Treatment Algorithm for Multiple Sclerosis Disease-Modifying Therapies

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1. Purpose of this algorithm

The purpose of this algorithm is to provide a framework to aid decision-making for multiple sclerosis (MS) specialists and patients, to help reduce excessive variation in practice, and to ensure safe and effective prescribing. It is understood that there may be situations where there is no single 'right' or 'wrong' therapeutic approach, and different experts may reasonably hold different views.

This algorithm is constrained by the regulatory status, NICE technology appraisal (TA) guidance and commissioning status of the disease-modifying drugs licensed for MS in England. Other guidance on disease-modifying drugs in MS, such as the Association of British Neurologists' guidelines[1] are different in scope and may make recommendations applying to the devolved administrations, outside the geographical and National Institute for Health and Care Excellence (NICE) constraints applying to NHS England.

NHS England's Neuroscience Clinical Reference Group (CRG) will review this algorithm to reflect any new NICE technology appraisal guidance or approvals within 3 months of guidance publication.

2. Principles of organisation of MS disease-modifying therapy services

The patient should be at the centre of any service for disease-modifying therapies. These services should be organised to optimise timely and equitable access of people with MS to disease-modifying therapies (DMTs).

Every region should make all NICE TA and NHS England commissioned MS drugs available to all people with MS in that region. It is expected that all DMT prescribers in a region will participate in a network of audit, quality control and education.

The minimum team for any prescribing service is a MS specialist consultant neurologist and a MS specialist nurse, working with support from a specialist MS centre and its multi-disciplinary team. Before prescribing, cases should be discussed in a multi-disciplinary team MDT meeting if the following criteria are met:

Criteria for discussion in multi-disciplinary team (MDT) meeting

- For first line therapy if higher risk DMTs are proposed e.g. cladribine and monoclonal antibody therapies
- All patients with rapidly evolving severe (RES) MS
- For second and third line therapy (includes all patients with highly active relapsing remitting (RR) MS
- Complex cases
- Children

In sections 7-11 the drugs that should have an MDT discussion have a star (*) next to them, in line with the MDT criteria above.

We define an MDT for adults as a minimum of at least two MS specialist consultant neurologists plus at least one specialist MS nurse, with access to neuro-radiology expertise. Ideally, the MDT would also incorporate additional specialist healthcare professionals, including a pharmacist with

[1] Scolding N, Barnes D, Cader S, Chataway J, Chaudhuri A, Coles A, Giovannoni G, Miller D, Rashid W, Schmierer K, Shehu A, Silber E, Young C, Zajicek J. Association of British Neurologists: revised(2015) guidelines for prescribing disease-modifying treatments in multiple sclerosis. Pract Neurol. 2015 Aug;15(4):273

expertise in MS. The MDT requirements for children is defined below.

At each prescribing centre, there should be an individual or team responsible for the governance of safety monitoring.

Services should be organised to facilitate collection of data for mandatory requirements (for instance, annual Expanded Disability Status Scale (EDSS) for reporting on a web-based clinical decision support system) and voluntary MS registers.

This treatment algorithm applies to all age groups, including children.[1] Children may receive DMTs if;

(i) they are licensed for children,

or

(ii) they have a recognised dose for children (for instance are cited in the British National Formulary for Children)

or: if neither of the previous two criteria apply

(iii) the child is post-pubescent. The management of pre-pubescent children with MS should be discussed at the meetings of the national network of paediatric MS centres.

In addition to the above criteria, ALL of the following conditions must apply as per Clinical Commissioning Policy: Commissioning Medicines for Children in Specialised Services, published by NHS England in 2017:[2]

1. The patient meets all the NICE TA/NHS England clinical commissioning policy criteria for the proposed medicine/indication.
2. The patient does not meet any exclusion criteria for the medicine/indication in question.
3. The use of the drug has been discussed at a multidisciplinary team (MDT) meeting which must include at least two consultants in the subspecialty with active and credible expertise in the relevant field of whom at least one must be a consultant paediatrician. The MDT should include a paediatric pharmacist and other professional groups appropriate to the disease area.
4. The patient has been registered via the NHS England prior approval web-based system

3. Definitions

The definitions below are taken from the Clinical Commissioning Policy for the use of Disease Modifying Therapies for patients with Multiple Sclerosis[3], published by NHS England in 2014. They represent explanations of terms used by the regulatory authorities, which were translated into NICE technology appraisal guidance. However, there is no difference in biological significance between relapses causing differing varying degrees of disability; all indicate disease activity.

Clinically significant relapse: All relapses are clinically significant, but in usual practice relapses contributing to the eligibility for Disease Modifying Therapies are:

- Any motor relapse
- Any brainstem relapse

[2] Clinical Commissioning Policy: Commissioning Medicines for Children in Specialised Services, Reference: NHS England: 170001/P

[3] NHS England. Clinical Commissioning Policy: Disease Modifying Therapies for Patients with Multiple Sclerosis (MS). May 2014. Reference: NHS ENGLAND/ D04/P/b

- A sensory relapse if it leads to functional impairment
- Relapse leading to sphincter dysfunction
- Optic neuritis
- Intrusive pain lasting more than 48 hours.

Disabling relapse: A disabling relapse is defined as any relapse which fulfils one or more of the following criteria:

- Affects the patient's social life or occupation, or is otherwise considered disabling by the patient
- Affects the patient's activities of daily living as assessed by an appropriate method
- Affects motor or sensory function sufficiently to impair the capacity or reserve to care for themselves or others
- Needs treatment/hospital admission.

Highly active disease: Patients with an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon. [From NICE TA254)[4]: Fingolimod for the treatment of highly active relapsing- remitting multiple sclerosis] The NICE TA on cladribine[5] offers a different definition: "defined as 1 relapse in the previous year and magnetic resonance imaging (MRI) evidence of disease activity."

Rapidly evolving severe (RES) relapsing–remitting disease: Defined by two or more disabling relapses in one year and one or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI. [From NICE TA127)[6]: Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis].

4. Starting criteria common to all DMTs

In general, treatment should be recommended as soon as a patient becomes eligible. For a patient to be eligible for any DMT, they must fulfil the following criteria:

- Sustained disability due to MS is less than EDSS 7.0, i.e. at least ambulant with two crutches. (Patients experiencing a relapse may transiently have disability greater than EDSS 7.0; if they recover to a sustained EDSS less than 7.0, they are eligible for DMTs)
- It is important that, at the start of treatment, the patient understands that treatment may be stopped if it is ineffective, intolerable adverse events arise, the patient becomes pregnant or they develop progressive disease or fixed disability above EDSS 6.5.
- MS Teams should proactively discuss the possibility of pregnancy as part of DMT selection. Where pregnancy is planned or desired, people with MS should usually be offered a DMT of at least similar efficacy which is compatible with pregnancy than if this were this not a consideration. The aim should be to allow people to make an informed choice about DMT use, taking into account safety around pregnancy alongside minimising the risk of relapse in the mother. DMTs in pregnancy must meet recognised commissioning criteria.
- Where generic or biosimilar options are available, treatment should be with the least expensive option (taking into account administration costs, dose needed and product price per dose).

5. Suggested common stopping criteria for all DMTs

The current DMT should be stopped if any of the following criteria are met:

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[4] National Institute for Health and Care Excellence Fingolimod for the treatment of highly active relapsing–remitting multiple sclerosis (TA 254) Published: 25 April 2012

5. National Institute for Health and Care Excellence: Cladribine for treating relapsing–remitting multiple sclerosis (TA 616) published 19 December 2019

[6] National Institute for Health and Care Excellence. Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (TA127). Published 22 August 2007

1. No reduction in frequency or severity of relapses compared with pre-treatment phase following adequate exposure to the DMTs (which varies for each DMT, but should be a minimum of 6 months)
2. Intolerable adverse effects of the drug
3. Development of inability to walk (EDSS 7.0), persistent for more than 6 months due to MS
4. Confirmed secondary progressive disease with an observable increase in disability for more than a 12-month period, in the absence of relapse activity. Secondary progressive disease would usually only be diagnosed in patients with an EDSS of 6.0 or greater.

Criteria 1, 2 and 4 may lead to switching to alternative licensed DMTs. Criteria 3 will lead to stopping all DMTs.

Past criteria have included pregnancy, breast feeding or attempting conception, but increasing evidence shows that some DMTs may be considered an option in these situations.

Stopping DMTs should lead to continued care within the MS team or transfer of care to services which can provide appropriate support, such as neurorehabilitation.

If a drug is stopped for a reason other than the criteria above, then it may be restarted at a later date, even though the patient may not have “requalified” through new lesions or relapses. This may apply, for instance, to people who come off a drug during pregnancy or participate in a clinical trial for MS.

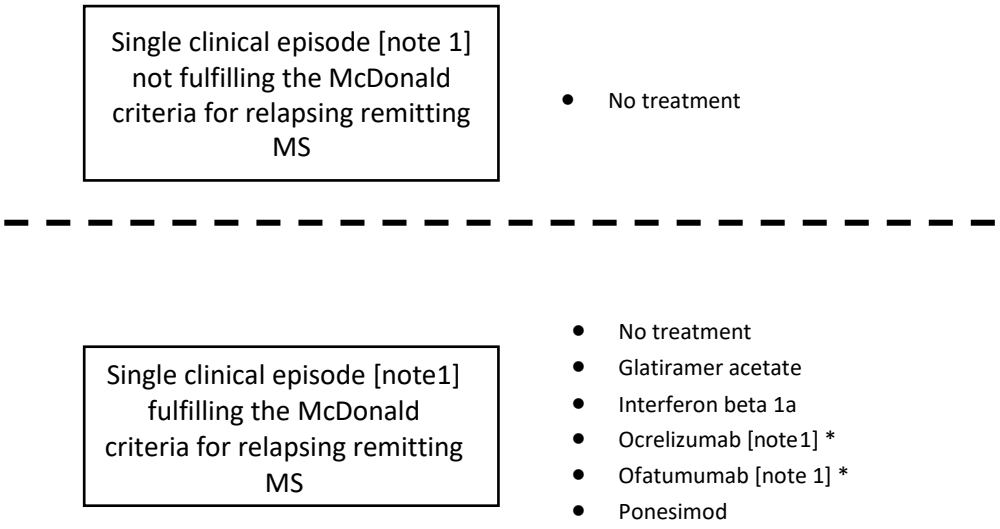
6. General principles of drug switching

Switching can be done for reasons of intolerance (which includes burdensome modes of administration), disease activity or cumulative risk of progressive multifocal leukoencephalopathy (PML) with natalizumab for example. None of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs.

Disease activity should prompt consideration of switching only if there has been adequate exposure, with good adherence, to the DMT (which varies for each DMT, but usually should be a minimum of 6 months).

Evidence for disease activity that should prompt consideration of switching for all DMTs is clinical relapses; magnetic resonance imaging (MRI) evidence of disease activity usefully supplements this assessment. NICE has approved the use of alemtuzumab, ocrelizumab, ofatumumab and ponesimod based on radiological disease activity alone.

7. Treatment algorithm for single clinical episode with radiological activity



* Drugs that should have an MDT discussion, as described in the criteria for an MDT discussion outlined in section 2 above

Note:

1. Where clinical or radiological markers indicate a poor prognosis for rapidly developing permanent disability, ofatumumab or ocrelizumab may be considered after a single clinical episode with MRI activity. Physicians and patients should weigh up the risks against the potential benefit[7,8]. This must be agreed by the MDT.

[7] National Institute for Health and Care Excellence. Ocrelizumab for treating relapsing-remitting multiple sclerosis. (TA533). Published 25 July 2018

[8] National Institute for Health and Care Excellence. Ofatumumab for treating relapsing-remitting multiple sclerosis (TA699). Published 19 May 2021)

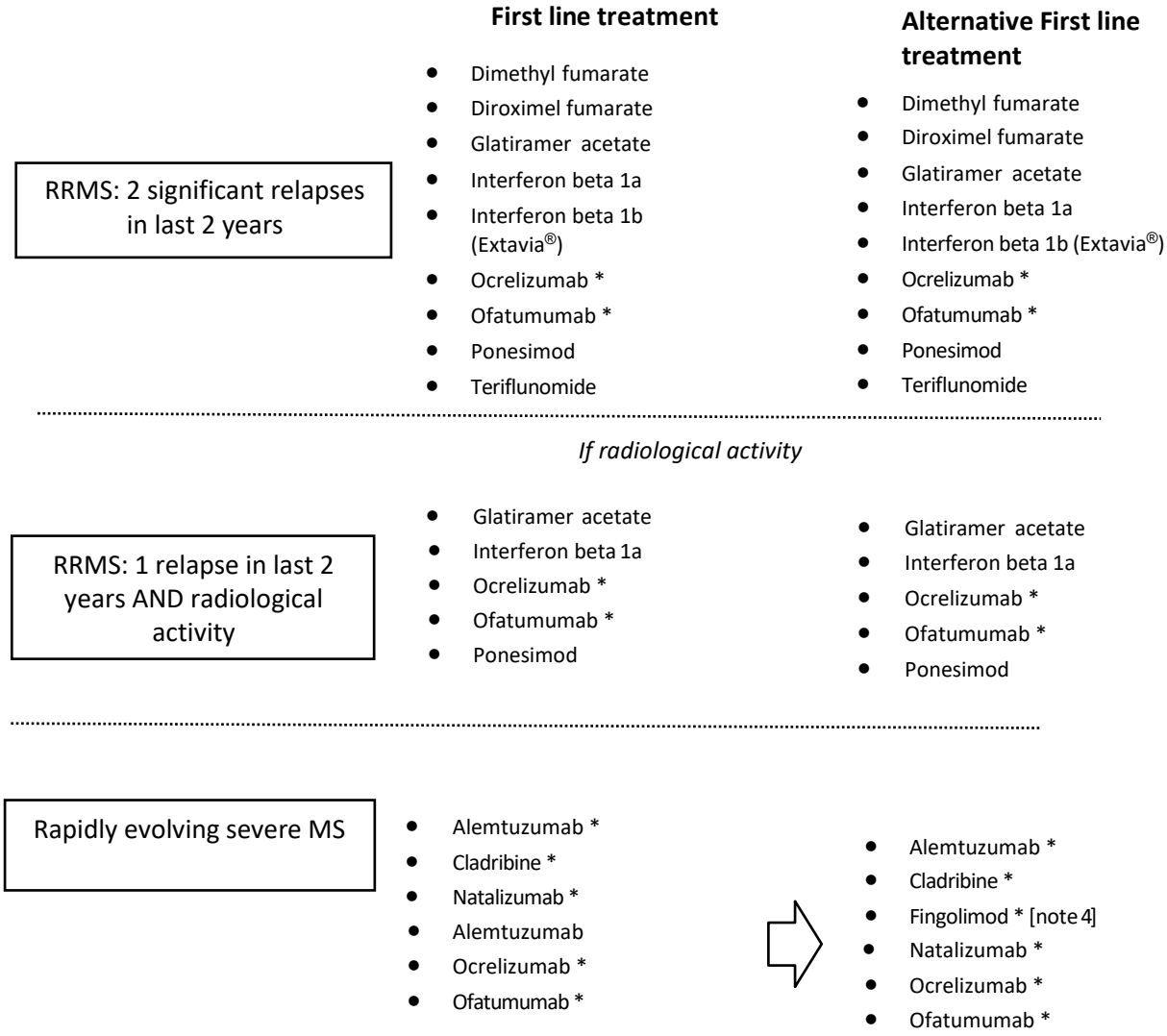
8. Treatment algorithm for first line therapy of relapsing-remitting multiple sclerosis (RRMS)

RRMS: 2 relapses in last 2 years	• Dimethyl fumarate • Diroximel fumarate • Glatiramer acetate • Interferon beta 1a • Interferon beta 1b (Extavia®) • Ocrelizumab * • Ofatumumab * • Ponesimod • Teriflunomide
RRMS: 1 relapse in last 2 years AND radiological activity	• Glatiramer acetate • Interferon beta 1a • Ocrelizumab * • Ofatumumab * • Ponesimod
Rapidly evolving severe MS	• Alemtuzumab or ocrelizumab [note 2] * • Cladribine [note 2] * • Natalizumab * • Ofatumumab *

Note:

2. Alemtuzumab, Ocrelizumab, ofatumumab and cladribine may be a safer option than natalizumab when John Cunningham virus (JCV) serology is high-index positive.

9. Treatment algorithm for intolerance to first line therapy [note 3]



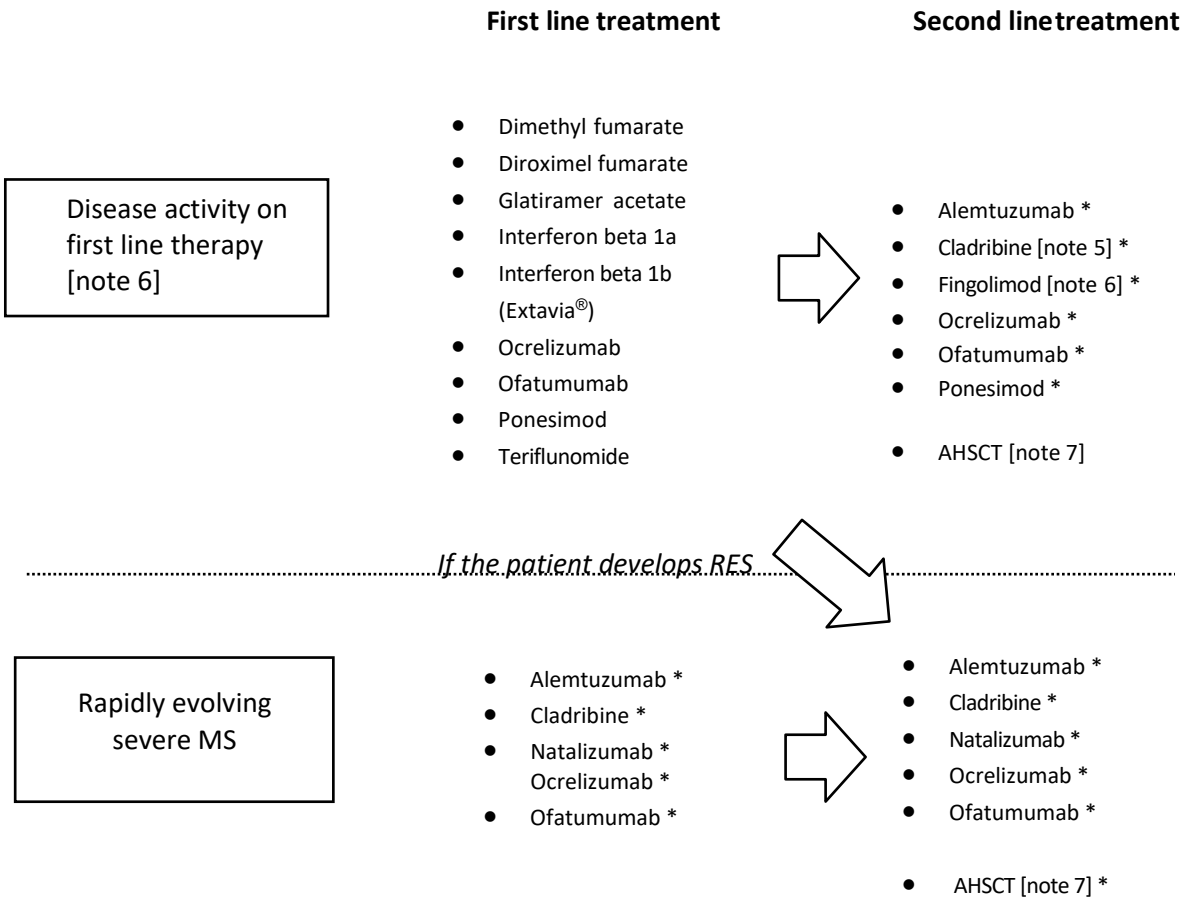
* Drugs that should have an MDT discussion, as described in the criteria for an MDT discussion outlined in section 2 above

Notes:

3. If a patient satisfies the eligibility criteria for a first line therapy, and then is relapse-free on a drug to which they become intolerant, they may be switched to another DMT even though their relapses may now fall outside the eligibility window.
4. NHS England 2014 clinical commissioning policy states that fingolimod can be used as an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing PML as defined by the following:
   (i) JCV exposure indicated by anti-JCV antibody positive status,
   (ii) Receiving an immunosuppressant prior to receiving natalizumab, or
   (iii) Natalizumab treatment duration of >2 years.

   If patients develop a severe adverse effect to natalizumab (e.g. anaphylaxis), and they have not previously received fingolimod, then it may be appropriate to use fingolimod.

10. Treatment algorithm for disease activity on first line therapy

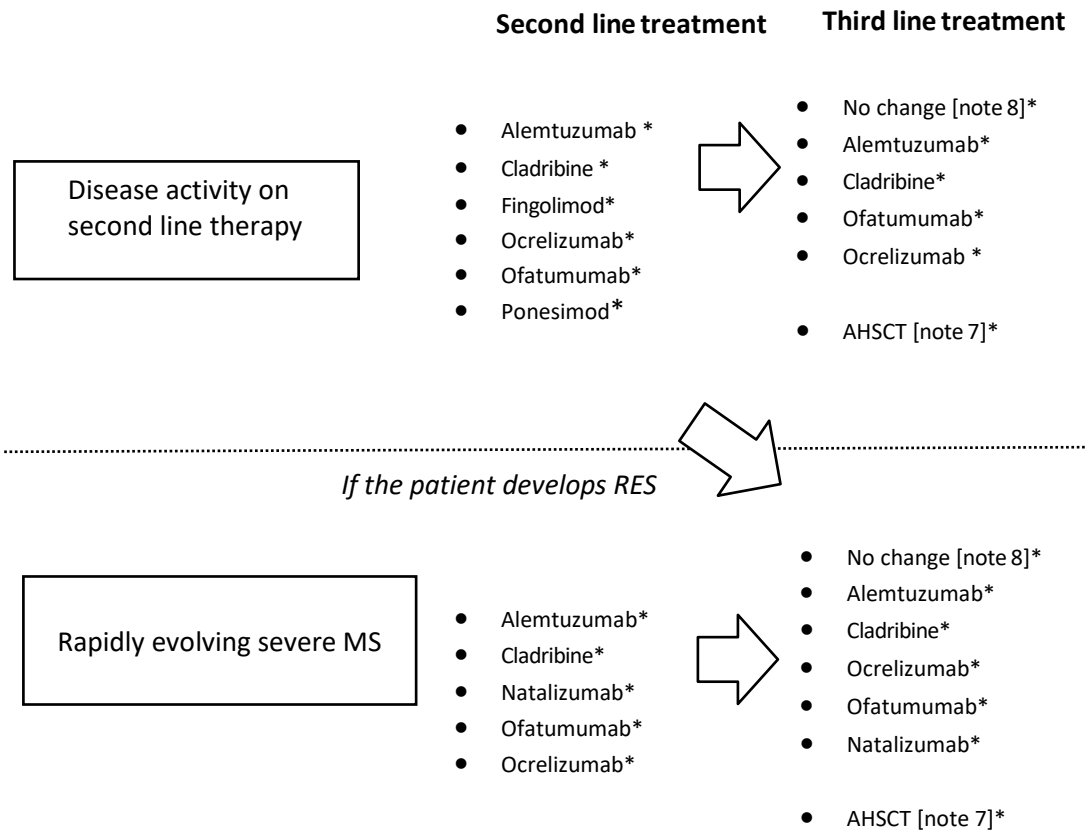


* Drugs that should have an MDT discussion, as described in the criteria for an MDT discussion outlined in section 2 above

Notes:

5. For cladribine to be given, NICE specifically defined treatment failure as “1 relapse in the previous year and MRI evidence of disease activity.”
6. For fingolimod: under previous guidance, fingolimod may be given if patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon or glatiramer acetate. This is now extended to include disease activity on dimethyl fumarate, diroximel fumarate, teriflunomide and ponesimod.
7. Autologous haematopoietic stem cell treatment for autoimmunity is commissioned at specialised centres and should be discussed at a specialist MDT. [b04-haematp-stem-cll-transplt.pdf (england.nhs.uk)]

11. Treatment algorithm for disease activity on second line therapy



*Drugs that should have an MDT discussion, as described in the criteria for an MDT discussion outlined in section 2 above

Note:

8. After considering all these options, it may be appropriate to continue the second line therapy, despite evidence of disease activity. None of the drugs promise 100% efficacy and some patients and physicians may choose to tolerate some disease activity without changing drugs.

12. Treatment algorithm for active secondary progressive multiple sclerosis

Interferon beta-1b (Extavia®) and siponimod are approved by NICE for active secondary progressive multiple sclerosis (NICE TA527[9], TA656[10]).

All of the following starting criteria must be met in general. The patient:

- is able to walk 10m or more (EDSS less than 7.0)
- is aged over 18 years
- has no contra-indications
- has been informed of and agreed to stopping criteria.

Starting criteria specific to interferon beta-1b (Extavia®):

- At least 2 disabling relapses in two years
- Disease progression by less than 2 EDSS points over the last year (other than relapse-related) where data have been recorded.

Starting criteria specific to siponimod:

- Active disease evidenced by at least one relapse in the previous two years

  and/or

- Active disease evidenced by imaging features of inflammatory activity (either a new T2 lesion in comparison to an appropriate previous scan or a new gadolinium enhancing lesion on a recent scan as agreed by MDT)

  and/or

- Evidence of progression independent of relapses within the last two years while being treated with DMT for RRMS: progression is defined as a 1-point increase in EDSS if the baseline score is ≤ 5.5, or a 0.5 point increase if the baseline score is ≥ 6.0, confirmed at least 6 months apart. The minimum EDSS score at baseline is 4. Due to the nature of SPMS, this progression can be identified retrospectively.
- Discussed in MDT

Stopping criteria:

One or more of the following criteria are met:

- No reduction in frequency or severity of relapses compared with pre-treatment phase following a minimum 6-month period
- Intolerable adverse effects of the drug
- Stopping criteria should be made known to patients and agreed before treatment is started

[9] National institute for Health and Care Excellence. Beta interferons and glatiramer acetate for treating multiple sclerosis 9TA527). Published 27 June 2018

[10] National Institute for Health and Care Excellence. Siponimod for treating secondary progressive multiple sclerosis TA656). Published 18 November 2020

13. Treatment algorithm for early primary progressive multiple sclerosis

Only ocrelizumab is approved by NICE for early primary progressive multiple sclerosis (PPMS) as determined by NICE and NHS England commissioning criteria (NICE TA 585[7]).

All of the following starting criteria must be met. The patient:

- is able to walk 10m or more (EDSS less than 7.0)
- is aged over 18 years (and in post-pubescent adolescents)
- has no contra-indications.
- has been discussed at MDT
- has been informed of and agreed to stopping criteria
- has a diagnosis of early PPMS with active disease defined by the appearance of new T2 lesions confirmed by two MRI studies at least six months apart or one or more gadolinium enhancing lesions on one MRI, either of these occurring over the last three years.

Early primary progressive multiple sclerosis is represented by an EDSS of between 3 - 6.5 with maximum disease duration of 15 years at start of ocrelizumab treatment.
For an EDSS of greater than 5.0 symptoms should be present for up to 15 years and for an EDSS of less than or equal to 5.0 symptoms should be present for up to 10 years.

Stopping criteria:

One or more of the following criteria are met:

- Intolerable adverse effects of the drug
- Stopping criteria should be made known to patients and agreed before treatment is started

Addendum 1: Table of drug authorisation, NICE indication and NHS England positioning

Drug	Marketing Authorisation	NICE indication	NHS ENGLAND 2014 clinical commissioning policy
Interferon beta-1a	AVONEX is indicated for the treatment of: (i) Patients diagnosed with relapsing multiple sclerosis (MS). In clinical trials, this was characterised by two or more acute exacerbations(relapses) in the previous three years without evidence of continuous progression between relapses; AVONEX slows the progression of disability and decreases the frequency of relapses; (ii) Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis (see section 5.1). REBIF is indicated for the treatment of relapsing multiple sclerosis. In clinical trials, this was characterised by two or more acute exacerbations in the previous two years. PLEGRIDY is indicated in adult patients for the treatment of relapsing remitting multiple sclerosis.	NICE TA527 (June 2018) Interferon beta-1a [AVONEX and REBIF] is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis. NICE TA624 (Feb 2020) Peginterferon beta-1a is recommended, within its marketing authorisation, as an option for treating relapsing–remitting multiple sclerosis in adults.	All of the following criteria must be met. The patient: (i) has had at least 2 clinically significant relapses in previous 2 years; (ii) is able to walk 10m or more**; (iii) is not pregnant or attempting conception. Neurologists may, in certain other circumstances where the evidence for efficacy is less secure, also consider advising treatment after discussion with the patient concerning the risks and benefits. For example; i) Patients within 12 months of a clinically significant clinically isolated syndrome when MRI evidence predicts a high likelihood of recurrent episodes (i.e. development of MS); (ii) patients with only a single major relapse in the preceding two years, but combined with MRI evidence of continuing disease activity (i.e. meet the revised McDonald criteria for MS); (iii) individuals aged less than 18 with relapsing remitting MS ** For patients who can walk between 10 and 99 m (aided or unaided, EDSS 6.0 to 6.5), treatment with DMTs is permitted bur recommended less strongly than for patients able to walk more than 100m unaided (EDSS 5.5 or less).
Interferon beta-1b	BETAFERON is indicated for the treatment of) (i) Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; (ii) Patients with relapsing-remitting multiple sclerosis and two or more relapses within the last two years) Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses. EXTAVIA® is indicated for the treatment of; (iii) Patients with a single demyelinating event with an active inflammatory process, if it is severe enough to warrant treatment with intravenous corticosteroids, if alternative diagnoses have been excluded, and if they are determined to be at high risk of developing clinically definite multiple sclerosis; (iv) Patients with relapsing remitting multiple sclerosis and two or more relapses within the last two years; (v) Patients with secondary progressive multiple sclerosis with active disease, evidenced by relapses.	NICE TA527 (June 2018) **BETAFERON is not recommended** NICE TA527 (June 2018) EXTAVIA® is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis and has had 2 or more relapses within the last 2 years or the person has secondary progressive multiple sclerosis with continuing relapses	As per interferon-1a guidance, but also permits the use of interferon-1b in relapsing-progressive disease.

Drug	Marketing Authorisation	NICE indication	NHS ENGLAND 2014 clinical commissioning policy
Glatiramer acetate	Indicated for the treatment of relapsing forms of multiple sclerosis (MS) (see section 5.1 for important information on the population for which efficacy has been established). Indicated in primary or secondary progressive MS	NICE TA527 (June 2018) Glatiramer acetate is recommended as an option for treating multiple sclerosis, only if the person has relapsing–remitting multiple sclerosis. (n.b. "Stakeholders consider glatiramer acetate to be the safest drug for anyone who is planning to become pregnant".)	As per interferon-beta guidance, but must be able to walk 100m or more
Teriflunomide	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS).	NICE TA303 (Jan 2014, last updated 01 June 2014) Teriflunomide is recommended as an option for treating adults with active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis	
Dimethyl fumarate	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis	NICE TA320 (Aug 2014) Dimethyl fumarate is recommended as an option for treating adults with active relapsing‑remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years), only if they do not have highly active or rapidly evolving severe relapsing‑remitting multiple sclerosis	
Fingolimod	(i) Indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following adult patient groups) Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy or (ii) Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	NICE TA254 (April 2012) Fingolimod is recommended as an option for the treatment of highly active multiple sclerosis: Patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon* or glatiramer acetate	Fingolimod is recommended as an option for the treatment of highly active multiple sclerosis: Patients have an unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon* or glatiramer acetate or As an alternative to natalizumab for those patients receiving natalizumab who are at high risk of developing progressive multifocal leukoencephalopathy (PML) as defined by the following: • JCV exposure indicated by anti-JCV antibody positive status • Receiving an immunosuppressant prior to receiving natalizumab • Natalizumab treatment duration of >2 years

Drug	Marketing Authorisation	NICE indication	NHS ENGLAND 2014 clinical commissioning policy
Natalizumab	Patients aged 18 years and over with highly active disease activity despite a full and adequate course of treatment with at least one disease modifying therapy (DMT), a beta-interferon or glatiramer acetate. These patients may be defined as those who have failed to respond to a full and adequate course (normally at least one year of treatment) of beta-interferon or glatiramer acetate. Patients should have had at least 1 relapse in the previous year while on therapy, and have at least 9 T2-hyperintense lesions in cranial Magnetic Resonance Image (MRI) or at least 1 Gadolinium-enhancing lesion. A "non-responder" could also be defined as a patient with an unchanged or increased relapse rate or ongoing severe relapses, as compared to the previous year. Adult patients aged 18 years and over with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI	NICE TA127 (Aug 2007) Rapidly evolving severe relapsing–remitting multiple sclerosis (RES). RES is defined by two or more disabling relapses in 1 year, and one or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI	For patients who • has had two or more disabling relapses in the past year • has one or more gadolinium-enhancing lesions on MRI or increase in T2 lesion load compared with previous MRI unless comparator MRI is unavailable or assessment of gadolinium-enhancement is unreliable as the patient is treated with steroids at around the time of scan. • has had no previous disease modifying therapy OR is receiving treatment with beta interferon and does not meet the agreed stopping criteria. *As per NICE Technology Appraisal Guidance 127 patients with high disease activity taking beta interferon or glatiramer acetate but do not fulfil the RES criteria will not be routinely funded for natalizumab.
Alemtuzumab	Indicated for adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features	NICE TA312 (May 2014; last updated March 2020) Alemtuzumab is recommended as an option, within its marketing authorisation, for treating highly active relapsing–remitting multiple sclerosis in adults with: • highly active disease despite a full and adequate course of treatment with at least 1 disease-modifying therapy or • rapidly-evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year, and with 1 or more gadolinium-enhancing lesions on brain MRI or a significant increase in T2 lesion load compared with a previous MRI	NHS England will fund up to three cycles of alemtuzumab. Any further cycles would need to be approved by NICE under a review of TA312.
Cladribine	Indicated for the treatment of adult patients with highly active relapsing multiple sclerosis (MS) as defined by clinical or imaging features	NICE TA616 (Dec 2019, replaces TA493) Cladribine is recommended as an option for treating highly active multiple sclerosis in adults, only if the person has: (1) rapidly evolving severe relapsing–remitting multiple sclerosis, that is, at least 2 relapses in the previous year and at least 1 T1 gadolinium-enhancing lesion at baseline MRI or a significant increase in T2-lesion load compared with a previous MRI, or (2) relapsing– remitting multiple sclerosis that has responded inadequately to treatment with disease-modifying therapy, defined as 1 relapse in the previous year and MRI evidence of disease activity.	

Drug	Marketing Authorisation	NICE indication	NHS ENGLAND 2014 clinical commissioning policy
Ocrelizumab for treating relapsing–remitting multiple sclerosis	Indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features. Indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	NICE TA533 (July 2018) Ocrelizumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features, only if alemtuzumab is contraindicated or otherwise unsuitable.	
Ocrelizumab for treating primary progressive multiple sclerosis	Indicated for the treatment of adult patients with early primary progressive multiple sclerosis (PPMS) in terms of disease duration and level of disability, and with imaging features characteristic of inflammatory activity.	NICE TA585 (June 2019) Ocrelizumab is recommended as an option for treating early primary progressive multiple sclerosis with imaging features characteristic of inflammatory activity in adults.	
Ofatumumab	Indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features	NICE TA699 (May 2021) Ofatumumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features.	
Ozanimod	Indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features.	NICE TA706 (June 2021) **Ozanimod is not recommended**	
Siponimod	Siponimod is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) with active disease evidenced by relapses or imaging features of inflammatory activity.	NICE TA656 (November 2020) Siponimod is recommended, within its marketing authorisation, as an option for treating secondary progressive multiple sclerosis with evidence of active disease (that is, relapses or imaging features of inflammatory activity) in adults.	
Ponesimod	Ponesimod is indicated for 'the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features'.	NICE [TA767] (February 2022) Ponesimod is recommended for treating relapsing–remitting multiple sclerosis with active disease defined by clinical or imaging features in adults.	
Diroximel fumarate	Diroximel fumarate has a marketing authorisation 'for the treatment of adult patients with relapsing–remitting multiple sclerosis'.	NICE [TA794] (08 June 2022) Diroximel fumarate is recommended as an option for treating active relapsing–remitting multiple sclerosis (normally defined as 2 clinically significant relapses in the previous 2 years) in adults, only if they do not have highly active or rapidly evolving severe relapsing–remitting multiple sclerosis.	

Appendix 1: Acronyms and abbreviations

ABN	The Association of British Neurologists
CRG	Clinical Reference Group
DMT	Disease-modifying Therapies – can reduce how many relapses someone has and how serious they are
EDSS	Expanded Disability Status Scale – a method of quantifying disability in multiple sclerosis and monitoring changes in disability over time
JCV	John Cunningham (JC) virus is a common infection completely unrelated to MS but which is normally kept under control by the immune system
MDT	Multidisciplinary team
MRI	Magnetic resonance imaging
MS	Multiple Sclerosis - involves an immune-mediated process in which an abnormal response of the body's immune system is directed against the central nervous system.
NICE	National Institute for Health and Care Excellence
NICE TA	NICE technology appraisal guidance
PML	Progressive Multifocal Leukoencephalopathy – a rare viral disease of the brain
RES	Rapidly evolving severe relapsing-remitting MS
RRMS	Relapsing-remitting MS

Summary of changes to this document

Describe what was stated in original document	Describe new text in the document	Section/Paragraph to which changes apply	Describe why document change required	Changes made by	Date change made
Ofatumumab	Indicated for the treatment of adult patients with relapsing forms of multiple sclerosis (RMS) with active disease defined by clinical or imaging features NICE TA699 (May 2021) Ofatumumab is recommended as an option for treating relapsing–remitting multiple sclerosis in adults with active disease defined by clinical or imaging features.	Addendum 1, and other relevant sections		Multiple Sclerosis (MS) Expert Working Group (EWG)	04/08/2021
Siponimod	Specific to Siponimod (active secondary progressive MS): • Active disease evidenced by at least one relapse in the previous two years And/Or • Active disease evidenced by imaging features of inflammatory activity	Section 12		MS EWG	16/11/2021
Starting criteria	Specify general starting criteria and specific for Extavia®	Section 12		MS EWG	04/08/2021 19/05/2022
Ponesimod	Included in the document as specified by Ponesimod for treating relapsing–remitting multiple sclerosis Technology appraisal guidance TA767. Published: February 2022	Section 7-11		MS EWG	13/06/2022
Diroximel fumarate	Included in the document as specified by Diroximel fumarate for treating relapsing–remitting multiple sclerosis Technology appraisal guidance TA794. Published: June 2022	Sections 8-10		MS EWG	13/06/2022
Note 1 on page 6 "Trials of first-line therapies in people with the original definition of Also known as Clinically Isolated Syndrome (CIS) at high risk of conversion have NOT shown a convincing long-term effect on the accumulation of disability. In 2018, NICE	Removed	Section 7	EWG believe that the following change is needed to update the document and will not impact the number of patients having access to treatment.	MS EWG	30/06/2022

concluded that it was "unable to make recommendations for treating clinically isolated syndrome because the diagnostic criteria for multiple sclerosis and clinically isolated syndrome have changed and the treatment pathway has evolved". These new diagnostic criteria are the revised 2017 McDonald criteria."					
"In exceptional circumstances" at the beginning of note 2 (or new note 1)	Removed	Section 7	EWG believe that the following change is needed to update the document and will not impact the number of patients having access to treatment.	MS EWG	30/06/2022
"we suggest this usually means 2 or more new MS lesions on MRI over a year" at the end of page 5	Removed	Section 6	EWG believe that the following change is needed to update the document and will not impact the number of patients having access to treatment.	MS EWG	30/06/2022
Treatment algorithm for early primary progressive multiple sclerosis	New section added	Section 13	EWG believe that the following change is needed to update the document and will not impact the number of patients having access to treatment.	MS EWG	30/06/2022
This treatment algorithm applies to all age groups, including children. Children may receive DMTs if; (i) they are licensed for children, Or (ii) they have a recognised dose for children (for instance are cited in the British National Formulary for Children)	New section added referring to Commissioning Medicines for Children in Specialised Services NHS E 170001/P	Section 2	EWG believe that the change is needed to include clear guidelines regarding the prescribing of DMTs for Children	MS EWG	15/08/22

or: if neither of the previous two criteria apply (i)(iii) the child is post-pubescent. The management of pre-pubescent children with MS should be discussed at the meetings of the national network of paediatric MS centres					
Complex cases or those where higher-risk DMTs (cladribine and monoclonal antibody therapies) are proposed, all rapidly evolving severe (RES) MS and highly active relapsing-remitting (RR)MS patients should be discussed at a multi-disciplinary team (MDT) meeting. In sections 7-11 the drugs or group of drugs that need MDT discussion have a star (*) next to them. We define an MDT as a minimum of at least two MS specialist consultant neurologists plus at least one specialist MS nurse, with access to neuro-radiology expertise. Ideally, the MDT would also incorporate additional specialist healthcare professionals, including a pharmacist with expertise in MS	New text makes clear the cases in which an MDT should take place	Section 2	The EWG believe that the change is needed to make the MDT arrangements clearer	MS EWG	22/08/22
N/A	MS Teams should proactively discuss the possibility of pregnancy as part of DMT selection. Where pregnancy is planned or desired, people with MS should usually be offered a DMT of at least similar efficacy which is compatible with pregnancy than if this were this not a consideration. The aim should be to allow people to make an informed choice about DMT use, taking into account safety around pregnancy alongside minimising the risk of relapse in the mother. DMTs in pregnancy must meet recognised commissioning criteria.	Section 4	The EWG believe that this statement is important in ensuring equity of access to DMTs for pregnant women or women planning pregnancy	MS EWG	15/03/23
N/A	Where generic or biosimilar options are available, treatment should be with the	Section 4	The EWG believe that this statement is	MS EWG	15/03/23

	least expensive option (taking into account administration costs, dose needed and product price per dose).		important in ensuring that cost effectiveness is a consideration when choosing treatment options		
1st bubble " RRMS: 2 significant relapses in last 2 years"	'Significant' has been removed	Visual Algorithm	The EWG felt that it is just as important to treat after a sensory relapse as a motor relapse as there has been activity	MS EWG	20/03/23
N/A	Visual Algorithm	Visual Algorithm	Siponimod/progressive MS has now been added to the visual algorithm. The group felt that this should be included for equity and better awareness and promotion of progressive MS generally.	MS EWG	20/03/23
Development of inability to walk, persistent for more than 6 months in stopping criteria	Removed	Section 12 and 13	The EWG felt that this needed to be removed to ensure equity of access to DMTs	MS EWG	23/03/23