National Institute for Health and Care Excellence

Single Technology Appraisal (STA)

Diroximel fumarate for treating relapsing-remitting multiple sclerosis

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Comment 1: the draft remit

Section	Consultee/ Commentator	Comments [sic]	Action
Appropriateness	Biogen Idec	We consider it appropriate to refer this topic to NICE for appraisal.	Thank you for your comment. No action required.
	Celgene	Yes	Thank you for your comment. No action required.
	Novartis	It is appropriate to refer this topic for appraisal. There are many disease modifying therapies (DMTs) with differing efficacy, safety and tolerability profiles recommended by NICE and a full appraisal is required to establish the place in therapy of diroximel fumarate, as well as its cost-effectiveness in relation to DMTs which are already approved.	Thank you for your comment. No action required.
	Roche	Yes, subject to marketing authorisation being granted.	Thank you for your comment. No action required.
	Teva	Teva has been unable to identify any information on the regulatory status of diroximel fumarate within Europe (and whether a regulatory submission has	Thank you for your comment. NICE will

Section	Consultee/ Commentator	Comments [sic]	Action
		yet been made). It is therefore unclear whether an appraisal is appropriate at this time or should occur at a late date.	liaise with the manufacturing company regarding regulatory timings. No action required.
	Association of British Neurologists	It is appropriate.	Thank you for your comment. No action required.
	MS Trust	Diroximel fumarate has completed phase III trials. The manufacturer has not yet indicated their intention to file for European marketing authorisation but it would be reasonable to anticipate this. It should therefore be referred to NICE for appraisal.	Thank you for your comment. No action required.
	NHS England & Improvement	Yes it will be appropriate.	Thank you for your comment. No action required.
Wording	Biogen Idec	We consider the wording of the remit to be appropriate.	Thank you for your comment. No action required.
	Celgene	Yes	Thank you for your comment. No action required.
	Novartis	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche	Yes	Thank you for your comment. No action required.
	Teva	No comments	No action required.
	Association of British Neurologists	The wording reflects the relevant issues.	Thank you for your comment. No action required.
	MS Trust	Yes	Thank you for your comment. No action required.
	NHS England & Improvement	Yes	Thank you for your comment. No action required.
Timing Issues	Biogen Idec	Diroximel fumarate offers a highly effective treatment option for patients with RRMS representing another oral fumarate treatment option for physicians and patients with relapsing forms of MS to consider compared to dimethyl fumarate with a differentiated GI tolerability profile, which is of interest to patients and other NHS stakeholders. We therefore believe that timely NICE guidance for diroximel fumarate would be valuable to the NHS.	Thank you for your comment. No action required.
	Celgene	No comments	No action required.
	Novartis	No comments	No action required.
	Roche	No comments	No action required.

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	Teva	Teva has been unable to identify any information on the regulatory status of diroximel fumarate within Europe (and whether a regulatory submission has yet been made). It is therefore unclear whether any appraisal is therefore appropriate at this time or whether this should be delayed until regulatory approval is expected.	Thank you for your comment. NICE will liaise with the manufacturing company regarding regulatory timings. No action required.
	Association of British Neurologists	Not urgent	Thank you for your comment. No action required.
	MS Trust	Diroximel fumarate has not yet been submitted to European drug regulators for marketing authorisation. We would recommend that NICE delays drawing up this Final Scope until diroximel fumarate is further advanced in the licensing process.	Thank you for your comment. NICE will liaise with the manufacturing company regarding regulatory timings. No action required.
	NHS England & Improvement	Not urgent	Thank you for your comment. No action required.
Additional comments on the draft remit	Biogen Idec	No comments	No action required.
	Celgene	No comments	No action required.
	Novartis	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Roche	No comments	No action required.
	Teva	No comments	No action required.
	Association of British Neurologists	No comments	No action required.
	MS Trust	No comments	No action required.
	NHS England & Improvement	No comments	No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Biogen Idec	No comments	No action required.
	Celgene	No comments	No action required.
	Novartis	The summary of TA312 given is now out of date given the publication of updated guidance published on NICE website on 17 March 2020	Thank you for your comment. The scope has been amended to reflect the TA312 update.
	Roche	No comments	No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Teva	No comments	No action required.
	Association of British Neurologists	It is accurate	Thank you for your comment. No action required.
	MS Trust	The use of the term 'remission' is potentially misleading as, between relapses, people continue to experience the full range of symptoms such as fatigue, pain and cognitive impairment. Most people with MS experience one or more symptoms continuously, but between relapses this background level remains more or less stable. Background information does not capture the impact of MS on work and family life. People with MS are commonly diagnosed between the ages of 20 and 40 and may live with MS for 30-40 years. The variable nature of MS means that people given a diagnosis of MS and their families face many years of uncertainty. The disease can have a significant impact on work and family life, both for the individual and for informal carers. Background information does not capture the importance of early initiation of disease modifying treatment. There is a considerable body of evidence and medical consensus that starting treatment as soon as possible after diagnosis leads to better outcomes.	Thank you for your comment. The scope has been amended to clarify that people may have minimal symptoms when in remission. The background section aims to provide a brief overview of the condition and treatment options. The first paragraph describes the unpredictable course of MS. The appraisal committee will consider the impact of RRMS on people with the condition during the appraisal.

Section	Consultee/ Commentator	Comments [sic]	Action
	NHS England & Improvement	It appears to be accurate.	Thank you for your comment. No action required.
The technology/ intervention	Biogen Idec	Yes	Thank you for your comment. No action required.
	Celgene	No comments	No action required.
	Novartis	The description of the technology as “a derivative of fumaric acid that helps prevent the degeneration of the myelin sheath of nerve fibers, *without leading to systemic immune suppression*” does not appear to be substantiated. Novartis is not aware of any evidence that supports this description and understands that diroximel fumarate may affect the immune system through decreases in lymphocyte counts which requires patient monitoring in the US prescribing information.	Thank you for your comment. We have removed ‘without leading to systemic immune suppression’ from the scope.
	Roche	Yes	Thank you for your comment. No action required.
	Teva	No comments	No action required.
	Association of British Neurologists	It is accurate.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	MS Trust	Yes, we believe so.	Thank you for your comment. No action required.
	NHS England & Improvement	Yes	Thank you for your comment. No action required.
Population	Biogen Idec	Appropriately defined	Thank you for your comment. No action required.
	Celgene	No comments	No action required.
	Novartis	The population (relapsing-remitting multiple sclerosis; RRMS) is defined appropriately with respect to what is published regarding the trial populations, however it does not align with the subgroups listed in the comparator section which includes active secondary progressive multiple sclerosis (SPMS) which is not a subgroup of the RRMS population.	Thank you for your comment. Treatments for SPMS have been removed as comparators.
	Roche	Given the single arm study comparison to dimethyl fumarate (DMF) and the subsequent reimbursement of DMF in a select population (RRMS not highly active or rapidly evolving severe), it would be unlikely that Diroximel would demonstrate clinical and cost effectiveness in these patient populations.	Thank you for your comment. No action required.
	Teva	'People with relapsing-remitting multiple sclerosis' describes the appropriate population. However, 'people' could more specifically be defined as 'adults' in line with other MS disease modifying treatments and the expected indication.	Thank you for your comment. 'People' has been used for consistency with other

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			scopes. No action required.
	Association of British Neurologists	It is appropriate	Thank you for your comment. No action required.
	MS Trust	Yes the population is defined correctly, subject to market authorisation.	Thank you for your comment. No action required.
	NHS England & Improvement	Yes	Thank you for your comment. No action required.
Comparators	Biogen Idec	For cladribine, Biogen considers this should be “cladribine tablets” to prevent confusion with other dosage forms (solution for injection and solution for infusion) not indicated for multiple sclerosis, but for forms of leukaemia only. Cladribine tablets are only indicated for adult patients with highly active RMS as defined by clinical or imaging features, and NICE has specifically, recommended cladribine tablets for people with highly active RRMS despite previous treatment and for people with rapidly-evolving severe RRMS (TA493). For people with active secondary progressive multiple sclerosis (evidenced by continuing relapses): Biogen requests this subgroup to be removed as this is anticipated to be outside the anticipated marketing authorisation for RRMS.	Thank you for your comment. Wording has been updated to ‘cladribine tablets’. Treatments for SPMS have been removed as comparators. Following the decision problem meeting, comparators for highly active RRMS and rapidly-evolving severe

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			RRMS have been removed.
	Celgene	Ozanimod is an appropriate comparator for people with active relapsing–remitting (RR) multiple sclerosis (MS). It is not an appropriate comparator for highly active RRMS or rapidly-evolving severe RRMS as it is not approved for use in these patient groups.	Thank you for your comment. The appropriateness of ozanimod as a comparator in these groups will be considered by the committee during the appraisal.
	Novartis	Given uncertainty in the timings of the technology appraisal of diroximel fumarate, the ongoing appraisal of ofatumumab (ID1677) should be added to each of the active RRMS, highly active (HA) RRMS and rapidly evolving severe (RES) RRMS comparator lists as "(subject to ongoing NICE appraisal)". In addition, depending on when the appraisal may be re-started, the same may also apply to ponesimod (ID1393). Some of the comparators listed under "active RRMS" have not been restricted by NICE to "active" RRMS (e.g. glatiramer acetate). The scope should instead simply describe this list as "RRMS", unless the anticipated licence for diroximel fumarate contains a restriction to "active" RRMS. Active SPMS is not a subgroup of RRMS – if the population remains defined as RRMS (rather than relapsing multiple sclerosis, RMS) this subgroup (and its comparator list) should be removed. If the population is amended to RMS (although such a change would not be aligned to the clinical trials for diroximel fumarate) then this comparator group should have the wording	Thank you for your comment. Ofatumumab and ponesimod have been added as comparators. The wording has been updated to remove 'active' as per your suggestion.

Section	Consultee/ Commentator	Comments [sic]	Action
		"evidenced by continuing relapses" amended to "evidenced by continuing disease activity" to align with the ongoing siponimod appraisal (ID1304).	Treatments for SPMS have been removed as comparators.
	Roche	Yes	Thank you for your comment. No action required.
	Teva	The use of disease modifying treatments in the NHS is set out within the NHS England algorithm: https://www.england.nhs.uk/commissioning/wp-content/uploads/sites/12/2019/03/Treatment-Algorithm-for-Multiple-Sclerosis-Disease-Modifying-Therapies-08-03-2019-1.pdf	Thank you for your comment. No action required.
	Association of British Neurologists	These are the standard treatments currently used in the NHS. Diroximel fumarate has very similar biological activity to dimethyl fumarate, and so dimethyl fumarate and the other treatments for active relapsing remitting multiple sclerosis are the most appropriate comparators. Diroximel fumarate has not been studied in people with highly active relapsing–remitting multiple sclerosis despite previous treatment, rapidly-evolving severe relapsing–remitting multiple sclerosis or active secondary progressive multiple sclerosis.	Thank you for your comment. Diroximel fumarate does not yet have a license so all potential comparators used for RRMS have been included at this stage. Treatments for SPMS have been removed.
	MS Trust	**For people with active relapsing-remitting MS** We believe this is correct. **For people with highly active RRMS despite previous treatment** We believe this is correct. **For people with rapidly evolving severe RRMS**	Thank you for your comment. Please note that some changes have been made to the scope based on comments from other

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		We believe this is correct **For people with active SPMS** We believe this is correct The subgroups of comparators listed have become increasingly complex and are not as mutually exclusive as these lists suggest. The use of the drugs within their licensed indications and NICE TAs overlaps to a much greater extent than these subgroups suggest. For example, for people who continue to relapse despite treatment, there may be good reason for a 'lateral' switch to agents of broadly similar efficacy, perhaps due to tolerability or compatibility with personal circumstances.	stakeholders. No further action required. The most appropriate comparators will be considered by the committee during the appraisal.
	NHS England & Improvement	Not sure why siponimod and ozanimod are included when ofatumumab and ponesimod aren't (noting the former have official dates for publication).	Thank you for your comment. Ofatumumab and ponesimod have been added as potential comparators.
Outcomes	Biogen Idec	We have a comments on the outcome measures listed. The outcome measure "Freedom of disease activity" is not an outcome included in the diroximel fumarate clinical studies and we request that this outcome is removed from outcomes listed. Biogen believes that consideration of radiological outcomes including MRI activity (T1 Gadolinium enhancement (Gd+) lesions and T2 Gd+ lesions) should be listed as individual components for detecting underlying inflammatory activity. Furthermore, in place of disease progression Biogen requests that the component confirmed disability progression (CDP) should be in the list, which is a commonly reported outcome in clinical studies.	Thank you for your comment. Freedom of disease activity has been removed as an outcome. Subclinical disease activity (e.g. MRI outcomes) has been added to the list of outcomes. NICE aims to keep the outcomes broad and does not usually specify which

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			measurement scales or tools should be used.
	Celgene	Yes	Thank you for your comment. No action required.
	Novartis	No comments	No action required.
	Roche	Yes	Thank you for your comment. No action required.
	Teva	The outcomes listed are appropriate and will capture the benefits and harms of this technology. The outcome 'freedom of disease activity' is more commonly referred to as 'freedom from disease activity' or 'no evidence of disease activity'.	Thank you for your comment. Thank you for your comment. Freedom of disease activity has been removed as an outcome. No further action required.
	Association of British Neurologists	The outcome measures are appropriate.	Thank you for your comment. No action required.
	MS Trust	Freedom from disease activity is an evolving concept in MS which recognises clinical measures of disease activity, such as relapse rate, but also recognises the critical importance of subclinical disease activity, such as the number of lesions on MRI scans. For every relapse there are approximately	Thank you for your comment. Freedom of disease activity has been removed as an outcome. Subclinical

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		10 MRI lesions that occur asymptomatically. For every visible white matter lesion there are many more microscopic white matter lesions. As there is not yet a fully settled definition of freedom from disease activity, we would recommend that number of lesions on MRI scan is separated out and included as an outcome measure of subclinical disease activity. Assessment tools for symptoms such as fatigue and cognition in MS is still an evolving area. Multiple instruments are currently in use across clinical trials in MS and it will be important to critically consider the choice of tools as well as the results they demonstrate in the data submitted. There is increasing recognition that in addition to using EDSS as a measure of disability, upper limb function should also be considered, using the nine hole peg test as an outcome measure.	disease activity (e.g. MRI outcomes) has been added to the list of outcomes. EDSS is listed as an example of a measure of disability, however this list of examples is not meant to be exhaustive, and other measures be relevant.
	NHS England & Improvement	Yes	Thank you for your comment. No action required.
Economic analysis	Biogen Idec	No comments	No action required.
	Celgene	No comments	No action required.
	Novartis	Given the large number of comparators and subgroups relevant in the scope it is important that a full cost-effectiveness analysis is undertaken to establish the place of diroximel fumarate in practice in relation to other DMTs. It is apparent that many comparators that are now relevant were not considered at the time that TA320 was undertaken on the related product dimethyl fumarate and therefore a cost-comparison approach considering only the related compound dimethyl fumarate would be inadequate as it would not establish the place in therapy of diroximel fumarate in relation to newer	Thank you for your comment. Comment noted.

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		DMTs, some of which are more effective and may be more cost-effective than dimethyl fumarate. The risk-sharing scheme mentioned in this section is now obsolete given that NICE TA527 established routine commissioning for the former risk-sharing scheme products; it is suggested that this text is removed.	The text relating to the risk-sharing scheme has been deleted.
	Roche	No comments	No action required.
	Teva	NICE has conducted numerous a number of appraisals in MS over recent years and the economic analysis in this appraisal should reflect the conclusions of these appraisals. In line with other appraisals, and the nature of MS as a chronic condition, a lifetime horizon would be most appropriate.	Thank you for your comment. No action required.
	Association of British Neurologists	No concerns	Thank you for your comment. No action required.
	MS Trust	The draft scope states that costs will be considered from an NHS and Personal Social Services perspective. With more examples of integrated health and social care budgets, economic cases based on a distinction between the two cost domains are less relevant for commissioners and payers. There is greater scope for recognising that costs avoided in social care should be included in analysis of a healthcare intervention. Economic analysis does not take into account the societal costs of relapses. Relapses have a significant impact on the ability to work or undertake normal daily activities. This is likely to lead to time off work (and potentially loss of employment) both for the person with MS and informal carers, resulting in a loss of productivity.	Thank you for your comment. The NICE reference case stipulates that costs should take an NHS and Personal Social Services perspective. The committee will discuss the most appropriate costs to take into account. Considerations about cost effectiveness are

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			explained in the Guide to the methods of technology appraisal.
	NHS England & Improvement	No comments	No action required.
Equality and Diversity	Biogen Idec	Within the scope, Biogen requests NICE to provide the definition for “active relapse-remitting multiple sclerosis” as this differs according to NICE guidance for the comparators listed.	Thank you for your comment. ‘Active’ has been removed from the first category of comparators. NICE guidance is aligned with marketing authorisations.
	Celgene	No comments	No action required.
	Novartis	No comments	No action required.
	Roche	No comments	No action required.
	Teva	No comments	No action required.
	Association of British Neurologists	No concerns	Thank you for your comment. No action required.
	MS Trust	No equality issues to highlight.	Thank you for your comment. No action required.

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	NHS England & Improvement	No issues identified.	Thank you for your comment. No action required.
Other considerations	Biogen Idec	The following subgroups listed in “other considerations” should be removed as these populations are already listed in the “comparators” section: • patients with relapsing–remitting multiple sclerosis whose disease has inadequately responded to treatment with disease-modifying therapy • patients with rapidly evolving severe relapsing–remitting multiple sclerosis The subgroup specified as “patients with highly active relapsing–remitting multiple sclerosis” is a combination of the two subgroups cited above and Biogen consider these as two distinct populations. For subgroup specified as “patients with relapsing–remitting multiple sclerosis whose disease is intolerant to treatment with disease-modifying therapy” is relevant to clinical practice, however it should be noted that intolerance to disease modifying therapies are commonly exclusion criteria for clinical trials and therefore evidence is sparse. The subgroups specified as “patients with active secondary progressive multiple sclerosis” should be removed aligned with prior comments as this is anticipated to be outside of marketing authorisation.	Thank you for your comment. The subgroups of highly active RRMS have been removed. Comment noted. If the evidence allows, people who could not tolerate previous treatment may be considered. SPMS has been removed as a subgroup. Following the decision problem meeting, both

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			highly active and rapidly-evolving severe subgroups of RRMS have also been removed.
	Celgene	No comments	No action required.
	Novartis	We suggest to remove the following subgroups from the scope as it is unlikely, based on prior NICE appraisals of DMTs, that separate trial evidence in these subgroups could be found for the majority of comparators: • patients with relapsing–remitting multiple sclerosis whose disease has inadequately responded to treatment with disease-modifying therapy • patients with relapsing–remitting multiple sclerosis whose disease is intolerant to treatment with disease-modifying therapy As commented in the Comparators section, the following subgroup is not a subgroup of the population RRMS, and should be removed unless the population for the appraisal is changed to RMS: • patients with active secondary progressive multiple sclerosis.	Thank you for your comment. The subgroups of people with highly active RRMS whose disease is intolerant to treatment, and people with SPMS, have been removed. If the evidence allows, people who could not tolerate previous treatment may be considered.
	Roche	No comments	No action required.
	Teva	Monitoring requirements and their effect on costs and patient quality of life should be considered throughout this appraisal.	Thank you for your comment. No action required.

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	Association of British Neurologists	No additional considerations	Thank you for your comment. No action required.
	MS Trust	No comments	No action required.
	NHS England & Improvement	No comments	No action required.
Innovation	Biogen Idec	Yes, each patient's journey can vary greatly in MS, and Biogen is committed to providing safe and effective therapeutic options for patients with multiple sclerosis to meet individual treatment goals. Diroximel fumarate is an oral fumarate for the treatment of RRMS offering less severe gastrointestinal events and fewer days of self-assessed gastrointestinal symptoms, fewer gastrointestinal adverse events (GI AEs), and lower discontinuation rates because of gastrointestinal adverse events when compared with dimethyl fumarate. Furthermore, multiple sclerosis specialised nurses (MSSN's) play an important role in educating MS patients and supporting treatment adherence. MS Trust suggests patient caseload per full time MSSN in the UK is 511, exceeding the recommended sustainable caseload of 358 (Burke et al., 2011; Mynors et al., 2015). Reduced time associated with counselling for adverse effects may improve case load management. In EVOLVE-MS-2, diroximethyl fumarate 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) compared with dimethyl	Thank you for your comment. The innovative nature of diroximel fumarate will be considered by the committee during the appraisal. No action required. Regarding the clinical outcomes and studies cited, the committee will consider all of the relevant evidence during the appraisal.

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		fumarate (adjusted rate ratio, 0.54; 95% CI, 0.39-0.75; 46% reduction; P = 0.0003) (Naismith et al., 2020). GI AEs have been among the most frequently reported AEs and were noted to be the most common AEs leading to study discontinuation in dimethyl fumarate studies (Fox et al., 2012; Gold et al., 2012; Gold et al., 2015; Gold et al., 2016). Lack of GI tolerability is an important concern for patients being treated with DMF and may negatively affect treatment adherence and ultimately result in in treatment interruption or discontinuation (Naismith et al., 2017). Dimethyl fumarate undergoes rapid pre-systemic conversion to monomethyl fumarate, the same active metabolite as dimethyl fumarate. It is expected that treatment with diroximel fumarate will provide efficacy similar to that established with dimethyl fumarate, with potentially improved GI tolerability compared with dimethyl fumarate. **References:** Burke T, Dishon S, McEwan L, Smrtka J. The evolving role of the multiple sclerosis nurse: an international perspective. Int J MS Care. 2011 Fall;13(3):105-12. doi: 10.7224/1537-2073-13.3.105. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1087-97. Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, et al. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012 Sep 20;367(12):1098-107. Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Meltzer L, et al. Efficacy and safety of delayed-release dimethyl fumarate in patients newly diagnosed	

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		with relapsing-remitting multiple sclerosis (RRMS). Mult Scler. 2015 Jan;21(1):57-66. Gold R, Giovannoni G, Phillips JT, Fox RJ, Zhang A, Marantz JL. Sustained effect of delayed-release dimethyl fumarate in newly diagnosed patients with relapsing-remitting multiple sclerosis: 6-year interim results from an extension of the DEFINE and CONFIRM studies. Neurol Ther. 2016 Jun;5(1):45-57. Mynors G, Suppiah J, Bowen A. Evidence for MS Specialist Services: Findings from the GEMSS MS specialist nurse evaluation project [Internet]. Multiple Sclerosis Trust. 2015 [cited 2020 Aug 20]. Available from: https://support.mstrust.org.uk/file/Evidence-for-MS-Specialist-Services.pdf Naismith RT, Wundes A, Ziemssen T, Jasinska E, Freedman MS, Lembo AJ, et al. 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. CNS Drugs. 2020 Feb;34(2):185-96.	
	Celgene	No comments	No action required.
	Novartis	No comments	No action required.
	Roche	No, the RRMS patient population is well served with multiple treatment options in each category of disease severity.	Thank you for your comment. No action required.
	Teva	Diroximel fumarate is a novel oral fumarate with a distinct chemical structure and metabolism pathway. Therefore, diroximel fumarate should be considered as a new molecular entity. However, diroximel fumarate is of limited innovation as it acts through the same mechanism as an established MS therapy.	Thank you for your comment. The innovative nature of diroximel fumarate will be considered by the committee during the

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			appraisal. No action required.
	Association of British Neurologists	Diroximel fumarate has very similar biological activity to dimethyl fumarate and so does not represent a step change in the management of multiple sclerosis. However, a small proportion of people taking dimethyl fumarate have to stop treatment because of gastrointestinal side effects. Diroximel fumarate is proposed to have fewer side effects which may allow more people to continue on treatment. Therefore, Diroximel fumarate has the potential to be of significant benefit to patients who are unable to tolerate dimethyl fumarate due to gastrointestinal side effects. Data will become available from the EVOLVE-MS-1 and EVOLVE-MS-2 studies of diroximel fumarate.	Thank you for your comment. The innovative nature of diroximel fumarate will be considered by the committee during the appraisal. No action required.
	MS Trust	Diroximel fumarate has a very similar mechanism of action and efficacy to dimethyl fumarate. Dimethyl fumarate has proven to be an effective first line treatment, but 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; this is likely to lead to improved treatment adherence.	Thank you for your comment. The innovative nature of diroximel fumarate will be considered by the committee during the appraisal. No action required.
	NHS England & Improvement	No comments	No action required.
Questions for consultation	Biogen Idec	**Have all relevant comparators for diroximel fumarate been included in the scope?** See comments in comparators section. **Which treatments are considered to be established clinical practice in the NHS for relapsing–remitting multiple sclerosis?**	Thank you for your comment. Points requiring action have been addressed in the sections above. No further action required.

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		The treatments used in clinical practice in the NHS are covered by the treatments specified in the comparators section. **Are the outcomes listed appropriate?** Yes **Where do you consider diroximel fumarate will fit into the existing NICE pathway on <u>Multiple sclerosis</u>?** We consider diroximel fumarate will fit in the "Disease-modifying therapies for multiple sclerosis" section of the multiple sclerosis NICE pathway. **NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which diroximel fumarate is licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.**	

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		We do not believe the proposed remit and scope raises any equality issues. **Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.** **Do you consider diroximel fumarate to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?** See innovation section. **Do you consider that the use of diroximel fumarate can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?** See innovation section. **Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.** See innovation section. **To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** We do not anticipate any barriers compared to current practice for adoption of diroximel fumarate into practice.	

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		NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction). The STA process is the appropriate route for the appraisal of diroximel fumarate. **NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.** • **Would it be appropriate to use the cost comparison methodology for this topic?** Until a full clinical and economic assessment of diroximel fumarate has been made based on the final label it is not possible to comment. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** • **Is there any substantial new evidence for the comparator technologies that has not been considered?** • **Are there any important ongoing trials reporting in the next year?**	

Section	Consultee/ Commentator	Comments [sic]	Action
	Celgene	**Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** There are issues with measuring disability with the expanded disability status scale [EDSS], the basis for confirmed disability progression which drives most cost-effectiveness models assessing MS. Issues with EDSS include: • The EDSS examination itself is largely subjective, and as a result, there is high intra-and inter-rater variability, especially in the minimal-to-moderate range of disability. A one-point difference on this ten-point scale signifies clinical change i.e. progression (1, 2). • The EDSS is differentially sensitive to change, depending on the patient's initial disability level. As it is a non-linear ordinal scale, a change of 1 point on the EDSS reflects more dramatic change at higher levels of disability. Scores of 4-7.5 are based primarily on the distance the patient can walk and the need for an assistive device. This reduces the responsiveness of the EDSS as well as the statistical power of any study that uses the EDSS as an outcome (3, 4). • The EDSS captures cognitive impairment poorly (3).	Thank you for your comment. The committee will consider the appropriateness of outcome measures in the evidence submitted by the company. No action required.
	Novartis	**NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).** **NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.**	Thank you for your comment. Your comments regarding cost comparison have been noted. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		• **Would it be appropriate to use the cost comparison methodology for this topic?** We consider a full STA on a cost-effectiveness basis the appropriate process, despite the similarity of diroximel fumarate with the related compound dimethyl fumarate. This is particularly pertinent given that a number of new DMTs have been recommended by NICE since the dimethyl fumarate appraisal, including some which are more efficacious than dimethyl fumarate. In addition, technologies appraised for RRMS since TA320 may be more cost-effective than dimethyl fumarate; for instance, beta interferons and glatiramer acetate now have patient access schemes since TA527 and the current prices of comparator DMTs should be used in the appraisal of diroximel fumarate. Novartis therefore considers it inappropriate to use the cost-comparison methodology for this topic given the choice of DMTs recommended by NICE for RRMS and the need to establish the relative positioning of diroximel fumarate among all of these. The related DMT, dimethyl fumarate, is only recommended as an option for treating adults with active RRMS (normally defined as 2 clinically significant relapses in the previous 2 years), if they do not have highly active or rapidly evolving severe RRMS (TA320). Therefore, if the population of the diroximel fumarate appraisal is to be broader than this (for instance including also HA or RES RRMS), as proposed, a cost-comparison approach vs dimethyl fumarate would not meet the criterion that "it is recommended in published NICE technology appraisal guidance for the same indication"[1]. 1. NICE Fast track appraisal: cost-comparison case User guide for company evidence submission template February 2018. Section 1.1, page 5. available from https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-technology-appraisal-guidance. last accessed 24/08/2020.	

Section	Consultee/ Commentator	Comments [sic]	Action
		Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? It appears from data on clinicaltrials.gov (NCT02634307 and NCT03093324) that the trial designs are focussed on demonstrating favourable tolerability, including in a single arm trial and head-to-head vs the related compound dimethyl fumarate. Since dimethyl fumarate was appraised by NICE a number of new DMTs have been recommended by NICE, including some with greater efficacy than dimethyl fumarate and having demonstrated cost-effectiveness vs dimethyl fumarate, necessitating a full cost-effectiveness analysis for diroximel fumarate. **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** From the data available publicly on clinicaltrials.gov (NCT02634307 and NCT03093324), the two trials for diroximel fumarate will not generate comparative data from their primary or secondary outcomes that will be usable in a standard NMA framework to establish relative efficacy vs other DMTs. **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** Multiple comparators have been appraised and recommended by NICE since the related compound dimethyl fumarate, including some with greater efficacy than dimethyl fumarate and having demonstrated cost-effectiveness vs	

Section	Consultee/ Commentator	Comments [sic]	Action
		dimethyl fumarate. This situation means it would be inappropriate to conduct a cost-comparison vs dimethyl fumarate alone.	
	Roche	No comments	No action required.
	Teva	**"To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly."** No comment **NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process.** The STA process is the most appropriate process for this technology. **NICE has published an addendum to its guide to the methods of technology appraisal, which states the methods to be used where a cost comparison case is made.** • **Would it be appropriate to use the cost comparison methodology for this topic?** Predicated on the publically available information, Teva does not feel that this is likely to be an appropriate methodology for this appraisal. There is very limited clinical trial evidence published around the efficacy of diroximel fumarate, which makes demonstration of any similarity in efficacy to a comparator very challenging. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** Diroximel fumarate is an oral fumarate and so is related to dimethyl fumarate. Teva has not seen sufficient evidence to judge whether these treatments are likely to be similar in clinical efficacy, although this is likely. To date, no head-	Thank you for your comment. Your comments regarding cost comparison have been noted. No changes to the scope required.

Section	Consultee/ Commentator	Comments [sic]	Action
		to-head clinical trial evidence is publically available reporting the clinical efficacy of diroximel fumarate compared to another MS drug. • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** No comment • **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** Teva is not aware of any substantial new evidence due imminently.	
	Association of British Neurologists	No comments	No action required.
	MS Trust	**Have all relevant comparators been included?** Yes, all the treatments currently approved (or subject to on-going NICE appraisal) for RRMS are included in the scope. **Which treatments are considered to be established clinical practice in the NHS?** All of the treatments would be considered standard clinical practice which recognises that early, proactive treatment is key to preventing disability accumulation. **Are the outcomes listed appropriate?** See our comments above. **Are the subgroups suggested in 'other considerations appropriate?** We anticipate that diroximel fumarate would be used for the same groups of patients as dimethyl fumarate. In practice this would include patients with RRMS whose disease has inadequately responded to disease-modifying therapy and patients with RRMS intolerant to treatment with disease-	Thank you for your comment. The position of diroximel fumarate in the treatment pathway and groups of people for whom it may be appropriate will be considered by the committee during the appraisal. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		modifying therapy. It is unlikely to include patients with highly active RRMS, patients with rapidly evolving severe RRMS or patients with active secondary progressive MS. **Are there any other subgroups that should be examined separately?** No, we believe that all the subgroups are covered in the draft scope. **Where do you consider diroximel fumarate will fit into the existing NICE pathway?** Diroximel fumarate would appear with other disease-modifying therapies under Managing multiple sclerosis. However, we wish to highlight the point made earlier in the section on comparators. Disease modifying treatment of multiple sclerosis is managed in partnership between the prescribing neurologist and the person living with MS. Many of the sub-groups defined in the marketing authorisation and then reflected in previous technology appraisals do not match well with the realities of prescribing in the real world clinical setting. **Do you consider diroximel fumarate to be innovative?** See our comments above. **Do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.** No, we do not consider there will be any barriers to adoption. **Appraisal this technology through its Single Technology Appraisal (STA) Process.** Yes, we do consider that the STA would be appropriate for diroximel fumarate. **Methods of technology appraisal** • **Would it be appropriate to use the cost comparison methodology for this topic?**	

Section	Consultee/ Commentator	Comments [sic]	Action
		Yes, we believe so. • **Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?** As noted above, diroximel fumarate is most similar to dimethyl fumarate in terms of clinical efficacy and resource use. • **Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes. • **Is there any substantial new evidence for the comparator technologies that has not been considered? Are there any important ongoing trials reporting in the next year?** None that we are aware of.	
	NHS England & Improvement	No comments	No action required.
Additional comments on the draft scope	Biogen Idec	No comments	No action required.
	Celgene	No comments	No action required.
	Novartis	The list of appraisals is out of date with respect to: • Omission of the ongoing ofatumumab appraisal (ID1677) as commented in the Comparators section. Novartis notes ofatumumab is already mentioned as a Novartis comparator in the provisional stakeholder matrix • In addition, depending on when the appraisal may be re-started, the same comment on omission may also apply to ponesimod (ID1393) • Listing of TA312 which does not capture the 17 March 2020 update issued by NICE	Thank you for your comment. Ofatumumab and ponesimod have been added as comparators. The scope has been updated with the correct dates.

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		• Listing of the review of NICE Guideline 186 which is scheduled to publish in July 2022 • Listing of the NICE Pathway as 2014 when this was last updated 10 July 2020 The list of related national policy is out of date with respect to: • NHS England DMT commissioning policy where a new version was published 4 Sept 2018 then subsequently updated 8 March 2019	
	Roche	No comments	No action required.
	Teva	No comments	No action required.
	Association of British Neurologists	Diroximel fumarate does not have marketing authorisation and the final results of the phase III studies are not published and so the above comments have been made within the limitations of the available data.	Thank you for your comment. No action required.
	MS Trust	No comments	No action required.
	NHS England & Improvement	No comments	No action required.

The following consultees/commentators indicated that they had no comments on the draft remit and/or the draft scope

None