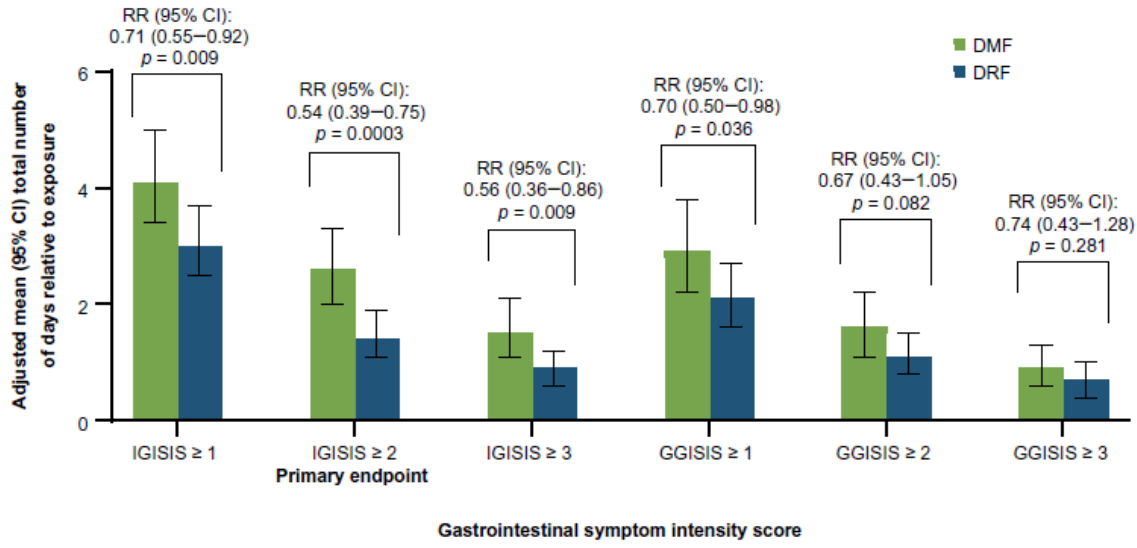
A.6. Key results of the clinical effectiveness evidence

A.6.1. Patient self-assessed GI tolerability, EVOLVE-MS-2

DRF met the primary endpoint of a statistically significant reduction in the number of days with a symptom intensity score ≥ 2 as measured by the patient-reported Individual Gastrointestinal Symptom and Impact Scale (IGISIS) with a 46% reduction compared with DMF (p = 0.0003), as presented in Figure 1.(12) Secondary endpoints exploring other measures of intensity as measured by the IGISIS and the patient-reported Global Gastrointestinal Symptom and Impact Scale (GGISIS) similarly showed favourable GI tolerability with DRF compared with DMF (Figure 1).

In patients with a worst IGISIS score ≥ 2, DRF was associated with a lower likelihood of experiencing GI symptoms that interfered with daily activities, led to missed work, or resulted in concomitant symptomatic medication use.(12) From a patient perspective, these clinically meaningful benefits could therefore positively impact HRQL.

Figure 1: Summary of primary and secondary endpoints, FAS population, EVOLVE-MS-2 – B.3.6.1.1 (page 47)



Key: CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; FAS, full analysis set; GGISIS, Global Gastrointestinal Symptom and Impact Scale; IGISIS, Individual Gastrointestinal Symptoms and Impact Scale; RR, rate ratio.
Source: Naismith et al. 2020.(12)

A.6.2. Relapse rates, EVOLVE-MS-1

A summary of the most recent MS relapse data from EVOLVE-MS-1 is provided in Table 4. Data are provided for the safety population defined as all patients who received at least one dose of DRF.

Overall, [redacted]% of patients did not experience a protocol-defined relapse (see notes in Table 4 for full definition) during the course of the study.(13) A total of [redacted]% of patients experienced between 1 and ≥ 4 relapses, with [redacted] experiencing 1 relapse; only [redacted]% of patients reported ≥ 4 relapses.

At Week 96, the adjusted annualised relapse rate (ARR) was [redacted], indicating a reduction in relapse rate compared with baseline (adjusted ARR in 12 months before study entry: 0.78 [95% CI: 0.72, 0.84](11)).(13) This is an important treatment goal for patients as relapses indicate an acute worsening of neurological function that subsequently impairs QoL in patients with RRMS, and relapses are thought to be associated with the development of residual effects.(14)

Table 4: Summary of MS relapse, Week 96, safety population, EVOLVE-MS-1 – B.3.6.2.1 & B.3.6.2.2 (pages 50-51)

	Total (N = 1,057)
Patients with relapse[a], n (%)	
0	[redacted]
1	[redacted]
2	[redacted]
3	[redacted]
≥ 4	[redacted]
Proportion of patients with relapse at Week 96, %	[redacted]
Total number of relapses	[redacted]

	Total (N = 1,057)
Adjusted ARR (95% CI)	[redacted]

Key: ARR, annualised relapse rate; CI, confidence interval; EDSS, Expanded Disability Status Scale; FS, functional systems; MS, multiple sclerosis.
Notes: Protocol-defined relapse consisted of new or recurrent neurological symptoms, not associated with fever or infection, lasting for at least 24 hours accompanied by one of the following: new objective neurological findings on examination by the treating neurologist that were functionally consistent with findings on the EDSS with an increase over the prior visit of ≥ 0.5 for the total score; an increase of ≥ 2 in 1 FS subscale scores, except bladder/cognitive changes; an increase of ≥ 1 in 2 FS subscale scores, except bladder/cognitive changes.
Source: EVOLVE-MS-1 CSR, 2020.(13)

A.6.3. Disability progression, EVOLVE-MS-1

A summary of EDSS scores over time is provided in Table 5. By Week 96, patients had a mean EDSS score of [redacted].(13) The EDSS scores remained consistent over the course of the study, with [redacted], supporting the sustained efficacy of DRF.

Table 5: Summary of EDSS scores, FAS population, EVOLVE-MS-1 – B.3.6.2.4 (pages 52-53)

	Total (N = 1,057)
Mean EDSS score (SD)	
Baseline	[redacted]
Week 12	[redacted]
Change from baseline	[redacted]
Week 24	[redacted]
Change from baseline	[redacted]
Week 36	[redacted]
Change from baseline	[redacted]
Week 48	[redacted]
Change from baseline	[redacted]
Week 60	[redacted]
Change from baseline	[redacted]
Week 72	[redacted]
Change from baseline	[redacted]
Week 84	[redacted]
Change from baseline	[redacted]

	Total (N = 1,057)
Week 96	[redacted]
Change from baseline	[redacted]
Key: EDSS, Expanded Disability Status Scale; FAS, full analysis set; N, number; SD, standard deviation. **Source:** EVOLVE-MS-1 CSR, 2020.(13)	

Confirmed disability progression is defined as the proportion of patients experiencing a worsening of ≥ 1.0 point in EDSS score from baseline (or 1.5 points if baseline EDSS is 0 or 0.5 points if baseline EDSS is 6) sustained for 12 weeks. Overall, just [redacted]% of patients had confirmed disability progression consistent with the stability of disease activity.(13)

Table 6: Summary of disability progression, FAS population, EVOLVE-MS-1 – B.3.6.2.5 (page 53)

	Total (N = 1,041)
Overall confirmed disability progression, n (%)	[redacted]
Time to disability progression, mean days (SD)	[redacted]
Proportion of patients with disability progression at each time point, %:	
Week 48	[redacted]
Week 60	[redacted]
Week 72	[redacted]
Week 84	[redacted]
Week 96	[redacted]
Key: FAS, full analysis set; N/n, number; SD, standard deviation. **Source:** EVOLVE-MS-1 CSR, 2020.(13)	

A.6.4. Patient self-assessed quality of life, EVOLVE-MS-1

Both the EuroQol-5 Dimension 5-level Questionnaire (EQ-5D-5L) and the Short Form Survey – 12 Item (SF-12) scores at baseline were similar across groups, and changes during the study were small and remained stable over time.(13) Overall, in the SF-12, there was a mean increase of [redacted] in the physical component score, while the mean mental component score showed a small decrease of [redacted] by Week 96. For the EQ-5D-5L, there was a mean decrease of [redacted] in the visual analogue scale (VAS) score and of [redacted] in the index score.

A.6.5. Safety outcomes, EVOLVE-MS-2

Overall, adverse events (AEs) were reported in 81% of patients in EVOLVE-MS-2: 78.3% of patients receiving DRF and 83.7% of patients receiving DMF.(12) Most AEs were mild to moderate in severity (DRF: 97.5% versus DMF: 93.3%). The overall rate of serious AEs (SAEs) was low, and none were related to the study drug. No deaths were reported. In DRF-treated patients, four AEs leading to discontinuation were reported, compared with 14 in the DMF-treated patients; of these, two and 12, respectively, were GI AEs.

GI AEs were among the most frequently reported: 34.8% in the DRF treatment group and 49.0% in the DMF treatment group.(12) In particular, GI AEs associated with an upper GI location appeared to be reported with less frequency in patients treated with DRF compared with in patients treated with DMF. Flushing was reported in 36.7% of patients overall (DRF: 32.8%; DMF: 40.6%).

A.6.6. Safety outcomes, EVOLVE-MS-1

Overall, [redacted]% of patients experienced at least one AE in EVOLVE-MS-1, with most considered mild ([redacted]%) or moderate ([redacted]%) in severity; [redacted]% were considered related to the study treatment as assessed by the investigator.(13) AEs with the highest incidence (≥ 10% of overall patients) were [redacted] followed by [redacted] and [redacted]

SAEs were experienced by [redacted]% of patients: [redacted] patients had SAEs of [redacted], and other SAEs occurring in more than one patient were [redacted](13) [redacted] died: [redacted].

GI treatment emergent adverse events (TEAEs) occurred in [redacted] of all patients, with the most commonly experienced AEs (≥ 5% of patients in any groups) being [redacted].(13) SAEs occurred in [redacted] of all patients and included [redacted] In [redacted]% of patients, GI AEs were considered related to the study treatment by the investigator, while in [redacted]% of patients, AEs led to a dose reduction or temporary interruption of the study treatment.

A.7. Evidence synthesis

Although DRF has received positive CHMP opinion to treat RRMS based on proven bioequivalence to DMF, formal indirect treatment comparison of the two fumarates has been explored. Specifically, a PSM analysis was conducted utilising 48 Week patient level data from the EVOLVE-MS-1 and DEFINE, CONFIRM and ENDORSE trials.(15)

Results of the PSM analysis for efficacy outcomes of Gd+ lesion count, new/newly enlarging T2 hyperintense lesion count, and ARR are summarised in B.3.9 – Table 24. There was no evidence of difference in efficacy after 1 year of treatment between DRF and DMF.(15) These data support the underlying assumptions of a similar efficacy profile for DRF and DMF due to their bioequivalence.

A.8. Overview of the cost-comparison analysis

The objective of this analysis was to evaluate the costs associated with DRF versus DMF for the treatment of RRMS from a UK (England and Wales) healthcare system perspective. No economic model has been submitted as the comparison is primarily based on drug acquisition costs. In past economic models where first line treatments are compared, a lower discontinuation rate in the intervention (DRF) versus comparator (DMF) groups would lead to higher lifetime overall costs in the former versus the latter as patients discontinue to no treatment (incurring no further drug costs). This is artificial since typically, patients would transition onto subsequent treatments following discontinuation from first line; however the complexity of modelling treatment sequences is not warranted in this case. Medicine acquisition cost (list price and PAS) for DRF and DMF are provided in Table 7.

Table 7: Acquisition costs of the intervention and comparator technologies

	DRF	DMF
Pharmaceutical formulation	Gastro-resistant capsules (231 mg)	Gastro-resistant capsules (120 mg, 240 mg)
(Anticipated) care setting	Primary care (patients take at home)	Primary care (patients take at home)
Acquisition cost (list price) (excluding VAT)	£17,849 per year	£17,849 per year
PAS discount	[redacted]	[redacted]
Net price (including PAS discount)	[redacted]	[redacted]
Method of administration	Oral	Oral
Doses/dosing frequency	231 mg twice daily for 7 days 426 mg twice daily thereafter	120 mg twice daily for 7 days 240 mg twice daily thereafter
Dose adjustments	Temporary dose reductions to 231 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended dose of 462 mg twice a day should be resumed	Temporary dose reduction to 120 mg twice a day may reduce the occurrence of flushing and gastrointestinal adverse reactions. Within 1 month, the recommended maintenance dose of 240 mg twice a day should be resumed

Key: DMF, dimethyl fumarate; DRF, diroximel fumarate; mg, milligrams; PAS, patient access scheme.

A.9. Interpretation and conclusions of the evidence

MS is a progressive, lifelong disease that requires lifelong management. It is important to have multiple treatment options available to help physicians and patients manage RRMS over their lifetime. Considering all pre-clinical and clinical data, DRF provides comparable health benefits and safety to DMF, with the potential for improved GI tolerability.

Moreover, the cost-comparison analysis conducted demonstrates that DRF results in incremental [redacted] of [redacted] per patient annually due to [redacted]. Therefore, DRF offers RRMS patients the potential to achieve similar, or improved outcomes (including improved GI tolerability), compared to DMF[redacted]. The robust economic benefits (in addition to the clinical benefits) of DRF are represented by the clear value for money for the NHS in using DRF to treat adults with RRMS..

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	MS Society
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Society is the UK's largest MS charity, with 26,000 members across the UK, 5,500 volunteers, over 260 local groups supporting people with MS, and over 300 employees. Our ultimate goal is to find a cure. Until then, we're working to make sure no one has to face MS alone. We are a registered charity, with the vast majority of our income coming from individual and philanthropic donations and legacies.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	From the manufacturer of the technology: The MS Society received an Educational Grant to the value of £91,902 from Biogen for our MS Active Together project, and funding of £7,166 from Biogen for our Core Case for Investment in MS project. From the manufacturers of the comparator products as listed in the current appraisal matrix: We received a £30,000 Grant for MS Special Nurses, and a £5000 grant for the UK MS Register from Merck. We received a £31,451 grant for our MS Specialist Helpline Nurses and a £25,645 grant for our MS Helpline from Novartis Pharmaceuticals We received a £7,166 grant for our Core Case for Investment Project, and a £25,000 Grant towards general Helpline for our Covid Rapid Response Appeal from Roche

	We received a £7,166 grant for our Core Case for Investment Project, and a £12,834 grant for our MS Specialist Helpline Nurses from Sanofi Genzyme
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have knowledge of the views and needs of people with MS gained from years of working alongside them and their carers, and from collecting evidence about their experiences. For this submission, we drew on our 2019 My MS My Needs survey of the experiences of people with MS in the UK (1), on our 2019 Friends and Family survey (2) of people supporting those with MS in the UK, on the experiences of those who have used the related disease modifying therapy (DMT) dimethyl fumarate, and on the results of an MS Society funded project that aimed to understand DMT treatment decisions from the perspective of people with relapsing remitting MS, the CRIMSON review (3). 1. https://www.mssociety.org.uk/sites/default/files/2020-08/MMMN3-UK-report.pdf 2. https://www.mssociety.org.uk/sites/default/files/2020-08/MS-family-and-friends-2019-survey-findings.pdf 3. Understanding treatment decisions from the perspective of people with relapsing remitting multiple Sclerosis: A critical interpretive synthesis - Multiple Sclerosis and Related Disorders (msard-journal.com)
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	More than 130,000 people in the UK live with MS, and nearly 7,000 people are newly diagnosed each year. This means around 1 in every 500 people in the UK has MS, and that each week over 130 people are diagnosed with MS. MS is the most common disabling neurological condition of young adults, and one of the most common in adults of working age. In the UK people are mostly commonly diagnosed in their thirties, forties and fifties, although the first signs of MS often start years earlier. MS affects two to three times as many women as men. MS can be relentless, painful and exhausting. It can make it harder to do everyday things like walk, talk, eat and think. Symptoms can fluctuate, making life unpredictable. They can include loss of balance, stiffness, spasms, speech problems, fatigue, pain, bladder and bowel, and vision problems.

	Living with a chronic, disabling and degenerative condition such as MS is hard. It is also expensive. There are often substantial extra costs, such as accessible transport, specialist equipment, medication and help with household activities – a neurological condition like MS can cost, on average, an additional £200 a week (4). Around 85% of people with multiple sclerosis are first diagnosed with relapsing remitting MS, enduring attacks of new and old symptoms. A relapse is defined as an episode of neurological symptoms which lasts for at least 24 hours and occurs at least 30 days after the onset of any previous episode. Symptoms may last from weeks to months. Relapses can vary from mild to severe. Some acute relapses may require hospital treatment, whilst many relapses are managed at home with the support of healthcare professionals. People with MS can experience a wide range of distressing and debilitating symptoms from fatigue to visual impairment, mobility problems to cognitive problems. Around half of all relapses can leave a range of residual problems. Evidence has highlighted that disability also progresses regardless of whether a person experiences relapse regularly (5). These are further important reasons to reduce the frequency and severity of relapses through ensuring that those who are eligible find the best treatment for them as soon as possible. Relapses can have a resonating emotional impact on a person. The loss of independence that can often come with a relapse mean that people can often feel a burden on their family. Relapses are often unpredictable and distressing, leaving people feeling frustrated, anxious and causing disruption to everyday life. The majority of people with MS experience a progression of disability over the course of the condition. It is estimated that approximately 65% of people with relapsing MS will eventually go on to develop secondary progressive MS 15 years after being diagnosed. Progressive forms of MS are characterised by a sustained accumulation of disability independent of relapses. People with MS live with great uncertainty, not knowing from one day to the next whether they will be able to move, to see or to live even a remotely normal life. As each person's response to DMTs is different, more effective options available on the NHS will result in more people finding a treatment which best suits them. Impact on Carers The progressive, fluctuating nature of MS presents particular challenges to families and carers. It can make balancing work, education and taking care of one's own health and wellbeing difficult. Our 2019 My MS My Needs survey found 32% of people living with MS hadn't received the care and support they needed to assist with daily living in the prior year (1).

	Of those, 40% relied on unpaid care from family members and friends to some extent. The care and support people required ranged from help to complete essential day-to-day tasks – such as washing and dressing, preparing meals, and administering medications – often alongside support to leave the house, socialise and 'mop and shop' tasks. Of those with unmet care needs, many had also experienced deteriorating health (58%) or felt lonely/isolated (65%) over the same time period. A significant minority (21%) had been unable to work. The survey found that the complexity of these needs increases with age, as the disease progresses. Treatments that slow the progression of disability therefore not only benefit the person with MS, but impact on their carer too. Our 2019 Friends and family survey (2) found 41% of respondents spent the equivalent of a full-time job or more each week supporting someone with MS. An overwhelming 90% of respondents reported negative impacts on their health and wellbeing, which is even more concerning considering that 40% of respondents were living with a long-term condition themselves. The fluctuating and progressive nature of MS adds a degree of complexity to their lives, as they may not know from one week to the next what support that person with MS will need. That can make juggling paid work and caring very difficult, which 60% of working-age respondents are doing. 4. Extra Costs Commission. Driving down the costs disabled people face: Final report, June 2015, pp. 13. 5. Giovanni et al, 'Brain health: Time Matters in Multiple Sclerosis', 2015
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Our 2019 "My MS My Needs" survey showed that people with MS report a variation in the standard of care they receive (1). There is a marked variation around the UK in the proportion of people with MS on a DMT, of those suitable to receive one. Whilst 81% of those eligible to receive a DMT in Northern Ireland are taking one, this is true for just 52% of those in Wales.

	The survey also showed a striking variation in ability to access healthcare professionals. 89% of people with MS had both needed to, and been able to, access an MS nurse withing the last year. However, this varies across the nations of the UK by 18 percentage points, from 75-93%. The survey showed that only 16% of people with MS had a care plan, whilst 23% would like one but do not have one at present. Whilst 55% said the professionals involved in their care worked well together completely or to some extent, 16 % said they didn't work well together at all. The survey showed that, across the UK, 60% of those who could benefit from a DMT are currently taking one. This is an improvement from the previous My MS My Needs survey of 2016, when the figure was 56%. There was a clear link between access to healthcare professionals and DMT use; amongst those who could benefit from a DMT who had not seen a specialist MS nurse or neurologist in the past year, just 17% were taking a DMT, compared to 65% of those who had seen a specialist within the past year.
8. Is there an unmet need for patients with this condition?	Those living with relapsing remitting MS now have access to a variety of treatment options including over a dozen DMTs available on the NHS. However, they can still face difficult choices when they come to consider the risks and benefits of the different interventions for their condition. Existing treatments for MS may have side effects that have a considerable effect on quality of life, meaning individual patients may be unable to tolerate them or may choose not to receive them. Considering that many people with relapsing MS may need to switch to an alternative DMT during the course of their disease, there remains a need for novel effective DMTs with a good side effect and safety profile for relapsing MS. One person with MS we spoke to, Lorraine, emphasised the importance of day-to-day side effects in choice and compliance in DMT use, saying that "*it's a very important part of decision making on whether you are prepared to take the medicine in the first place as well as being able to cope with medicine in the longer term"*. She stated that she had made the decision not to commence some DMTs due to her concern over safety profiles, and had switched DMT several times due to side effects which "*impacted my home life, my work life and my ability to get on with my day".* She went on to say that "*medicines with a more tolerable side effect profile are very very important. Medicine side effects impact the choice of medicine people will take meaning some really effective medicines won't be taken, for a good reason".*

	Patient decisions on which DMT to take are determined by a variety of factors including eligibility, efficacy, side effects, the method and frequency of administration, and lifestyle factors. Each DMT carries with it different levels of efficacy and risk. The more effective treatments that are available, the greater the choice for patients and the greater the likelihood that individuals will find a DMT that works for them. Lorraine stated that it is *"essential there is a suite of medicine as people react to the medicines differently, both in whether they think the risk/benefit is appropriate for them and if they can tolerate the side effects as well as how well the medicines work for them at that time it their MS journey……it's very easy to dismiss improvement in side effect profile if it's not you actually with the choice on which to use or actually having to tolerate the side effects"* Within the currently available DMT treatment range, oral options are limited, and people with relapsing MS would benefit from any further safe and effective oral alternative. New treatment options which do not require clinic or hospital appointments to administer have an obvious advantage, potentially reducing pressure on NHS services.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Whilst we were not able to speak to anyone with MS who has used diroximel fumarate, we drew on the general experience of people with MS who have used DMTs, including those who have used the related drug dimethyl fumarate. As mentioned, we also drew on the results of an MS Society funded project that aimed to understand DMT treatment decisions from the perspective of people with relapsing remitting MS, and our 2019 My MS My Needs survey. When it comes to making decisions on DMTs, outcomes important to people with MS include a reduction in relapse rate, the slowing of disability progression, and a reduction in evidence of active disease. People with MS also emphasise ease and convenience of use, effect on lifestyle, safety and side effects as being important considerations. They may face complex choices in balancing up both the safety of an individual DMT and its effect on quality of life with the overall benefit derived from taking the drug. Day-to-day side effects were seen as relating to drug compliance by some people with MS. Perceptions of the safety of an individual DMT may be viewed as distinct from its effect on day-to-day effect on quality of life and lifestyle.

	We understand that diroximel fumarate and dimethyl fumarate have the same active metabolite, with both drugs converted to monomethyl fumarate in the body, and that they may reasonably be expected to have a similar therapeutic effect. Diroximel fumarate has been shown in Phase III clinical trial (EVOLVE-MS-1, 6) to reduce the number of new lesions on MRI, as compared to placebo, in relapsing remitting MS. Annualized relapse rates at 48 weeks were low. A further head-to-head Phase III clinical trial (EVOLVE-MS-2,7) comparing diroximel fumarate with dimethyl fumarate showed lower rates of gastrointestinal side effects for diroximel fumarate, with significantly fewer patients discontinuing diroximel fumarate than dimethyl fumarate due adverse events, and gastrointestinal adverse events. Our 2019 My MS My Needs survey (1) found that, of those patients currently being treated with a disease modifying therapy, one in four were using dimethyl fumarate. Given the importance of a favourable DMT side effect profile to people with MS, a similar drug of equivalent efficacy which caused fewer gastrointestinal side effects would clearly be of benefit to a significant number of those with relapsing MS. A further post-hoc analysis of EVOLVE-MS-2 (8) assessed the impact of gastrointestinal tolerability events on quality of life for patients with relapsing–remitting MS who received diroximel fumarate or dimethyl fumarate. Diroximel fumarate showed improved gastrointestinal tolerability. In particular, with diroximel fumarate, gastrointestinal symptoms were less likely to interfere with regular daily activities or work productivity. The CRIMSON review (3) indicated that whilst DMTs may allow people with MS to participate in the workplace, DMT treatment-related side effects may burden the experience of paid work for people with MS and are likely to play a role in decisions not to start, or to delay at DMT, or on which DMTs to take. Provided that efficacy is equivalent, a treatment proven to reduce impact on work productivity and daily activities relative to a comparator is likely to be of benefit to people with MS. Whilst people with MS described gastrointestinal side effects they had experienced with dimethyl fumarate; some emphasised the bothersome nature of the “flushing” sometimes experienced whilst on this treatment. People with MS require a range of safe and effective treatments which they can take in a way that suits their clinical needs and lifestyle. If made available, diroximel fumarate would represent a new and potentially more tolerable oral option for patients with relapsing remitting MS.

	Whilst oral treatment options may not be suitable for all, many people with MS tell us about the convenience of DMTs that can be taken at home. For people with MS of working age and for those with limited mobility, taking time out of work or the need to travel to attend hospital appointments can sometimes be challenging. 6. Diroximel fumarate (diroximel fumarate) in patients with relapsing-remitting multiple sclerosis: Interim safety and efficacy results from the phase 3 EVOLVE-MS-1 study - PubMed (nih.gov) 7. Diroximel Fumarate Demonstrates an Improved Gastrointestinal Tolerability Profile Compared with Dimethyl Fumarate in Patients with Relapsing-Remitting Multiple Sclerosis: Results from the Randomized, Double-Blind, Phase III EVOLVE-MS-2 Study - PubMed (nih.gov) 8. Improved gastrointestinal profile with diroximel fumarate is associated with a positive impact on quality of life compared with dimethyl fumarate: results from the randomized, double-blind, phase III EVOLVE-MS-2 study (nih.gov)
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As noted above, for some people with MS who are of working age, and for some of those with limited mobility, or finances, time away from work or the need to travel to hospital can be challenging. Some of these people may benefit from the availability of another treatment option which can be taken at home.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	MS affects two to three times as many women as men. Any decision that resulted in a reduction in the available treatment options for people with MS would have a disproportionate effect on women.

Other issues	
13. There are numerous treatment options for relapsing – remitting MS. What factors would influence a patient's choice of therapy?	This was covered previously in the submission.
14. Are there any other issues that you would like the committee to consider?	

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- DMT decision making can be complex. The more effective treatment options for people with relapsing remitting MS that are available, the greater the choice for patients and the greater the likelihood that individuals will find a DMT that works for them.

- Within the currently available DMT treatment range, oral options are limited, and people with relapsing MS would benefit from any further safe and effective oral alternative.

- Our 2019 My MS My Needs survey (1) found that, of those patients currently being treated with a disease modifying therapy, fully one in four were using dimethyl fumarate. Given the importance of a favourable DMT side effect profile to people with MS, a similar drug of equivalent efficacy which caused fewer gastrointestinal side effects would clearly be of benefit to a significant number of those with relapsing MS.

Thank you for your time.

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NICE National Institute for Health and Care Excellence

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- Your response should not be longer than 10 pages.

About you	
1.Your name	[redacted]

2. Name of organisation	Multiple Sclerosis Trust
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	The MS Trust is a UK charity dedicated to making life better for anyone affected by MS. 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. Our core belief is that the best outcomes will come from well-informed people with MS making decisions in partnership with their specialist health professionals, and our aim is to support both sides of this partnership as much as we can. We provide expert information to help people with MS manage their own condition, and, uniquely, we inform and educate the health and social care professionals who work with them about best practice in MS treatment and care. We receive no government funding. We are not a membership organisation. We rely on donations, fundraising and gifts in wills to fund our services.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**Bayer** – no funding **Biogen** – £344.00 – advisory board **Celgene/BristolMyersSquibb** – no funding **Genzyme/Sanofi** – £36,000 – mapping MS services **Merck** – £400 – advisory board **Mylan** – no funding **Novartis** – £10,385 – advisory board; conference/study day **Teva** – no funding **Roche** – £50,000 – funding for specialist nurse programme

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	We have prepared this submission based on our experience of supporting people affected by MS at all stages of the condition. 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, concern about switching to a new disease modifying drug (DMD), dealing with difficulties of self-injection or side effects, and coping with physical and financial consequences of relapses. Since diroximel fumarate is not currently available in the UK and clinical trials have not taken place in the UK, we have not been able to speak to anyone who has direct experience of taking this medicine. Instead, we have gathered feedback from people taking other disease modifying drugs. Their experiences provide a valuable personal perspective of being diagnosed with relapsing remitting MS, the issues around taking a disease modifying drug and how this affects their daily lives.
Living with the condition	
6. What is it like to live with the condition? What do carers	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. It is a complex and unpredictable condition which has an impact on all aspects of life - physical, emotional, social and economic. These are profoundly important not just for the person diagnosed with MS, but for their families as well and not taken account of in cost effectiveness calculations.

experience when caring for someone with the condition?	MS is sometimes mild, frequently relapsing remitting, but often progressive with gradually increasing disability. Although the degree of disability will vary, the uncertainty is universal. Even in the early stages of MS, cognition, quality of life, day-to-day activities and the ability to work can be markedly affected. As the disease progresses, increasing disability – such as difficulties in walking – imposes a heavy burden on people with MS and on their families, who often act as informal carers. It also leads to substantial economic losses for society, owing to diminished working capacity. Good management of MS can be a huge challenge to health professionals because the disease course is unpredictable, symptoms endlessly variable and the psychosocial consequences can impact as severely as the physical symptoms. People with MS require health services that are responsive to this breadth of need and which take a holistic view of the condition including its impact on the individual and their carers. Approximately 80% of people with MS will have relapsing remitting MS (RRMS). 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 obvious symptoms. Many of these invisible symptoms are sensitive areas and can be difficult to recognise or talk about, putting an extra burden on a person with MS to deal with on their own. 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 the effects of 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. For example, a 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 with disease modifying drugs (DMDs) early in the disease to prevent axonal damage and irreversible disability. Current practice in the management of RRMS is active and acknowledges that if people with MS continue to have relapses while on therapy, this should prompt a discussion about switching treatments. State of the art approach to treating relapsing remitting MS aspires to minimal or no evidence of disease activity; signs of MS activity trigger a treatment review and escalation to an alternative disease modifying drug is considered. A treatment which either eliminates or reduces the frequency and severity of relapses is a major benefit for people affected by relapsing forms of MS.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	MS care involves a mix of clinical management of symptoms, responsive services to manage relapses and other acute deteriorations, therapies including physiotherapy and occupational therapy, tailored, evidence-based information, support for effective self-management and, for those with RRMS, access to the range of DMDs and support to make the choice that is right for their condition, their lifestyle and their treatment goals. The majority of people with RRMS are eager to start treatment with one of the DMDs and

	aware of the importance of starting treatment soon after diagnosis. A number of DMDs are available for relapsing remitting MS: • beta interferons • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • cladribine • ocrelizumab • ofatumumab • natalizumab • alemtuzumab The impact of relapses has been outlined in the previous section of this submission. All of these treatments are effective at reducing the frequency of relapses and the severity of relapses that do occur. It is not possible to say which of these treatments are preferred; the widening range of DMDs gives greater scope for personalised treatments. If MS remains active despite taking one of the DMDs there is more potential to switch to a treatment with a different mechanism of action. Different responses to DMDs from one person to another are not easily captured in clinical trial data but are important to address in clinical practice. Through different aspects of our work with people affected by MS, we are aware that a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Other issues will also be important such as the number of years a drug has been in routine use, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes

	account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. During the coronavirus pandemic, patients needing to attend a hospital outpatient clinic for infusions or for monitoring have faced cancellation or postponement of planned treatments. This has been a cause of concern for those affected; treatments which are taken at home, require minimal testing for potential side effects, and do not need initial training and supervision of injection technique will avoid delays in starting treatment, avoid treatment interruption and minimize demands on NHS services. People with MS rely heavily on their MS specialist team to provide information and guidance to help with treatment choices. MS teams are skilled and experienced in helping an individual make the choice that is the best match for their level of disease activity, their personal circumstances, their attitude to risk and their treatment goals.
8. Is there an unmet need for patients with this condition?	The most significant unmet need for people with MS is a cure. In the absence of a cure, people with MS want to live a life free from the impact of their disease. For many people, the ultimate goal of taking one of the DMDs is to reduce their risk of disease progression and future disability. Inevitably, the frequency and severity of relapses rank highly for those with RRMS, not just for the disruption and distress that relapses cause, but also because of the risk of residual disability and increased chances of conversion to secondary progressive MS. Ranking the impact of individual symptoms is difficult and ultimately inadequate as the condition varies so widely between individuals. People with MS are increasingly aware of the significance of reducing or eliminating signs of sub-clinical disease activity in improving long term outcomes. There is a growing recognition that regular clinical evaluation and regular MRI scans are required to fully assess MS activity and response to DMDs. For those people with very active relapsing MS - either rapidly evolving severe or highly active despite treatment - the side effects associated with the current, more effective DMDs are a cause for concern, for example the risk of PML with natalizumab and secondary autoimmune conditions with alemtuzumab. For people with very active relapsing MS, the option to switch to a more effective DMD with minimal or reversible side effects would be a major benefit. Remaining in employment is of critical importance to people with MS. Within 10 years of diagnosis, around 50% of people with MS will have left employment, with all the associated financial, social and

	psychological consequences. Cost effectiveness calculations do not take account of the burden of loss of employment on the individual, their family and society.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	Diroximel fumarate is similar to dimethyl fumarate; both drugs are converted to the active metabolite monomethyl fumarate. At the anticipated dose of 462 mg, diroximel fumarate is bioequivalent to dimethyl fumarate 240 mg. In terms of reduction of relapse rate and disability progression, diroximel fumarate is expected to have efficacy equivalent to dimethyl fumarate. Dimethyl fumarate is a well-established treatment; the benefit-risk profile is well known; it is widely prescribed; and MS teams have built up extensive experience of managing patients on this treatment. Experience gained from dimethyl fumarate will support the introduction of diroximel fumarate. Although dimethyl fumarate has proven to be an effective first line treatment, a significant proportion of patients discontinue treatment because of gastrointestinal side effects. Because diroximel fumarate has been shown to cause fewer gastrointestinal side effects, it offers a significant improvement over dimethyl fumarate, while retaining similar levels of effectiveness, ease of use; this is likely to lead to improved adherence and reduced discontinuation.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	There will always be individual preferences about route of administration, benefit and risk balance and practicalities linked to daily routines. Compared to dimethyl fumarate, gastrointestinal side effects are reduced but not eliminated and may continue to be a problem for some people. In a real-world, retrospective study 3.8% (6/160) of patients discontinued diroximel fumarate because of gastrointestinal side effects[1]. However, this is less than has been reported for dimethyl fumarate and other disease modifying drugs.

[1] Liseno J, et al.. Multiple Sclerosis Patients Treated With Diroximel Fumarate in the Real-World Setting Have High Rates of Persistence and Adherence. Neurol Ther. 2021 Apr 12. doi: 10.1007/s40120-021-00242-7.

	Flushing continues to be a problem for people taking diroximel fumarate, in common with dimethyl fumarate. For most people, flushing is mild to moderate, reduces after the first month of treatment and is less likely to lead to discontinuation compared to gastrointestinal side effects. Compared to once daily dosing, twice daily dosing is associated with lower adherence[2].
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	None that we are aware of.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	None that we are aware of.

[2] Coleman CI, et al. Dosing frequency and medication adherence in chronic disease. J Manag Care Pharm. 2012 Sep;18(7):527-39.

Other issues	
13. There are numerous treatment options for relapsing – remitting MS. What factors would influence a patient's choice of therapy?	We would challenge the assertion that there are numerous treatment options for relapsing remitting MS. There is a growing list of treatment options for relapsing remitting MS but the committee will be aware that indications, NICE guidance and NHSEngland prescribing criteria significantly reduce the options available to an individual at any particular stage of their MS. In addition, a patient may have other circumstances, such as pre-existing conditions or level of MS activity, which rule out treatment options. As noted above, a very wide range of factors can contribute to an individual's preferences for treatments. The balance between effectiveness of a drug (reduction in relapses) and the risk of side effects are key factors, as is evidence of their effect on the underlying course of the condition and their impact on disease progression. Attitudes to side effects vary widely: some people cannot tolerate persistent, mild but reversible side effects but are prepared to trade-off efficacy against the risk of a rare but more serious side effect, while more risk-averse people will take the opposite view. Issues which are also important include the number of years a drug has been in routine use, options for second-line treatment, route of administration, tolerability and the impact it has on daily life, family and work commitments or plans to start a family. Shared decision making which takes account of personal preferences and clinical advice will result in selection of a treatment that is best for an individual. This in turn leads to greater adherence and, consequently, effectiveness of the DMD. For a recent survey, we asked people with MS what was important to them when making a choice between disease modifying drugs. A selection of the answers gives an impression of the range of criteria which people apply: "I would like to know all my options; the side effects, the results they have so far from people, how long they stay in my system, their effect on fertility etc. all in depth. It is a huge decision." "How the drug is stored and how easy it is to travel with was a serious consideration for me." "One of the factors in making my decision was reversibility of the effect." "With each relapse came a reminder that I have a progressive neurological disease that I can't control and the emotions I had experienced at diagnosis came back. The care, patience and understanding of my MS team has been amazing and now that I am settled on a new drug things are looking up. It is very

	reassuring to know going forward that if my MS takes another unexpected turn there are still other treatment options out there." As already noted, new unanticipated factors can emerge, such as recent concerns about exposure to infections in hospital clinics or blunted effectiveness of vaccinations. A wide range of DMDs gives greater scope for accommodating new factors which might influence a patient's choice of treatment.
14. Are there any other issues that you would like the committee to consider?	The oral route of administration means that diroximel fumarate can be taken at home, without any need for training or supervision, eliminating potential delays in starting treatment which has occurred with DMDs which require access to outpatient clinics or training in how to inject. Overall, this route of administration minimises demands on NHS services and is strongly preferred over self-injection. At-home treatment avoids the risk of exposure to infections, which has emerged as a significant concern for patients during the coronavirus pandemic. Given the heterogeneous nature of MS, both in disease course and in response to treatments, a broadening range of drugs which work in different ways increases the potential for personalisation of treatment.

Key messages

15. In up to 5 bullet points, please summarise the key messages of your submission:

- Diroximel fumarate shows efficacy comparable to dimethyl fumarate, a well-established treatment for relapsing remitting MS, but with fewer gastrointestinal side effects
- Twice daily, at-home oral route of administration aids adherence, minimises service usage, delays in starting treatment and exposure to infection
- Improved quality of life, reduced steroid administration and fewer hospital admissions (resulting from lower relapse rate)
- MS is a complex and unpredictable condition which has an impact on all aspects of life, early proactive treatment is essential to prevent future disability.

- Given the heterogeneous nature of MS, both in disease course and in response to treatments, adding diroximel fumarate to the range of disease modifying treatments gives greater scope for personalisation of treatment.

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	Association of British Neurologists

3. Job title or position	Consultant Neurologist
4. Are you (please tick all that apply):	☐ **x** an employee or representative of a healthcare professional organisation that represents clinicians? ☐ **x** a specialist in the treatment of people with this condition? ☐ **x** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	The Association of British Neurologists is a professional organisation which aims to promote excellent standards of care and champion high-quality education and world-class research in neurology. It is a registered charity funded by the subscriptions of its members.
5b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	The Association of British Neurologists has received financial sponsorship for its annual educational conferences from Biogen, Novartis, Roche, Sanofi Genzyme and Teva.

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To prevent relapse and disability progression
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	To be at least as effective as the currently licensed treatments – i.e., a reduction in annualised relapse rate of at least 30%.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, there are several unmet needs including that none of the currently available disease modifying therapies are completely effective or safe/tolerated.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	Relapsing remitting multiple sclerosis may currently be treated with the following disease-modifying therapies subject to prescribing guidelines: alemtuzumab, beta interferon, cladribine, dimethyl fumarate, fingolimod, glatiramer acetate, natalizumab, ocrelizumab, ofatumumab, teriflunomide. It may also be treated with drugs for symptomatic management and physical rehabilitation.
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Yes, the NHS England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies (2019) provides guidance on the treatment of multiple sclerosis with disease-modifying therapies. The NICE clinical guideline “Multiple sclerosis in adults: management” (2014) also provides guidance on management including symptomatic treatments but does not cover disease-modifying therapies.
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please	To some extent but there are variations in care. The NHSE England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies provides a framework to aid decision-making for multiple sclerosis specialists and to help reduce excessive variation in practice, but it is understood that different experts may reasonably hold different views.

state if your experience is from outside England.)	
• What impact would the technology have on the current pathway of care?	It would provide a useful treatment option within the pathway, particularly for patients requiring an oral therapy and who may have difficulty tolerating dimethyl fumarate due to gastrointestinal side effects. Currently, the options for oral first-line therapies are limited to just Teriflunomide (which has a large blood monitoring burden within the first 6 months of treatment, requires an accelerated elimination procedure for women wishing to become pregnant after treatment, and has the lowest efficacy of the oral therapies) and Dimethyl Fumarate (which may not be tolerated due to gastrointestinal and other side effects). Oral therapies are often the preferred choice of patients for first-line treatment and there is an unmet need to have additional oral therapies with improved tolerability. Diroximel fumarate would help meet this need.
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Diroximel fumarate 462 mg and dimethyl fumarate 240 mg produce bioequivalent exposure of the active metabolite monomethyl fumarate. Therefore, diroximel fumarate is expected to have similar efficacy and safety profiles to dimethyl fumarate. Interim findings from the open-label EVOLVE-MS-1 study (Naismith, RT et al. *Multiple Sclerosis Journal* 2020;26:1729–1739) suggest it has a favourable efficacy/safety profile. It is not yet used in NHS clinical practice but it is expected to be used as an alternative to dimethyl fumarate.
• How does healthcare resource use differ between the technology and current care?	There is expected to be no difference in healthcare resource use between diroximel fumarate and dimethyl fumarate, subject to whether the marketing authorisation and the cost of the drug will be the same for both drugs.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	In specialist multiple sclerosis clinics

• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. In the randomised controlled EVOLVE-MS-2 study (Naismith, RT et al. CNS Drugs 2020;34:185–196), people treated with diroximel fumarate reported less severe gastrointestinal events lasting fewer days compared with people treated with dimethyl fumarate and had lower rates of treatment discontinuation due to gastrointestinal adverse events.
• Do you expect the technology to increase length of life more than current care?	No
• Do you expect the technology to increase health-related quality of life more than current care?	Yes. In the EVOLVE-MS-2 study, people treated with diroximel fumarate experienced less impact on daily life and work and required less concomitant symptomatic medication use than people treated with dimethyl fumarate (Wundes, A et al. *Ther Adv Neurol Disord* 2021;14:1–14).
12. Are there any groups of people for whom the technology would be more or	There should be no difference in efficacy for any group of people. It may be more appropriate to use, rather than dimethyl fumarate, in people with pre-existing gastro-intestinal symptoms or who have been unable to tolerate dimethyl fumarate.

less effective (or appropriate) than the general population?	
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	No. The ease of use and practical implications should be the same as for dimethyl fumarate

14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Stopping and starting criteria should be the same as for other first-line disease-modifying therapies for relapsing-remitting multiple sclerosis as outlined in the NHS England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Diroximel fumarate has been reported to increase quality of life compared with dimethyl fumarate which may improve QALY. As well as improving overall health, it could reduce the burden on healthcare resources. Reducing the need to switch therapy for tolerance reduces the time spent by specialist MS services in addressing this. Reducing gastrointestinal side effects reduces the time and money spent on prescribing symptomatic medication.
16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Although it is not expected to have a substantial impact for the whole relapsing-remitting multiple sclerosis population, it may provide significant health-related benefits to patients who have poor gastrointestinal tolerability of dimethyl fumarate. It will help meet the unmet need to have additional options for oral first-line therapies with improved tolerability.

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	No
• Does the use of the technology address any particular unmet need of the patient population?	It addresses the need of patients who have been unable to tolerate dimethyl fumarate due to gastro-intestinal side-effects to continue treatment with an oral first-line drug with equivalent efficacy to dimethyl fumarate. It also helps address the wider need to have increased options for oral first-line therapies with improved tolerability.
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Side effects may lead to discontinuation of treatment and affect quality of life. In the EVOLVE-MS-2 study, fewer patients discontinued diroximel fumarate than dimethyl fumarate because of adverse events (1.6% vs 5.6%). Gastro-intestinal side effects were less likely with diroximel fumarate than dimethyl fumarate to interfere with regular daily activities (9.5% vs 28.9%) and work productivity (6.1% vs 11.3%) and to require concomitant symptomatic medication use (19.3% vs 30.6%).
Sources of evidence	

18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	The objective of the EVOLVE-MS-2 study was to compare the gastrointestinal tolerability of diroximel fumarate and dimethyl fumarate. The outcome measures used were the Individual Gastrointestinal Symptom and Impact Scale and Global Gastrointestinal Symptom and Impact Scale. These measures seem to be clinically relevant but, as evaluation of GI events is not a typical assessment for the management of multiple sclerosis, no validated scales are currently available to measure such outcomes.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	Not applicable
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not to my knowledge

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance TA624?	Ofatumumab has been approved as a treatment for relapsing remitting multiple sclerosis in April 2021.
21. How do data on real-world experience compare with the trial data?	There is one published retrospective study of real-world experience of diroximel fumarate (Liseno J, et al. *Neurol Ther* 2021 doi: 10.1007/s40120-021-00242-7) which reported high overall persistence, low discontinuation rate due to gastrointestinal events, and high adherence to therapy, aligning with expectations based on clinical trials. A prospective observational study in the real-word setting (EXPERIENCE-US Study) has recently started. There is no real-world experience in the UK or Europe as it does not yet have marketing authorisation.
Equality	
22a. Are there any potential equality issues that should be	No

taken into account when considering this treatment?	
22b. Consider whether these issues are different from issues with current care and why.	
Topic-specific questions	
23. What definition (or source) is used in NHS clinical practice for relapsing-remitting MS in terms of progression on disease modifying therapy (including timeframe for assessment)?	Definitions for relapsing-remitting multiple sclerosis are outlined in the NHS England Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies
Key messages	

24. In up to 5 bullet points, please summarise the key messages of your submission.

- Diroximel fumarate is a first-line treatment option for relapsing remitting multiple sclerosis with similar efficacy to dimethyl fumarate.
- It improves gastrointestinal tolerability, treatment persistence and quality of life compared to dimethyl fumarate.
- It is a direct alternative to dimethyl fumarate and requires no additional healthcare resources.
- There are limited options for oral first-line therapies and it helps address the unmet need to have additional oral therapies with improved tolerability.
- It may reduce the need to switch therapies and reduce burden on healthcare resources.

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Diroximel fumarate for treating relapsing–remitting multiple sclerosis [ID1673]. A Fast Track Appraisal

Produced by	School of Health and Related Research (ScHARR), The University of Sheffield
Author	Matt Stevenson, Professor of Health Technology Assessment, ScHARR, University of Sheffield, Sheffield, UK
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Date completed	28/12/2021

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Declared competing interests of the authors

None of the authors has any conflicts of interest to declare.

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Rider on responsibility for report

The views expressed in this report are those of the author and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the author.

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Diroximel fumarate for treating relapsing–remitting multiple sclerosis [ID1673]. A Fast Track Appraisal. A Single Technology Appraisal. School of Health and Related Research (ScHARR), 2021.

Contributions of authors

Matt Stevenson summarised and critiqued the clinical effectiveness data reported within the company's submission. He also critiqued the statistical aspects of the submission and critiqued the health economic case submitted by the company. Matt wrote the final report.

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Abbreviations

AEs	Adverse Events
CHMP	Committee for Medicinal Products for Human Use
CS	Company Submission
DMF	Diroximel fumarate
DRF	Dimethyl fumarate
EDSS	Expanded Disability Status Score
EMA	European Medicines Agency
FTA	Fast Track Appraisal
GGISIS	Global Gastrointestinal Symptom and Impact Scale
GI	Gastrointestinal
IGISIS	Individual Gastrointestinal Symptom and Impact Scale
PML	Progressive Multifocal Leukoencephalopathy
RRMS	Relapsing-remitting multiple sclerosis

1. Executive summary

The company (Biogen) has made a case that diroximel fumarate (DRF) is cost-effective compared with dimethyl fumarate (DMF) using the cost-comparison option available within a Fast Track Appraisal (FTA). Further information on the NICE FTA process is contained at methods-guide-addendum-cost-comparison.pdf (nice.org.uk). Table 1 from this source indicates that if the appraisal committee believes that a '*Technology provides similar or greater benefits at a similar or lower overall costs than the comparator(s)*' then it would be '*Recommended as an option*'.

The company's case was based on three key points.

1. That DRF has been established as having bioequivalence to DMF and thus has the same clinical efficacy.
2. That DRF has an improved side-effect profile compared with DMF.
3. [redacted].

The ERG is content that points one and three are accurate and notes that DRF appears to have a better safety and tolerability profile that DMF. As such, the ERG supports the company's case that DRF provides similar or greater benefits at a similar or lower overall cost than DMF.

Given this conclusion, the ERG has purposefully produced a short report which includes key data, and where components believed to be of secondary importance are omitted with a reference provided to the relevant sections of the company submission (CS).

1.1 Overview of the ERG's key issues

The ERG has no issues with the company submission.

1.2 Overview of key model outcomes

Not applicable - within a cost-comparison FTA the company is instructed by NICE to not provide a mathematical model.

1.3 The decision problem: summary of the ERG's key issues

The ERG is content that the decision problem is appropriate.

1.4 The clinical effectiveness evidence: summary of the ERG's key issues

The company highlight that the Committee for Medicinal Products for Human Use (CHMP) and the European Medicines Agency have both given positive opinions relating to the bioequivalence of DRF and DMF. Evidence from a head-to-head study of DRF and DMF indicate that DRF has a better safety and tolerability profile than DMF. Safety and tolerability data generated from a single-arm, open-label study does not suggest that DRF has additional safety concerns than does DMF.

1.5 The cost-effectiveness evidence: summary of the ERG's key issues

The ERG is content with the analyses provided by the company which compares the acquisition costs of DRF and DMF.

2 BACKGROUND

Discussions were undertaken between NICE, the company and the ERG to facilitate this FTA being appraised by NICE in a timely manner. Prior to this call, the ERG had informally critiqued the original submission and concurred with the company (and NICE) that this technology was a prime candidate for a cost-comparison FTA. Following the discussions, the company submitted a shortened report[1] without a mathematical model, to comply with the requirements of a cost-comparison FTA. The structure of this ERG report has been adapted to allow a coherent abbreviated critique of the CS.

2.1 Critique of company's description of underlying health problem

The company has provided an acceptable description of the disease area of relapsing-remitting multiple sclerosis (RRMS). In a cost-comparison FTA, where one technology is attempting to position itself as an alternative option to a current technology, the significance of the disease burden prognosis is reduced compared with a single technology appraisal (STA).

2.2 Critique of company's overview of current service provision

The company has provided an acceptable overview of current service provision for people with RRMS. In a cost-comparison FTA, where one technology is attempting to position itself as an alternative option to a current technology the importance of the treatment pathway is reduced compared with an STA as the primary objective of a company is to replace (in part, or in whole) technology A with technology B with all other parts of the pathway unchanged.

2.3 Critique of company's definition of the decision problem

Table 1 of the CS provides a comparison of the decision problem addressed and the deviations from the NICE scope as highlighted by the company. Table 1 in this report, provides the ERG's interpretation of the appropriateness of these deviations. The ERG is content that none of the deviations pose a problem in the appraisal of DRF. Further details are provided in Sections 2.3.1 to 2.3.5.

Table 1: Decision problem (adapted from Table 1 of the CS)

Aspect	NICE Final Scope	Deviation in the CS from the NICE scope and the rationale provided by the company	Assessment by the ERG of the appropriateness of the deviation
Population	People with RRMS.	Additional details added for clarity. "*People with RRMS who do not have highly active or rapidly evolving severe RRMS*"	This deviation is appropriate.
Intervention	DRF	None	Not applicable.
Comparators	Beta interferon, DMF, ocrelizumab, ofatumumab, ozanimod, peginterferon beta-1a, ponesimod, teriflunomide.	Only DMF	This is appropriate given that a cost-comparison case is being made against DMF.
Outcomes	Relapse rate, Severity of relapse, Disability, Disease Progression, Symptoms of MS, Subclinical disease activity, Mortality, Adverse events of treatment, Health-related quality of life.	A number of changes (see Table 1 of the CS) such that the outcomes reported were aligned to the EVOLVE clinical trial programme providing evidence for DRF	The ERG believes that the deviations are appropriate. The ERG notes that as DRF has received positive opinions regarding being bioequivalent to DMF, then there is not expected to be a difference in clinical outcomes between DRF and DMF. Adverse events may differ for DRF and DMF, these outcomes have been appropriately detailed.
Subgroups to be considered	People who could not tolerate previous treatment.	The company states that the clinical trials did not generate evidence for people who not tolerate previous treatments.	The ERG believes that omitting this subgroup is appropriate.

2.3.1 Population

The population in the decision problem represents people with RRMS who do not have highly active or rapidly evolving severe RRMS

2.3.2 Intervention

The intervention is DRF, which is administered orally at a starting dose of 231mg twice daily, with the dose increased after one week to 462mg twice daily. Temporary dose reductions (to 231mg twice daily) are permitted following flushing or gastrointestinal adverse reactions, although the dose of 462mg twice daily should be resumed within one month. The proposed list price for DRF is [redacted] per pack of 120 231mg capsules although a patient access scheme has been accepted that discounts this price by [redacted]% resulting in a pack cost of [redacted].

2.3.3 Comparator

The comparison within the FTA is with DMF, which is administered orally at a starting dose of 120mg twice daily, with the dose increased after one week to 240mg twice daily. Temporary dose reductions (to 120mg twice daily) are permitted following flushing or gastrointestinal adverse reactions, although the dose of 240mg twice daily should be resumed within one month. The list price for DMF is £1373.00 per pack of 56 240mg capsules although a patient access scheme has been accepted that discounts this price by [redacted]% resulting in a pack cost of [redacted].

2.3.4 Outcomes

All key outcomes relevant to the evidence comparing DRF and DMF have been considered. Given that the CHMP and the EMA have both given positive opinions relating to the bioequivalence of DRF and DMF, the most pertinent outcome was adverse events.

2.3.5 Subgroups

The subgroup suggested by NICE could not be undertaken the company states that the relevant clinical trials did not generate evidence for people who not tolerate previous treatments.

3 CLINICAL EFFECTIVENESS

The CHMP and the EMA have given positive opinions relating to the bioequivalence of DRF and DMF with the benefits of DRF '*expected to be the same*' as those of DMF. The CHMP stated that [redacted][2] whilst the EMA concluded that [redacted][3]

Given the positive opinions provided by regulatory bodies the ERG is content to accept that DMF and DRF are bioequivalent.

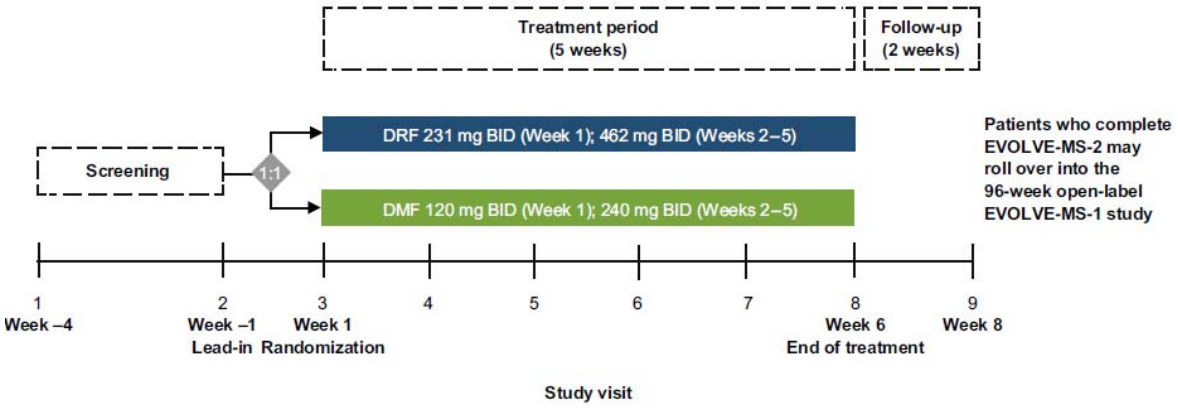
3.1 Description of the pivotal studies of DRF

The company reports the details of two studies: EVOLVE-MS-2,[4] and EVOLVE-MS-1.[5] Patients who completed the 5-week treatment period of EVOLVE-MS-2 were eligible to enrol in the EVOLVE-MS-1 study which is a longer-term open-label study. These studies are discussed individually in Section 3.1.1 and 3.1.2. The company assessed the EVOLVE studies for risk of bias and generalisability with results reported in Appendix D of the CS. The ERG is not concerned with the quality level of either study.

3.1.1 EVOLVE-MS-2

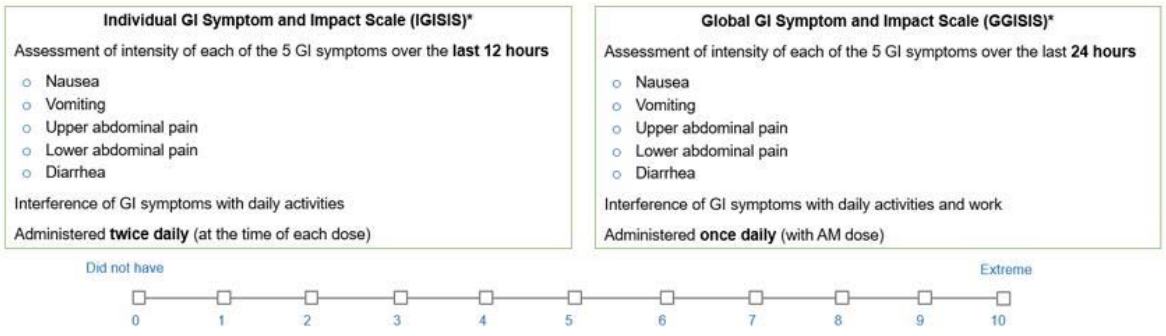
EVOLVE-MS-2 was a Phase III, randomised, double-blind, head-to-head, 5-week study evaluating the gastrointestinal (GI) tolerability of DRF versus DMF.[4] The study design is shown in Figure 1. The study had a screening period of up to 4 weeks followed by a double-blinded treatment period, with either DRF or DMF, for 5 weeks, and a 2-week follow-up period. Patients were randomised 1:1 into one of the two treatment groups. Block randomisation was performed using a block size of 4, and all patients received two capsules twice daily for all doses to maintain blinding. No dose reductions or escalations were permitted during the study. Symptomatic therapies were permitted and recorded as concomitant medications. Eligibility criteria for EVOLVE-MS-2 are shown in Table 5 of the CS, with baseline characteristics shown in Table 6 of the CS. The company states that baseline demographics and disease characteristics were generally well balanced; the ERG agrees with this. The primary outcome of EVOLVE-MS-2 was the number of days, relative to exposure, with any Individual Gastrointestinal Symptom and Impact Scale (IGISIS) intensity score ≥ 2 in the overall study population, with secondary outcomes measures reported in Table 5 of the CS.

Figure 1: The study design for EVOLVE-MS-2 (reproduced from Figure 2 of the CS)



As EVOLVE-MS-2 was designed to evaluate GI tolerability, patients were required to use two electronic diary symptom scales to evaluate the duration and severity of any GI symptoms: these were the IGISIS and Global Gastrointestinal Symptom and Impact Scale (GGISIS). These scales were designed for EVOLVE-MS-2 and were adapted from a validated measure: the Global Flushing Severity Scale.[6] Full details are provided in Appendix L of the CS, although the company provide a visual summary of both scales, which has been reproduced in Figure 2. Investigator-assessed adverse events (AEs) were also recorded.

Figure 2: The scales used to evaluate key GI symptoms in EVOLVE-MS-2 (reproduced from Figure 1 of the CS)



Key: AE, adverse event; GI, gastrointestinal.
Note: *, scales have not been validated and were novel endpoints designed uniquely for EVOLVE-MS-2.

As the IGISIS and GGISIS scales had not been used previously, a pre-planned unblinded analysis of data was conducted after the first 120 patients were randomised (denoted Part A of the study). Following this, modifications to the scales were permitted. Subsequently randomised patients (denoted Part B of the study) were enrolled, bringing the number of patients in the overall planned population to 500.

Pre-specified exploratory endpoints included the number of days relative to exposure with any IGISIS individual symptom intensity score of ≥ 1 and ≥ 3, or a GGISIS intensity score of ≥ 1, ≥ 2, or ≥ 3, (in Part B of the study only). Investigator-assessed AEs were summarised. A summary of the statistical analyses undertaken for EVOLVE-MS-2 is provided in Table 9 of the CS.

3.1.2 EVOLVE-MS-1

EVOLVE-MS-1 is a Phase III, open-label, single-arm study of DRF in adult patients with RRMS.[5] It had a 4-week screening period followed by a 96-week treatment period and 2 weeks of follow-up. Patients could enter EVOLVE-MS-1 from EVOLVE-MS-2, or as new study patients. The final data for EVOLVE-MS-1 is expected in [redacted]. Table 7 of the CS provides a summary of the design of EVOLVE-MS-1 and Table 8 of the CS providing the baseline characteristics of 1057 patients ([redacted] of which had entered after recruitment to EVOLVE-MS-2). A summary of the statistical analyses undertaken for EVOLVE-MS-1 is provided in Table 9 of the CS. The primary outcome of EVOLVE-MS-1 was safety and tolerability, including AEs. Secondary outcomes are provided in Table 7 of the CS.

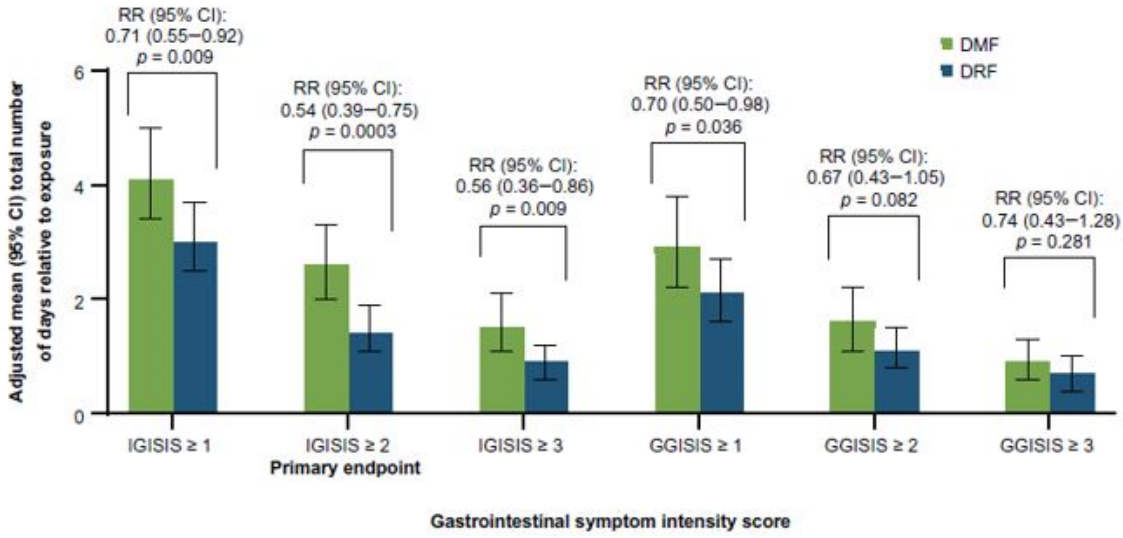
3.2 Key results from the pivotal DRF studies

3.2.1 Clinical results from EVOLVE-MS-2

A summary of patient-assessed GI tolerability using the full analysis set was provided in Figure 4 of the CS and is reproduced in Figure 3. As shown, the study met its primary endpoint, with a rate ratio of IGISIS ≥ 2 for DRF compared with DMF of 0.54, (95% confidence interval 0.39-0.75). Further analyses also indicated a statistically significant benefit of DRF over DMF for IGISIS ≥ 1, IGISIS ≥ 3, and GGISIS ≥ 1.

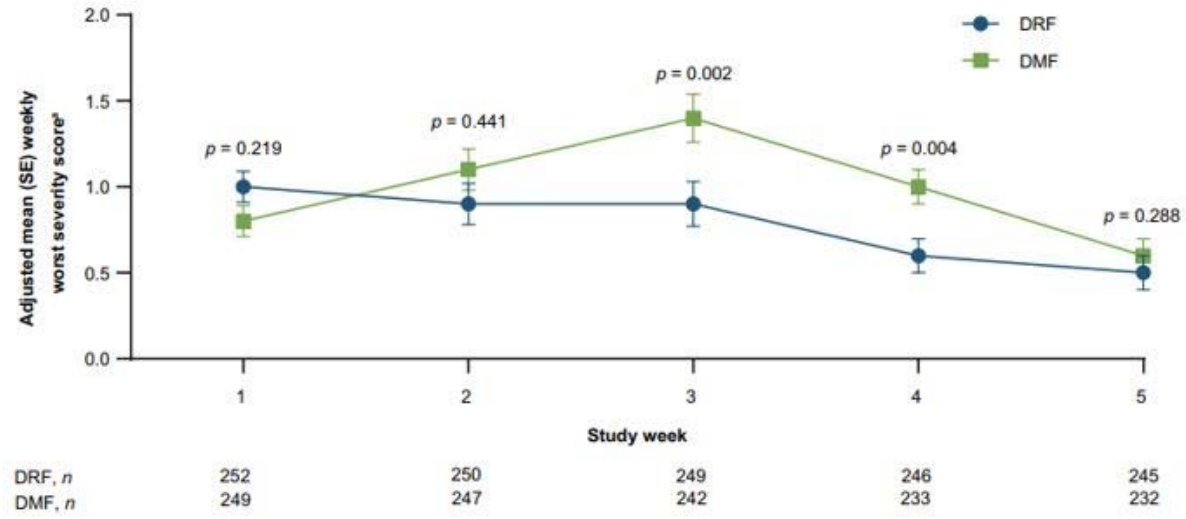
Analysis of mean worst IGISIS severity score in EVOLVE-MS-2 using the full analysis set is shown in Figure 4, which is a reproduction of Figure 5 in the CS. These results show a statistically significant benefit of DRF compared with DMF in weeks 3 and 4 of the study. The CS also provides data on the worst interference of GI symptoms with regular daily activities and missed hours of work due to GI symptoms (Figures 6 and 7 of the CS respectively) all of which favour DRF compared with DMF.

Figure 3: Summary of primary and secondary endpoints in EVOLVE-MS-2



Key: CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; FAS, full analysis set; GGISIS, Global Gastrointestinal Symptom and Impact Scale; IGISIS, Individual Gastrointestinal Symptoms and Impact Scale; RR, rate ratio.

Figure 4: Mean worst IGISIS severity score in EVOLVE-MS-2



Key: DMF, dimethyl fumarate; DRF, diroximel fumarate; FAS, full analysis set; IGISIS, Individual Gastrointestinal Symptom and Impact Scale; SE, standard error.

Overall, the safety and tolerability of DRF appeared better than DMF: 78.3% of patients treated with DRF experienced a treatment-emergent AE compared with 83.7% of patients treated with DMF; GI-related AEs were reported by 34.8% of DRF-treated patients compared with 49.0% of DMF-treated patients; 1.6% of patients discontinued DRF treatment due to AEs compared with 5.6% of DMR-treated patients; 2.0% of patients treated with DRF had severe treatment-emergent AEs with this value being 5.6% in the DMF arm; 1.6% of patients treated with DRF had serious treatment-emergent AEs compared with 1.2% for patients treated with DMF; 6.7% of DRF-treated patients reported abdominal pain compared with 15.5% in DMF-treated patients; [redacted]% of patients in the DRF arm used concomitant GI medication for a mean of [redacted] days compared with [redacted]% of patients treated with DMF who used these for a mean of [redacted] days. More detailed results for these endpoints are provided in the CS.

3.2.2 Clinical results from EVOLVE-MS-1

EVOLVE-MS-1 is an open-label single-arm study and as such no comparative data was generated. The primary study outcome was establishing the safety and tolerability of DRF. Multiple endpoints related to safety and tolerability are presented in the CS with a broad summary provided in the following bullet points. Further details on these bullet points are provided in the CS.

- [redacted] patients experienced a relapse, with an average of [redacted] relapses for these patients, with [redacted] experiencing four or more relapses.
- Average change in Expanded Disability Status Scale (EDSS) was small with a mean change over 96 weeks of [redacted] with a standard deviation of [redacted], with the patients who provided values at Week 96 having an EDSS score of [redacted].
- [redacted] patients experienced confirmed disease progression, with an average of [redacted] relapses for these patients, with [redacted] experiencing four or more relapses.
- Change from baseline in the timed 25-foot walk test of [redacted] seconds over a period of 96 weeks.
- Change from baseline in the mean number of Gd+ lesions of [redacted] (standard deviation [redacted]), mean change in new or enlarging T2 lesions of [redacted] (standard deviation [redacted]) between baseline and Week 48, and of [redacted] (standard deviation [redacted]) between Week 48 and Week 96.
- Change in EQ-5D-5L index score of [redacted].
- [redacted]% of patients experienced at least one treatment-emergent AE, with [redacted] being the most commonly reported. The majority of events were either mild ([redacted]%) or moderate ([redacted]%) in severity.
- GI treatment-emergent AE occurred in [redacted]% of patients with the most commonly reported conditions being [redacted]
- Serious GI treatment-emergent AE occurred in [redacted]% of patients and led to study discontinuation in [redacted] patients.
- [redacted] patients died [redacted].
- For patients treated with DMF prolonged (>6 months) moderate to severe lymphopenia appears to increase the risk of progressive multifocal leukoencephalopathy (PML). Prolonged lymphopenia occurred in [redacted]% of patients with [redacted]% experiencing prolonged moderated lymphopenia. None of these patients developed a serious infection or opportunistic infection. The SmPC for DRF states that treatment should not be initiated in patients with severe lymphoma and that if any sign or symptom suggestive of PML is observed that DRF treatment

should be withheld and appropriate diagnostic evaluations performed. DRF treatment cannot be provided to patients with PML.

The company states that the safety profile observed with DRF treatment is aligned with the safety profile observed with DMF in the DEFINE, CONFIRM and ENDORSE studies. The ERG concurs with this view.

The company also explored an indirect treatment comparison between DRF and DMF. A propensity score matched analysis was conducted with the results presented in Table 14 of the CS. The analysis which was presented at a conference[7] used 48-week patient level data from EVOLVE-MS-1, and the following studies including DMF: DEFINE,[8] CONFIRM,[9] and ENDORSE,[10] which is an ongoing 12-year extension of DEFINE/CONFIRM. The results which are replicated in Table 2 and show that there are no significant differences in GD+ lesion count, new/newly enlarging T2 lesion count or in annualised relapse rate. These results are not unexpected given the positive opinions related to the bioequivalence of DRF and DMF.

Table 2: Results from a propensity score matched model comparing DRF and DMF (reproduced from Table 14 of the CS)

Outcome	Treatment	Sample size	Outcome	Ratio (95% CI) (DRF vs DMF) p-value
Gd+ lesion count, Mean (SD)	DRF	250	0.20 (0.82)	Odds ratio 0.98 (0.55, 1.77) p = 0.955
	DMF	250	0.26 (1.23)	
New/newly enlarging T2 lesion count, Adjusted mean (95% CI)	DRF	250	1.94 (1.43, 2.64)	Mean ratio 1.12 (0.86, 1.46) p = 0.384
	DMF	250	1.73 (1.27, 2.35)	
ARR, Adjusted rate (95% CI)	DRF	387	0.17 (0.11, 0.26)	ARR ratio 0.82 (0.58, 1.16) p = 0.255
	DMF	387	0.21 (0.14, 0.32)	

Key: ARR, annualised relapse rate; CI, confidence interval; DMF, dimethyl fumarate; DRF, diroximel fumarate; Gd+, gadolinium-enhancing; SD, standard deviation.

3 COST COMPARISON

In line with the FTA cost-comparison process, the company compared the acquisition costs of DRF with DMF. With the patient access schemes of both drugs considered the company state that the cost of treatment with DRF is [redacted] per year, and that the cost of a year's treatment with DMF is [redacted]

4 OVERALL CONCLUSIONS

Based on the evidence supplied by the company the ERG is satisfied that: DRF and DMF are bioequivalent; that the safety and tolerability of DRF appears to be better than of DMF; and that [redacted]

5 REFERENCES

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ERG report – factual accuracy check and confidential information check

Diroximel fumarate for treating relapsing-remitting multiple sclerosis [ID1673]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Friday 14 January 2022** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as '[redacted]' in turquoise, all information submitted as '[redacted]' in yellow, and all information submitted as '[redacted] in pink.

Issue 1

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Section 2.3.3 Comparator p9. The final sentence has an incorrect description of DMF: "The list price for DRF is £1471.07 per pack of 120 120mg capsules although a patient access scheme has been accepted that discounts this price by [redacted]% resulting in a pack cost of [redacted]	The sentence should be amended to "The list price of DMF is £1,373.00 per pack of 56 240 mg capsules although a patient access scheme has been accepted that discounts this price by [redacted]% resulting in a pack cost of [redacted].(1) 1. National Institute for Health and Care Excellence (NICE). TA320: Dimethyl fumarate for treating relapsing-remitting multiple sclerosis: National Institute for Care Excellence; 2014 [Available from: https://www.nice.org.uk/guidance/ta320/chapter/1-guidance.	Under the section 2.3.3 outlining details of the comparator, the aforementioned treatment is DMF (dimethyl fumarate, Tecfidera), not DRF (diroximel fumarate, Vumerity). Per pack details (list price, pack size) are not described in the manufacturer submission, only the annual cost.	Typos corrected as requested.