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la littérature (Anglais)

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La prise en charge de la Sclérose en Plaques

**INSTITUT NATIONAL D'ASSURANCE
MALADIE-INVALIDITÉ
SERVICE DES SOINS DE SANTÉ**
Comité d'évaluation des pratiques
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medische praktijk inzake geneesmiddelen

Multiple Sclerosis

Literature review: synopsis
report

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1 Abbreviations

AWMF: Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften

CBT: Cognitive Behavioral Therapy

DMT: disease modifying treatment

EDSS: Expanded Disability Status Scale

FMS: Federatie Medisch Specialisten

GP: general practitioner

MS: multiple sclerosis

NICE: National Institute for Health and Care Excellence

PPMS: primary progressive MS

RRMS: relapsing-remitting MS

SPMS: secondary progressive MS

2 Methodology

2.1 Introduction

This literature report was conducted in preparation of the consensus conference “Multiple Sclerosis” which will take place on October 23 2025.

2.2 Questions to the jury

The questions to the jury to be considered in this literature report, as they were phrased by the organising committee of the RIZIV/INAMI are:

2) How to monitor treatment in primary care?

- How can the general practitioner monitor the treatment of MS?
 - What can the GP do themselves in terms of follow-up and treatment of MS?
 - When is it necessary to seek advice from or refer to a specialist?
 - How can MS exacerbations (flare-ups) be recognized, and what measures should be taken?
- What is the impact of MS medication on blood counts, and when should results be considered abnormal?
- What are the implications of MS medication for vaccinations?
- What are the most common short- and long-term adverse effects of MS medication?

3) Symptoms that may at first seem unrelated to MS ("invisible" symptoms)

- How should symptoms such as bladder and bowel issues, pain, and fatigue (that are often not spontaneously reported by patients) be addressed and managed??
- How can collaboration between the general practitioner and the specialist be optimized in identifying and managing such symptoms?

4) Target groups at different life stages

- Considerations for children and adolescents living with MS.
- General principles for managing MS in individuals with an active desire to have children.
- Considerations for older adults living with MS.
- Considerations for patients with MS who also have cardiovascular comorbidities.
- Considerations related to employment and work disability.

5) Non-pharmacological approach

- What is the importance of lifestyle measures in the treatment of MS?
- What role do physical activity and sports play in the treatment of MS?

- What role does rehabilitation play in the treatment of MS, including the role of the physiotherapist and the specialist in physical and rehabilitation medicine?

Jury questions 1 and 6 fall outside the scope of this report and will be addressed during the consensus meeting itself by expert speakers and/or through a debate.

2.3 Research task of the literature group

The organising committee has specified the research task for the literature review as follows:

- To discuss **selected guidelines**.
 - See 2.3.1 for guideline inclusion criteria.
- To discuss information from **additional sources** for information on safety, contra-indications, specific subgroups, precautions and monitoring.
 - See section 2.3.2 “Sources for safety information”.

In the table below, we provide an overview of the research task of the literature group per jury question. We also indicate in what chapter the results can be found.

<p>2) How to monitor treatment in primary care?</p> <p>Recommendations from guidelines: chapter 5.1; 5.2; 5.3; 5.4</p> <p>Additional safety information: chapter 6</p>
<p>3) Symptoms that may at first seem unrelated to MS ("invisible" symptoms)</p> <p>Recommendations from guidelines: chapter 5.5</p>
<p>4) Target groups at different life stages</p> <p>Recommendations from guidelines: chapter 5.6</p>
<p>5) Non-pharmacological approach</p> <p>Recommendations from guidelines: chapter 5.7</p>

2.3.1 Guidelines

Guidelines will be selected and agreed upon through discussion with the organising committee, based on relevance for the Belgian situation and certain quality criteria:

- Publication date: only guidelines from 2020 onwards are to be selected. Exceptions can be made when only older guidelines regarding a certain topic are available.
- Quality assessment: Only guidelines that report levels of evidence/recommendation are to be selected.

- Systematic review: the guideline needs to be based on a good systematic search and review of the literature and/or a formal consensus process.

In order to make an assessment on the rigour of development of the guidelines, guidelines will be scored according to Agree II score, for the domain “Rigour of development”. More information can be found on <http://www.agreetrust.org/>.¹

This table gives an overview of the items assessed in this domain according to the Agree II score.¹

No.	Description of the item
7	Systematic methods were used to search for evidence
8	The criteria for selecting the evidence are clearly described
9	The strengths and limitations of the body of evidence are clearly described
10	The methods for formulating the recommendations are clearly described
11	Health benefits, side effects, and risks have been considered in formulating the recommendations.
12	There is an explicit link between the recommendations and the supporting evidence.
13	The guideline has been externally reviewed by experts prior to its publication
14	A procedure for updating the guideline is provided

Table: Items assessed by the domain "Rigour of development" in Agree II score.

Domain scores are calculated by summing up all the scores of the individual items in a domain and by scaling the total as a percentage of the maximum possible score for that domain. The domain score “Rigour of development” can be used to assess the process used to gather and synthesize the evidence, the methods to formulate the recommendations, and to update them, though be careful with the interpretation because this scoring is also subjective and the resulting scores can thus be disputable. In the chapter about the guidelines, the Domain scores as assessed by the literature group, are given for each guideline.

The literature group will also report whether the guideline was developed together with other stakeholders (other healthcare professionals: pharmacists, nurses,... or patient representatives) and whether these guidelines are also targeting these groups.

Similarities and discrepancies between guidelines are to be reported.

2.3.2 Sources for safety information, contra-indications, precautions and monitoring

- Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI) / Centre Belge d'Information Pharmacothérapeutique (CBIP)
 - *Gecommentarieerd geneesmiddelenrepertorium/ Répertoire Commenté des Médicaments*(CBIP)(1)
 - *Folia Pharmacotherapeutica*
- Martindale: The complete drug reference (online)(2)

2.4 Guideline identification and selection

A targeted search was conducted to identify clinical guidelines on multiple sclerosis (MS) published between 2020 and 2025. The following sources were consulted:

- CDLH
- G-I-N Guideline Library
- EBPnet
- TRIP Database
- MEDLINE via PubMed

After removal of duplicates and screening based on titles and abstracts, a list of 20 potentially relevant guidelines was compiled.

A preliminary methodological appraisal was undertaken to assess:

- Relevance to primary care settings
- Whether the guideline was informed by a systematic review of the evidence and/or a formal consensus procedure
- Inclusion of levels of evidence or graded recommendations

Eight guidelines met these appraisal criteria. Following discussion with members of the OC expert group, two guidelines were excluded due to limited relevance to the defined scope of the project.

One extra guideline about the management of MS in pregnancy that was not found via search was suggested by the OC and included.

The following seven guidelines were selected for further analysis and comparison:

Abbreviation	Guideline
Dutch FMS 2023(3)	Federatie Medisch Specialisten; 2023; Multiple Sclerose (MS)
ECTRIMS/EAN 2023(4)	S. Otero-Romero et al.; European Committee for Treatment and Research in Multiple Sclerosis and European Academy of Neurology consensus on vaccination in people with multiple sclerosis: Improving immunization strategies in the era of highly active immunotherapeutic drugs – European journal of neurology (2023) ; 30(8):2144-2176.
German AWMF 2024(5)	AWMF; 2024; S2k-Leitlinie Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis Optica Spektrum und MOG-IgG-assoziierte Erkrankungen - Living Guideline [v 8.0]
FR MS Pregnancy 2022(6)	Pregnancy and multiple sclerosis: 2022 recommendations from the French multiple sclerosis society

FR URINARY 2020(7)	Donzé, C., Papeix, C., Lebrun-Frenay, C.; 2020; Urinary tract infections and multiple sclerosis: Recommendations from the French Multiple Sclerosis Society
NICE 2022(8)	NICE; 2022; Multiple sclerosis in adults: management (NG220)
NICE URINARY 2012 UPD2023(9)	NICE ; 2012 [last updated 2023] ; Urinary incontinence in neurological disease: assessment and management (CG148)

2.5 Synopsis of the study results

The synopsis report contains:

- Methodology
- Critical reflections from the bibliography group
- General information on selected guidelines
- A summary and comparison of recommendations from guidelines.
- Additional safety information
- References

The complete report contains:

- The synopsis report
- **An appendix**, containing relevant recommendations and information from guidelines

3 Critical reflections from the literature group

3.1 Rationale

Multiple sclerosis (MS) is a relatively rare condition in primary care, with a prevalence estimated to be about 104/100 000 in Belgium(10). MS care is a highly specialized field, particularly when it comes to initiating and monitoring disease-modifying therapies (DMTs), which are typically prescribed and followed up exclusively in secondary care. This raises the question: what role can the general practitioner (GP) or other primary care providers play in the care of a person with MS?

3.2 Guidelines

This report did not involve a systematic review of the literature, as the goal was not to assess the efficacy of treatments. Instead, we critically examined and compared selected guidelines. Most of these guidelines are aimed at specialists and do not include specific recommendations for primary care. However, in some cases, a possible role for the GP is implied. These are not formal recommendations, but rather considerations for practice.

Three general guidelines on the management on MS were reviewed (NICE 2022, German AWMF 2024 and Dutch FMS 2023). One guideline (NICE 2022) includes specific recommendations for non-specialists, advising that local agreements be made to ensure timely access to appropriate care. On the contrary, the Dutch FMS and German AWMF guidelines are heavily specialized and secondary care-oriented, with little explicit consideration of the role of general practitioners.

In addition, four guidelines with a more specific scope were selected.

One guideline addressed the management of MS in pregnancy (FR MS Pregnancy 2022), one guideline addressed only the vaccination strategy in people with MS (ECTRIMS/EAN 2023).

Two specific guidelines were considered for the management of bladder symptoms. One guideline did not specifically address MS patients but focused on neurogenic lower urinary tract dysfunction (NLUTD) across all neurological conditions (NICE URINARY), and another guideline specifically addressed urinary tract infections in MS (FR URINARY).

It is important to note that many of the recommendations in these guidelines are based on consensus procedures or expert opinion, rather than systematic evidence reviews. This makes it more difficult to assess the reliability of each recommendation, but it reflects the reality that for many practical aspects of MS care, there is little or no substantiated evidence.

3.3 Role of primary care

None of the guidelines outline specific responsibilities for the general practitioner in the follow-up or treatment of multiple sclerosis. Both the NICE and the Dutch guideline acknowledge the need for a

single point of contact within the multidisciplinary MS team to help **coordinate care** and help the patient access services.

In the Dutch guideline this coordinating role is specifically assigned to the **MS nurse**.

Although the role of primary care is not explicitly defined, we will highlight potential areas of involvement for general practitioners in response to each of the following jury questions.

3.4 Treatment of MS relapses

Some discrepancies exist between the guidelines in the role of primary care in the treatment of exacerbations.

Notably, the Dutch FMS and German AWMF guidelines target specialist care exclusively. In contrast, the NICE 2022 acknowledges a potential role for non-specialist healthcare providers and offers an approach **in collaboration with the specialist**. The NICE guideline recommends to develop local guidance and care pathways to manage MS relapses in a timely manner.

3.5 Safety concerns of DMT

Reflecting its specialist-oriented scope, the Dutch FMS guideline provides detailed and actionable guidance on the initiation and monitoring of disease-modifying therapies (DMTs). While much of the content is aimed at specialists, it also highlights areas where primary care can contribute, particularly in **recognizing red flag symptoms** such as persistent fever, neurological deterioration, or signs of opportunistic infection. The increased risk of infections (e.g. respiratory or herpetic) is a concern across many DMTs, especially those with stronger immunosuppressive action. Early detection and timely referral are essential to avoid complications or delays in treatment adaptation. However, the FR urinary guideline formally reported that most DMTs are not associated with an increased risk of urinary tract infection (UTI).

Concerning vaccination, primary care can potentially play a proactive role by checking for recent live vaccines, screening for infection risks, and ensuring that patients are up to date with both routine and risk-based immunizations (e.g., varicella-zoster virus, HPV, pneumococcus). This is particularly relevant before the initiation of immunosuppressive disease-modifying therapies (DMTs) in people with MS.

While not specifically written from a primary care perspective, theECTRIMS/EAN and Dutch FMS guidelines offer detailed, structured recommendations on vaccination timing, screening, and coordination prior to starting DMTs. The NICE guideline, in contrast, refers more broadly to national immunization advice through the Green Book, leaving room for local protocols but providing less practical detail.

In Belgium, vaccination of immunocompromised patients (including those about to start immunosuppressive treatment for MS) is covered by the advisory report of the Superior Health Council (Hoge Gezondheidsraad; Conseil Supérieur de la Santé) *“Vaccination of immunocompromised or chronically ill children and/or adults”*(11). This advisory report provides guidance on the timing and type of vaccines to be considered and supports a proactive role for

primary care in anticipating immunization needs before treatment initiation. However, an update of this report is warranted, as several more recently approved MS therapies are not yet included, and no recommendation on Herpes Zoster vaccination was available at the time. In the meantime, a separate advisory report (no. 9684)(12); (13) has been published by the Council specifically addressing vaccination against Herpes Zoster.

3.6 “Invisible” symptoms of MS

In addition to the more well-known motor or visual symptoms, multiple sclerosis can cause a wide range of other symptoms that are less visible and not always recognized by patients as being related to MS. For this jury question, the organizing committee chose to focus on several common but often overlooked symptoms: bladder and bowel dysfunction, fatigue, and pain. Other “invisible” symptoms, such as cognitive problems or mood disorders, were not covered in this report.

Overall, the guidelines agree on the critical importance of symptom assessment and monitoring as well as patient education in the management of multiple sclerosis symptoms, particularly concerning bladder and bowel dysfunctions, pain, and fatigue. They also generally encourage use of diaries, behavioral measures, and basic physical therapies.

Bladder symptoms

Bladder dysfunction is addressed the German AWMF as well as two dedicated guidelines (NICE URINARY and FR URINARY).

While complex diagnostics and management largely fall under specialist (urological) care (as highlighted by the German AWMF), NICE URINARY provides clear **referral criteria** pointing out some red flag signs and the need to refer if urinary changes could reflect evolving neurological conditions or when urinary symptoms could be contributing to neurological deterioration.

In addition, the management of **urinary tract infections (UTIs)** is particularly relevant for general practitioners, as UTIs are a common reason for consultation in primary care. The German AWMF guideline states that UTIs in people with MS should always be considered complicated.

All three guidelines advise against the routine use of antibiotic prophylaxis in MS patients. However, both NICE URINARY and FR URINARY recommend considering targeted prophylaxis in selected patients with recurrent UTIs.

Regarding symptomatic UTIs, both German AWMF and FR URINARY agree on the need to treat symptomatic urinary tract infections. AWMF emphasizes that symptoms may be non-specific or even absent and that pathogen testing is the gold standard for diagnosis.

Regarding **asymptomatic bacteriuria** FR URINARY explicitly advises against screening or treating asymptomatic bacteriuria in MS patients, except in cases where it would be indicated for the general population. FR URINARY recommends managing UTIs in MS patients according to the same principles used in the general population.

Bowel symptoms

Only the German AWMF guideline addresses bowel symptoms in MS and outlines various evidence-based interventions for both constipation and incontinence.

Fatigue

All three guidelines address fatigue, emphasizing thorough assessment and **prioritizing non-pharmacological strategies**, though they differ in the specific interventions they support.

The Dutch FMS and NICE guidelines both discuss pharmacological options; the Dutch guideline recommends them only if non-drug approaches prove insufficient, while NICE provides formal guidance for specialist-initiated treatment within a shared-care model. The German AWMF focuses solely on non-drug interventions.

Pain

Pain management is covered by both NICE and German AWMF. Their recommendations largely refer to existing pain guidelines (for neuropathic pain, musculoskeletal pain or headache), and both stress the importance of recognizing and addressing pain's multifactorial impact in MS.

3.7 Managing MS across the life course

People with multiple sclerosis often live with the condition for decades, during which their needs and priorities may shift significantly. General practitioners are uniquely positioned to follow patients across the life course and in relation to all aspects of their health.

Family planning and pregnancy

One important topic where the GP could play a meaningful role is family planning. This topic is addressed in the Dutch FMS 2023, German AWMF 2024, NICE 2022 guidelines and an additional guideline dedicated to the topic of pregnancy in MS (FR MS Pregnancy 2022).

As emphasized in all guidelines, it is essential to address this topic proactively and early, ensuring that patients receive accurate and tailored information.

A key message is that MS itself is not a contraindication for pregnancy, but that some medications may need to be adjusted before conception.

Another important point is that, aside from early planning and consultation with a neurologist to adjust disease-modifying therapy if needed, most aspects of pregnancy care, including fertility treatment, pain management during childbirth, and routine obstetric care, are the same as for the general population and should not be withheld from women with MS.

Work and MS

When it comes to work and MS, the main message is to address potential issues proactively (Dutch FMS 2023). GPs can help identify difficulties early and refer patients to occupational health services or rehabilitation specialists. For this to be effective, such services must be available and accessible.

Older adults and cardiovascular comorbidities

Another issue highlighted by the Organizing Committee concerns the ageing MS population and the increasing prevalence of cardiovascular and other age-related comorbidities.

While disease activity tends to decline with age, older adults may be more vulnerable to adverse effects of disease-modifying treatments (DMTs). However, DMTs have been poorly studied in individuals over the age of 55, which creates important knowledge gaps.

The guidelines (Dutch FMS 2023, German AWMF 2024, NICE 2022) include some relevant recommendations, such as guidance on when to discontinue DMTs or how to approach diagnosis later in life. However, these recommendations only partially address the broader question raised by the jury. In this context, general practitioners, with their broader perspective on comorbidities and ageing, may play an important role in ensuring holistic and person-centered care.

Children

None of the selected guidelines provide recommendations on the management of MS in children and adolescents; the German AWMF 2024 guideline notes that care generally follows adult principles and refers to a separate specialist guideline for pediatric MS, which falls outside the scope of this review.

3.8 Lifestyle, Exercise, and Rehabilitation

The role of lifestyle, exercise, and rehabilitation is well recognized across the MS guidelines, though the scope and depth of recommendations vary. All three guidelines (Dutch FMS, German AWMF, and NICE) encourage regular physical activity for people with MS, emphasizing its safety and general health benefits. The Dutch FMS provides practical advice on assessing barriers and supporting adherence, while AWMF incorporates WHO-based activity targets. Only the Dutch guideline explicitly states that exercise does not worsen disease progression.

On nutrition, the AWMF offers the most detailed guidance, including a heart-healthy diet, vitamin D monitoring, and limits on high-dose supplementation. The Dutch guideline aligns broadly, adding national thresholds for vitamin D. NICE takes a cautious stance, advising against the use of vitamin D or omega-3 supplements specifically for treating MS, citing lack of evidence for clinical benefit.

Smoking cessation is addressed in both AWMF and NICE, with AWMF offering practical support tools (e.g., digital apps), while NICE emphasizes the link with disability progression.

Rehabilitation is covered extensively only in the Dutch FMS guideline, which outlines a tailored, multidisciplinary approach for managing fatigue, mobility issues, and arm-hand function. It stresses shared decision-making, early intervention, and coordination across physiotherapy, occupational therapy, and rehabilitation medicine.

For primary care, this domain offers several concrete entry points: promoting exercise, addressing smoking, monitoring vitamin D, and identifying when referral to rehabilitation or allied health

professionals is needed. These contributions enhance continuity of care and support quality of life, without requiring specialist expertise.

3.9 Conclusion

Overall, MS is a condition that exemplifies the need for multidisciplinary collaboration. Clear role definitions and well-structured, preferably local, agreements are essential to ensure that patients receive the right care at the right time. While primary care may not be involved in prescribing or monitoring specialized treatments, it could have an important role in the broader care of people living with MS.

4 General information on selected guidelines

4.1 Selected guidelines

The selected guidelines and their abbreviations as used in this report can be found in the following table.

Abbreviation	Guideline
Dutch FMS 2023(3)	Federatie Medisch Specialisten; 2023; Multiple Sclerose (MS)
ECTRIMS/EAN 2023(4)	S. Otero-Romero et al.; European Committee for Treatment and Research in Multiple Sclerosis and European Academy of Neurology consensus on vaccination in people with multiple sclerosis: Improving immunization strategies in the era of highly active immunotherapeutic drugs – European journal of neurology (2023) ; 30(8):2144-2176.
German AWMF 2024(5)	AWMF; 2024; S2k-Leitlinie Diagnose und Therapie der Multiplen Sklerose, Neuromyelitis Optica Spektrum und MOG-IgG-assoziierte Erkrankungen - Living Guideline [v 8.0]
FR MS Pregnancy 2022(6)	Pregnancy and multiple sclerosis: 2022 recommendations from the French multiple sclerosis society
FR URINARY 2020(7)	Donzé, C., Papeix, C., Lebrun-Frenay, C.; 2020; Urinary tract infections and multiple sclerosis: Recommendations from the French Multiple Sclerosis Society
NICE 2022(8)	NICE; 2022; Multiple sclerosis in adults: management (NG220)
NICE URINARY 2012 UPD2023(9)	NICE ; 2012 [last updated 2023] ; Urinary incontinence in neurological disease: assessment and management (CG148)

Table 1: Selected guidelines and their abbreviations

4.2 Grades of recommendation

Grades of recommendation and levels of evidence as defined in each guideline, can be found in the following tables.

NICE 2022		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used (strong recommendation) are worded in the text using the term	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.

	“offer”, “refer”, “advise” or similar...	
	Intervention that could (or could not) be used (weak recommendation) are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 2: Grades of recommendation and Level of evidence of the NICE 2022 guideline.

NICE URINARY 2012 upd 2023		
Grades of recommendation:	Interventions that must (or must not) be used worded as such in the text.	Generally used if there is a legal duty to apply the recommendation. But used as well if the consequences of not following the recommendation could be extremely serious or potentially life threatening.
	Intervention that should (or should not) be used (strong recommendation) are worded in the text using the term “offer”, “refer”, “advise” or similar...	There is clear evidence of benefit. We are confident that, for the vast majority of patients, an intervention will do more good than harm, and be cost effective.
	Intervention that could (or could not) be used (weak recommendation) are worded in the text using the term “consider”	Reflects a recommendation for which the evidence of benefit is less certain. We are confident that an intervention will do more good than harm for most patients, and be cost effective, but other options may be similarly cost effective. The choice of intervention, and whether or not to have the intervention at all, is more likely to depend on the patient’s values.
Levels of evidence	While levels of evidence have been evaluated using described procedures (GRADE, CASP RCT, cohort study, case-control checklists, CERQual) NICE does not explicitly attribute strength levels to each particular recommendation.	

Table 3: Grades of recommendation and Level of evidence of the NICE URINARY 2012 upd 2023 guideline.

Grades of recommendation:	Formulation and agreement of the recommendations was conducted using the modified Nominal Group Technique, a highly structured procedure based on iterative ratings with feedback to reach consensus in a small group of experts on topics for which expert opinion is relevant. However no grade of recommendation are reported.	
Levels of evidence using standards from the Oxford Centre for Evidence-Based Medicine (as reported for Therapy/Prevention, Aetiology/Harm).	1a	SR (with homogeneity*) of RCT
	1b	Individual RCT (with narrow Confidence Interval"i)
	1c	All or none (Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it)
	2a	SR (with homogeneity*) of cohort studies
	2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)
	2c	"Outcomes" Research; Ecological studies
	3a	SR (with homogeneity*) of case-control studies
	3b	Individual Case-Control Study
	4	Case-series (and poor quality cohort and case-control studies§§)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	

Table 4: Grades of recommendation and Level of evidence of the ECTRIMs/EAN 2023 guideline.

FR MS Pregnancy 2022		
Grades of recommendation (linked to Levels of Evidence)	A	Established scientific evidence <ul style="list-style-type: none"> - High-power randomised comparative studies - Meta-analysis of randomised comparative studies - Decision analysis based on well-conducted studies
	B	Scientific presumption <ul style="list-style-type: none"> - Low-power randomised comparative studies - Well-conducted non-randomised comparative studies - Cohort studies
	C	Low level of evidence <ul style="list-style-type: none"> - Case-control studies - Comparative studies with a significant bias - Retrospective studies - Case series
	Expert opinion	

Table 5: Grades of recommendation and Level of evidence of the FR MS Pregnancy 2022 guideline.

Fr URINARY 2020		
Grades of recommendation: Grades of recommendation is not indicative of the strength of the recommendation but is dependent on the quality of the evidence.	A	Established scientific evidence: recommendation based on Level 1 evidence
	B	Scientific presumption: recommendation based on Level 2 evidence
	C	Low level of evidence: recommendation based on Level 3 or Level 4 evidence.
	Expert agreement	Absence of sufficient data
Degree of agreement Rather than using strength of recommendation the proposals were scored based on the degree of agreement between 1 (total disagreement) and 9 (total agreement)	Appropriate with strong agreement	median value ≥ 7 and distribution of rating in the interval [7–9]
	Appropriate with relative agreement	median value ≥ 7 and distribution of rating in the interval [5–9]
	Inappropriate with strong agreement	median value ≤ 3 and distribution of rating in the interval [1-3]
	Inappropriate with relative agreement	median value ≤ 3.5 and distribution of rating in the interval [1-5]
	Undecided	$4 \leq \text{median} \leq 6.5$ and rating in [1-9]
	Lack of consensus	All other situations
Levels of evidence	Level 1	High-power randomized comparative studies Meta-analysis of randomized comparative studies Decision analysis based on well-conducted studies
	Level 2	Low-power randomized comparative studies Well-conducted non-randomized comparative studies Cohort studies
	Level 3	Case control studies
	Level 4	Comparative studies with major bias Retrospective studies Case series

Table 6: Grades of recommendation and Level of evidence of the Fr URINARY 2020 guideline.

AWMF 2024		
Grades of recommendation:	“Soll” / “Soll nicht”	Starke Empfehlung
	“Sollte” / “Sollte nicht”	Empfehlung
	“Kann“	Offene Empfehlun

Strength of consensus (in absence of adequate evidence)	Starker Konsens	>95% consensus
	Konsens	>75% to 90% consensus
	Mehrheitliche Zustimmung	>50% to 75% consensus
	Kein Konsens	<50% consensus
Levels of evidence	No levels of evidence accorded	

Table 7: Grades of recommendation and Level of evidence of the GERMAN AWMF 2024 guideline.

Dutch FMS 2023		
Grades of recommendation	Hoog	<ul style="list-style-type: none"> er is hoge zekerheid dat het ware effect dicht bij het geschatte effect ligt; het is zeer onwaarschijnlijk dat de literatuurconclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
	Redelijk	<ul style="list-style-type: none"> er is redelijke zekerheid dat het ware effect dicht bij het geschatte effect ligt; het is mogelijk dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
	Laag	<ul style="list-style-type: none"> er is lage zekerheid dat het ware effect dicht bij het geschatte effect ligt; er is een reële kans dat de conclusie klinisch relevant verandert wanneer er resultaten van nieuw grootschalig onderzoek aan de literatuuranalyse worden toegevoegd.
	Zeer laag	<ul style="list-style-type: none"> er is zeer lage zekerheid dat het ware effect dicht bij het geschatte effect ligt; de literatuurconclusie is zeer onzeker.
Strength of recommendation	Sterke aanbeveling	<ul style="list-style-type: none"> Voor patiënten: De meeste patiënten zouden de aanbevolen interventie of aanpak kiezen en slechts een klein aantal niet. Voor zorgverleners: De meeste patiënten zouden de aanbevolen interventie of aanpak moeten ontvangen. Voor beleidsmakers: De aanbevolen interventie of aanpak kan worden gezien als standaardbeleid.
	Conditionele aanbeveling	<ul style="list-style-type: none"> Voor patiënten: Een aanzienlijk deel van de patiënten zouden de aanbevolen interventie of aanpak kiezen, maar veel patiënten ook niet. Voor zorgverleners: Er zijn meerdere geschikte interventies of aanpakken. De patiënt moet worden ondersteund bij de keuze voor de interventie of

		<p>aanpak die het beste aansluit bij zijn of haar waarden en voorkeuren.</p> <ul style="list-style-type: none"> • Voor beleidsmakers: Beleidsbepaling vereist uitvoerige discussie met betrokkenheid van veel stakeholders. Er is een grotere kans op lokale beleidsverschillen.
Levels of evidence	No levels of evidence accorded	

Table 8: Grades of recommendation and Level of evidence of the Dutch FMS 2023 guideline.

4.3 Agree II score

Information about the Agree II score can be found in the section “Methodology”.

A summary of the assessment by the literature group of the individual items of the domain score for each guideline can be found in the following table. The total domain score is also reported in this table.

Rigour of development item	7	8	9	10	11	12	13	14	Total	Domain score
NICE 2022	6	7	7	5	7	7	6	7	52	93%
Dutch FMS 2023	7	7	7	6	5	3	2	2	39	70%
ECTRIMS/EAN 2023	7	7	6	4	4	5	4	1	38	68%
NICE URINARY 2012 upd2023	6	7	6	5	7	5	6	7	49	88%
FR MS Pregnancy 2022	6	3	4	7	5	5	4	1	35	63 %
FR URINARY 2020	6	3	7	7	3	5	5	1	37	66%
German AMWF 2024	1	2	4	7	4	5	5	6	34	61%

Table 9: AGREE score of selected guidelines on item “Rigour of development”, see methodology for a description of the items.

4.4 Included populations – interventions – main outcomes

In the following tables, the populations, interventions and main outcomes considered in the selected guidelines are represented.

NICE 2022	
Population	<p>Adults who have a diagnosis of MS or possible MS, or are having investigations for MS.</p> <p>Exclusion: children and young people under the age of 18 years who have a diagnosis of MS or possible MS, or are being investigated for MS</p>
Interventions	<ul style="list-style-type: none"> • Management of disability • rehabilitation

	<ul style="list-style-type: none"> • Other treatments <p><u>Exclusions:</u></p> <ul style="list-style-type: none"> • disease-modifying treatments • non-pharmacological interventions for ataxia and tremor, • interventions for weakness, cardiorespiratory fitness, sensory loss, visual problems (apart from oscillopsia), and secondary complications of immobility such as deconditioning and contractures <p><u>Concerning Fatigue:</u></p> <ul style="list-style-type: none"> • non-pharmacological intervention for fatigue • pharmacological intervention for fatigue: <ul style="list-style-type: none"> ○ Amantadine ○ SSRIs ○ Aspirin specifically before exercise ○ Modafinil ○ Combinations of the above <p><u>Concerning pain:</u></p> <ul style="list-style-type: none"> • any non-pharmacological intervention • pharmacological interventions are included in another NICE guideline on pain (out of scope)
Outcomes	<p><u>Concerning fatigue</u></p> <ul style="list-style-type: none"> • patient-reported outcome measures to assess MS fatigue (MFIS Fatigue Severity Scale (FSS), National Fatigue Index

	<p>(NFI), MS specific FSS (MFSS), Modified Fatigue Impact Scale (MFIS))</p> <ul style="list-style-type: none"> • visual Analogue Scale (VAS) • health-related Quality of Life (EQ-5D, SF-36, Leeds MS quality of life scale, MS Impact Scale) • impact on carers. • cognitive functions (memory and concentration) • psychological symptoms assessed by validated and disease-specific scales, questionnaire or similar instruments. • epworth sleepiness scale • adverse effects <ul style="list-style-type: none"> ○ incidence of adverse events ○ adverse events leading to withdrawal ○ disruption of sleep ○ cardiac events/arrhythmias <p>Concerning pain:</p> <ul style="list-style-type: none"> • pain intensity using validated pain scales (Visual Analogue Scale (VAS) and Numerical Rating Scale (NRS)) • pain reduction for example >30% and 50% pain reduction from baseline • patient-reported outcome measures (quality of life, scales of Multiple Sclerosis Quality of Life Inventory (MSQLI); life satisfaction, EQ5D, SF-36) • adverse effects of treatment (Adverse events leading to withdrawal or lack of efficacy) • expanded Disability Status Scale (EDSS) • MS Functional Composite or its subscales if not reported (MSFC). • functional improvement • reduction of care • mood related outcomes (validated depression scales and anxiety scales) • changes in sleep quality/sleep related impairments/ sleep disturbance
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Table 10: Included population, intervention and main outcomes of the NICE 2022 guideline.

NICE URINARY 2012 upd 2023	
Population	Adults and children (from birth) with lower urinary tract dysfunction resulting from neurological disease or injury.
Interventions	<ul style="list-style-type: none"> • Physical interventions to aid urinary storage including behaviour and bladder training, pelvic floor muscle exercises and neuromuscular stimulation. • Pharmacological therapies to aid urinary storage • surgical procedures to treat incontinence and improve bladder storage capacity. • Physical aids and drug therapy to improve bladder emptying • Urinary diversion procedures

	<ul style="list-style-type: none"> • Appliances and equipment to contain urinary incontinence
Outcomes	<p><u>Treatment of incontinence (to improve bladder storage)</u></p> <ul style="list-style-type: none"> • quality of life. • frequency of voiding by day and night. • number of incontinence episodes per week. • maximum cystometric capacity • bladder compliance • residual urine • patients and carers' perception of symptoms. • kidney function (hydronephrosis) • adverse events including <ul style="list-style-type: none"> ○ urinary tract infections ○ renal complications ○ unscheduled hospital admissions • treatment adherence <p><u>Treatment to improve bladder emptying</u></p> <ul style="list-style-type: none"> • quality of life • frequency of voiding by day and night • urgency Symptoms relating to bladder emptying, for example poor urinary stream Q-max (maximum flow rate) • residual urine volume • adverse events including <ul style="list-style-type: none"> ○ postural hypotension ○ other unscheduled hospital admissions. • treatment adherence

Table 11: Included population, intervention and main outcomes of the NICE URINARY 2012 upd 2023 guideline.

ECTRIM/EAN 2023	
Population	<p>Patients (adult and children) with confirmed MS (according to diagnostic criteria available at the time of the study) or patients with a CIS (clinically isolated syndrome) including particular subpopulations (children, elderly people, pregnant women, and international travelers)</p> <p><u>Exclusion:</u> pwMS receiving hemopoietic stem cell transplantation were not considered in this consensus either, and specific guidance on immunization post-hemopoietic stem cell transplantation can be found elsewhere.</p>
Interventions	<p><u>Disease-modifying therapies:</u></p> <ul style="list-style-type: none"> • interferon beta/peg-interferon • glatiramer acetate • teriflunomide • dimethyl fumarate • fingolimod • siponimod • ponesimod

- natalizumab
- alemtuzumab
- cladribine
- ocrelizumab
- rituximab
- ofatumumab

Vaccine

- Seasonal influenza
 - Inactivated (fractioned or subunits)
 - Attenuated (intranasal)
- Pneumococcal 13v
 - Inactivated (conjugated polysaccharide)
- Pneumococcal 20v
 - Inactivated (conjugated polysaccharide)
- Pneumococcal 23v
 - Inactivated (polysaccharide)
- Polio vaccine (VPI)
 - Inactivated
- Hepatitis B
 - Non-enhanced vaccines (20 mcg/10 mcg)a
 - Inactivated. Surface antigen
 - Enhanced Immunity Vaccines High load (40 mcg)
 - Enhanced Immunity Vaccines Adjuvanted AS03/CpG 1018
- Tetanus-Diphtheria
 - Inactivated (tetanus and diphtheria toxoids)
- Varicella
 - Live-attenuated (whole virus)
- Measles-mumps-rubella
 - Live-attenuated (whole virus)
- Meningococcal B
 - Inactivated (surface antigen)
- Meningococcal ACWY
 - Inactivated (polysaccharide conjugated with protein)
- Haemophilus influenzae type b
 - Inactivated (polysaccharide conjugated with protein)
- Herpes zoster
 - Inactivated (recombinant)
 - Attenuated
- Human papillomavirus (HPV)
 - Inactivated (recombinant)
- Yellow fever
 - Attenuated
- Dengue
 - Attenuated
- Hepatitis A
 - Inactivated (whole viruses)
- Meningococcal quadrivalent vaccine

	<ul style="list-style-type: none"> ○ Inactivated conjugated ● Japanese encephalitis <ul style="list-style-type: none"> ○ Inactivated ● Rabies <ul style="list-style-type: none"> ○ Inactivated ● Typhoid <ul style="list-style-type: none"> ○ Oral attenuated ○ Inactivated ● Cholera <ul style="list-style-type: none"> ○ Inactivated ● Tick-borne encephalitis <ul style="list-style-type: none"> ○ Inactivated <p><u>Exclusions:</u></p> <p>Due to the fast-changing developments on vaccination against SARS-CoV-2 infection, this document does not include specific recommendation for these vaccines that can be found in recent documents.</p>
Outcomes	<p><u>Vaccine response:</u></p> <ul style="list-style-type: none"> ● Risk of relapses ● Risk of MS ● Side effects <p><u>Vaccine effectiveness:</u></p> <ul style="list-style-type: none"> ● Immunogenicity (with any immune correlate considered in the study) ● Prevention of the considered infection <p><u>Vaccination strategy:</u></p> <ul style="list-style-type: none"> ● recommended vaccines (what) ● intervals to be considered (when) ● other specific precautions and contraindications of depending on the therapeutic approach

Table 12: Included population, intervention and main outcomes of the ECTRIMs/EAN 2023 guideline.

FR MS Pregnancy 2022	
Population	Women with MS who could or wishes to become pregnant, are pregnant, postpartum, during delivery, during breastfeeding
Interventions	pregnancy planning , relapse therapy, prevention of relapse, DMT and gadolinium, symptomatic therapy, assisted reproduction technology, follow-up, delivery modalities, analgesia/anaesthesia during delivery, breastfeeding,
Outcomes	Not defined

Table 13: Included population, intervention and main outcomes of the FR MS Pregnancy 2022 guideline.

FR URINARY 2020	
Population	MS patients
Interventions	<ul style="list-style-type: none"> • Urinary tract infections • treatment of bacteriuria • MS treatment: <ul style="list-style-type: none"> ○ Interferon betas, ○ glatiramer acetate, ○ teriflunomide, ○ dimethyl fumarate, ○ fingolimod, ○ natalizumab, ○ mitoxantrone, ○ alemtuzumab, ○ cladribine, ○ ocrelizumab, ○ cyclophosphamide, ○ mycophenolate mofetil, ○ azathioprine, ○ rituximab, ○ plasma exchange, ○ high dose methylprednisolone ○ fampridine
Outcomes	risk of relapse risk of a urinary tract infection

Table 14: Included population, intervention and main outcomes of the FR URINARY 2020 guideline.

GERMAN AWMF 2024	
Population	People with a suspected diagnosis of a chronic inflammatory CNS disease, people with relapsing or progressive MS (including children/adolescents, pregnant women and the elderly), people with Neuromyelitis Optica Spectrum Disorder (NMOSD); people with Myelin Oligodendrocyte Glycoprotein Antibody-associated disease (MOGAD)
Interventions	Relapse therapy, immunotherapy, symptomatic therapy, lifestyle modifications
Outcomes	Not defined

Table 15: Included population, intervention and main outcomes of the GERMAN AWMF 2024 guideline.

Dutch FMS 2023	
Population	<ul style="list-style-type: none"> -Radiologically Isolated Syndrome -Patients with a first MS relapse -Patients with relapsing-remitting MS -Patients with secondary progressive MS

	-Patients with primary progressive MS
Interventions	<ul style="list-style-type: none"> -disease-modifying therapies -autologous stem cell transplantation (ASCT) -symptomatic treatment of MS <p>Detailed information can be found in the guideline in each module under “zoeken en selecteren”.</p>
Outcomes	Outcomes can be found in the guideline in each module under “zoeken en selecteren”.

Table 16: Included population, intervention and main outcomes of the Dutch FMS 2023 guideline.

4.5 Members of development group – target audience

Members of the development group that produced the guidelines, and the target audience for whom the guidelines are intended, can be found in the following tables.

NICE 2022	
Development group	Our independent committees are made up of health and care professionals, people who use services, and carers. The group included practitioners, professionals, care providers, commissioners, those who use services and family members or carers.
Target audience	The guideline is aimed primarily at services provided in primary and secondary care. <ul style="list-style-type: none"> • Healthcare professionals • Social care practitioners • Commissioners and providers • People with multiple sclerosis and their families and carers

Table 17: Members of the development group and target audience of the Nice 2022 guideline.

NICE URINARY 2012 upd 2023	
Development group	A multidisciplinary Guideline Development Group (GDG) comprising professional group members and consumer representatives of the main stakeholders developed this guideline.
Target audience	<ul style="list-style-type: none"> • Healthcare professionals • Commissioners and providers • People with urinary incontinence and neurological disease and their families and carers

Table 18: Members of the development group and target audience of the NICE URINARY 2012 upd 2023 guideline.

ECTRIMS/EAN 2023	
Development group	an expert committee was set up, comprising a steering committee (involving six members with high expertise in MS and vaccines) and a multidisciplinary core working group composed of MS experts, vaccine advisors, and a patient representative.
Target audience	physicians, pwMS, healthcare providers, and health policymakers

Table 19: Members of the development group and target audience of the ECTRIMS/EAN 2023 guideline.

FR MS Pregnancy 2022	
Development group	A group of 56 MS-experts

Target audience	Not defined in guideline Published in MS specialist website and journal
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Table 20: Members of the development group and target audience of the FR MS Pregnancy 2022 guideline.

FR URINARY 2020	
Development group	The French Group for Recommendations in MS (France4MS) did a systematic review , 26 MS experts worked on the full-text review and a group of 70 multidisciplinary health care specialists validated the final evaluation of summarized evidences.
Target audience	professionals, patients and users, decision-makers

Table 21: Members of the development group and target audience of the FR URINARY 2020 guideline.

GERMAN AWMF 2024	
Development group	The development group included representatives from the neurology societies of Switzerland, Austria, and Germany, as well as experts in occupational therapy, gynecology, pediatrics, neuroradiology, neurorehabilitation, psychiatry and psychotherapy, urology, paraplegiatrics, neuropediatrics, and advocacy for independent living. Additional contributors included representatives from the German Multiple Sclerosis Association and the Neuromyelitis Optica Study Group. No general practitioners were involved.
Target audience	All areas of care (outpatient, day clinic, inpatient, acute clinic, rehabilitation clinic) The guideline is aimed at neurologists, neuroradiologists, gynaecologists, paediatricians, urologists, psychiatrists, rehabilitation physicians, physiotherapists, occupational therapists working in private practice / outpatient and (partial) inpatient care, and to the patients themselves.

Table 22: Members of the development group and target audience of the GERMAN AWMF 2024 guideline.

Dutch FMS 2023	
Development group	De samenstelling van de werkgroep per module van de richtlijn <i>Multiple Sclerose</i> , kan geraadpleegd worden via https://richtlijndatabase.nl/
Target audience	Deze richtlijn is ontwikkeld voor alle leden van de beroepsgroepen die betrokken zijn bij de zorg van patiënten met MS. Dit betreffen neurologen, revalidatieartsen, urologen, oogartsen, verpleegkundigen, huisartsen, fysiotherapeuten, apothekers, ergotherapeuten, psychologen, logopedisten, bedrijfsartsen, specialisten ouderengeneeskunde, verzekeringsartsen, psychiaters, seksuologen en maatschappelijk werkers.

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Table 23: Members of the development group and target audience of the Dutch FMS 2023 guideline.

5 Summary and comparisons of recommendations from guidelines

5.1 Role of primary care in MS

What can a general practitioner (GP) do themselves in the follow-up and treatment of MS?

Most of the recommendations made in the NICE 2022 guideline are aimed at non-specialist healthcare providers unless specified.

The recommendations in the Dutch FMS 2023 guideline and the German AWMF 2024 guideline are aimed at MS specialists.

However, none of the guidelines outline specific responsibilities for the general practitioner in the follow-up or treatment of multiple sclerosis.

The NICE guideline mentions the “primary healthcare team” as part of a coordinated multidisciplinary team, which may also include MS nurses, neurologists, physiotherapists with expertise in MS, occupational therapists, speech and language therapists, psychologists, dietitians, social care, continence specialists, specialist neuropharmacists or specialist MS pharmacists, and specialists in rehabilitation medicine.

The NICE guideline recommends to offer the person with MS an appropriate **single point of contact** with **knowledge of MS services** to coordinate care and help them access services. Depending on local resources, this could be a GP.

In the Dutch FMS guideline, this coordinating role is specifically assigned to the **MS nurse**.

Additionally, it is *implied* in the NICE guideline that the GP could be involved in :
Providing (basic) patient information, ensuring a yearly comprehensive review of all aspects of their care (although it is specified that the review itself should be carried out by healthcare professionals with expertise in MS), diagnosing and initial management of symptoms like fatigue and pain, management of relapses and referral and communicating with the MS team.

The NICE guideline does not make recommendations aimed at non-specialist healthcare professionals regarding the monitoring of disease-modifying therapy (DMT).

Referral to a specialist

According to the NICE 2022 guideline, referral is recommended in (but not limited to) the following situations:

Referral to an MS Specialist (neurologist)

- for the diagnosis of MS;

- for advice on the management of relapses (see the part on management of relapses for details);
- when the patient wishes to try medication for fatigue;
- for prescribing certain second-line medications for neuropathic pain

Referral to a healthcare professional with expertise in MS

- for a follow-up appointment within 6 weeks after diagnosis;
- for a yearly comprehensive review of all aspects of care;
- for information and counselling about family planning (see chapter on family planning);
- for information and support regarding advanced MS and end of life care.

Because DMT and monitoring of DMT is not discussed in this guideline, it is implied that their initiating and follow-up are the responsibility of specialist services.

5.2 Recognizing and Managing MS Exacerbations in primary care

Role of primary care

The role of primary care in the diagnosis and management of an MS relapse is not addressed in the Dutch FMS 2023 and German AWMF 2024 guideline, as these guidelines target specialist care.

While the NICE 2022 guideline does not explicitly outline a role for primary care in the MS care pathway, it implicitly allows for one. NICE recommends developing local guidance and care pathways for timely relapse treatment and follow-up.

Depending on how services are organized locally, the NICE guideline leaves room for primary care to potentially contribute to the following elements of MS relapse care:

- Recognizing (potential) relapses
- Ruling out infection (especially UTI and respiratory tract infection)
- Discussing diagnosis and indication for therapy with an MS specialist
- Initiating oral high-dose corticosteroid treatment after discussion with MS specialist
- Providing patients with information about side effects of treatment
- Communicating with the MS multidisciplinary team about the relapse

Diagnosis of relapse

The German AWMF guideline and NICE provide similar definitions of a relapse, containing the following elements:

- new symptoms or worsening of existing symptoms lasting at least 24 hours;
- >30 days since previous relapse,

- not caused by infection or other cause

The NICE guideline recommends to rule out infection (focusing on UTI and respiratory tract infection) and to discuss diagnosis and indication for therapy with an MS specialist.

Indication for treatment

Both the German AWMF and NICE guidelines suggest that treatment is not indicated for every MS relapse.

The German AWMF guideline recommends to base indication on the severity of the symptoms, as well as the tolerability and efficacy of previous steroid therapies, comorbidities, and relative contra-indications.

The German AWMF guideline recommends the following investigations before a initiating treatment for an MS relapse:

- Neurological examination with the best possible quantification of deficits (including EDSS)
- Exclusion of an infection (clinical, laboratory) as a possible explanation for the symptoms or contraindication for high-dose steroid therapy
- Blood glucose levels, electrolytes
- MRI diagnostics if the clinical situation is unclear
- Pregnancy test if the status is unclear

The NICE guideline states that steroid treatment is indicated in relapses that affect the person's ability to perform their usual tasks. **The NICE guideline recommends (for non-specialists) to discuss the diagnosis and indication for treatment with an MS specialist.**

Timing

NICE recommends to offer treatment as early as possible and within 14 days of onset of symptoms. The German AWMF guideline recommends to treat as soon as possible after onset of symptoms.

Dose

All three guidelines recommend high-dose methylprednisolone to treat an MS relapse.

The NICE guideline recommends oral methylprednisolone 0.5 g/day for 5 days; and IV 1g daily for 3 to 5 days as an alternative.

The German AWMF guideline gives a dose range for oral or IV routes: 500–1000 mg/day for 3–5 days.

NICE specifically recommends AGAINST using lower doses than 500 mg/day for 5 days.

IV or oral administration

The Dutch FMS and NICE guidelines recommend to treat the patient at home with oral methylprednisolone, with IV methylprednisolone being an alternative when hospitalization or extra monitoring is warranted, or in whom oral steroids have failed or are not tolerated.

The German AWMF guideline considers IV treatment to be the standard, but oral methylprednisolone an equivalent alternative.

Practical consideration during treatment

The German AWMF guideline advises morning administration to reduce sleep disturbances and recommends monitoring blood pressure, glucose and electrolytes during and after treatment.

Patient information

The NICE guideline recommends to discuss the benefits and risks of steroid treatment with the patient.

Both the German AWMF and NICE guidelines recommend to inform the patient about side effects of high-dose steroid treatments, including temporary effects on mental health and worsening blood glucose control in diabetes.

The NICE guideline recommends to give this information in a format that the patient (or their family members or carers) can take home.

The NICE guideline recommends AGAINST giving people with MS a supply of steroids to self-administer at home for future relapses.

Communication between primary and specialist care

The NICE guideline recommends that the MS multidisciplinary team is notified about the relapse and treatment to guide disease-modifying therapy decisions.

5.3 Common side effects of MS drugs

Before initiating disease modifying therapy (DMT), Dutch FMS recommends to:

- **Reassess whether the indication** for starting the treatment is appropriate.
- **Confirm with the patient** that they agree with the decision to start the disease-modifying therapy, that they understand the indication and possible side effects.
- Check for any **contraindications** or potential **drug interactions** *
- Check for any signs (including from medical history) of **active infections or malignancies**. Treat these, where possible, before initiating disease-modifying therapy.

During treatment with DMT, Dutch FMS recommends to:

- **Ask the patient** whether they are experiencing any **side effects**, including (recent) infections.
- Perform **additional investigations** at the recommended intervals*
- **If infections and/or malignancies** occur, **consider (temporarily) discontinuing** the DMTs, weighing the risks of MS reactivation against the need to treat the infection, malignancy, or other condition.
- Consider the possibility of **progressive multifocal leukoencephalopathy (PML)** or carry-over PML, and conduct further diagnostics and treatment if needed.

***Note from bibliography group:** for information on specific medication, see also

“Tabel: Middel-specifieke handelingen bij screening en monitoring van ziektemodulerende behandeling bij MS, in aanvulling op optimalisatie van vaccinatiestatus” and

“Tabel: Overzicht van ziektemodulerende middelen met contra-indicaties, risico’s en adviezen voor monitoring (update: tabel 5.1)” chapter 8.3.1 of the Appendix

According to the Dutch FMS, DMTs for multiple sclerosis are associated with a the following adverse effects (*not formal recommendations*).

Hematological Disorders

Many DMTs cause blood count abnormalities, often tied to their mechanism of action.

- **Lymphopenia** is common and can increase infection risk. Agents like alemtuzumab, cladribine, dimethyl fumarate, ocrelizumab, and ofatumumab (which deplete lymphocytes) carry higher risks than interferon- β or S1P modulators (which cause redistribution).

Severe lymphopenia (grade 3 (200-500 cells/mm³) and grade 4 (<200 cells/mm³)) requires enhanced infection monitoring, initiating antiviral prophylaxis, and potential treatment delays or discontinuation.

Natalizumab may increase lymphocyte counts in peripheral blood due to redistribution.

- **Thrombocytopenia and thrombotic microangiopathy** can occur with interferon- β , alemtuzumab, and teriflunomide.
- **Anemia** is relatively common with interferon- β , natalizumab, alemtuzumab and teriflunomide.

Infections:

- Most DMTs raise the risk of common infections (e.g., respiratory or urinary tract infections). Individual factors such as frequent sexual contacts, travel to high-infection areas, residence or working in asylum centers, older age, comorbidities, prior immunosuppression, or severe disability can increase susceptibility.

- Glatiramer acetate and interferon- β are not linked to increased infection risks.
- Alemtuzumab, natalizumab, S1P receptor modulators, cladribine and anti-CD20 therapies carry a higher risk of specific infection:
 - **herpesvirus infections** (HSV, VZV, CMV), which can occasionally be more severe or even life-threatening;
 - **opportunistic infections**, such as listeria meningitis, cryptococcal meningitis, and nocardiosis;
 - **reactivation of latent infections**, including TBC, HBV, and possibly HPV;
 - **rare viral CNS complications**, including PML and GCN (e.g. natalizumab-treated JC virus-seropositive patients).

Immunogenicity

Anti-drug antibodies (ADAs) can develop against any disease-modifying therapy. The likelihood varies per drug, increases with patient age, and depends on the degree of humanization (monoclonal antibodies). ADAs may manifest as infusion-related reactions or disease exacerbations. Clinically relevant ADAs have been demonstrated for natalizumab and interferon- β .

Autoimmune Diseases

Alemtuzumab can induce autoantibodies and autoimmune diseases in 30–40% of patients, typically 2–3 years after initiation.

Malignancies

While current data are inconclusive, a slightly increased cancer risk cannot be excluded.

- **Skin cancers** (basal cell carcinoma, melanoma) are reported with S1P modulators.
- Associations with cancer have been described for natalizumab, interferon- β , dimethyl fumarate, and fingolimod.

Cardiovascular Effects

- S1P modulators may cause bradycardia or conduction disturbances. The EMA recommends performing an ECG before starting these medications.
- Alemtuzumab has been linked to tachycardia, chest pain, and rare cardiac/cerebrovascular events.
- Blood pressure changes (hypertension/hypotension) may occur with S1P modulators, teriflunomide, and alemtuzumab. Blood pressure monitoring and treatment if indicated are recommended.

Liver function

Several DMTs (Interferon- β , S1P modulators, teriflunomide, dimethyl fumarate, cladribine, glatiramer acetate, and natalizumab) can cause serious liver injury, including acute liver failure. Most severe cases occur within the first six months. The risk is higher in patients with liver disease, alcohol use, or concurrent hepatotoxic drugs.

Thyroid function

Thyroid dysfunction may occur with the use of interferon- β -1. It is recommended to determine thyroid function at the start of treatment and during the first year and, if abnormal, every 6 to 12 months after the start of treatment.

Alemtuzumab-associated thyroid disorders are frequently described (one third of users).

Others

- Interferon- β has been associated with nephrotic syndrome.
- S1P modulators may cause macular edema, particularly in diabetic patients, as well as a decreased FEV1 and DLCO.

For additional details: see also the tables included in the full document summarizing medication-specific actions for screening and monitoring DMTs, including blood tests, as well as medication-specific contraindications, risks, and recommendations.

The French Urinary guideline specifically assessed the **risk of urinary tract infection** associated with the different treatments used in multiple sclerosis."

- Treatments with interferon beta, glatiramer acetate, teriflunomide, dimethylfumarate, fingolimod, cladribine, natalizumab, ocrelizumab, mycophenolate mofetil, azathioprine and fampridine (Level B, Appropriate, strong agreement), as well treatments with plasma exchange and high doses of methyl-prednisolone (Level C, Appropriate, strong agreement) are **NOT associated** with an increased risk of developing a urinary tract infection
- Regarding ocrelizumab, due to the effect of anti-CD20, the risk of infection was increased in cases of hypogammaglobulinemia (expert recommendation, Appropriate, strong agreement)
- Treatments with mitoxantrone, alemtuzumab, cyclophosphamide and rituximab **are associated** with an increased risk of developing a urinary tract infection (Level B, Appropriate, strong agreement)

Adverse effects are also reported from our other sources in the 'Safety' section.

5.4 Vaccination Considerations with MS Treatment

The ECTRIM/EAN 2023 guidelines provide a comprehensive and detailed guideline on vaccine safety and efficacy as well as general vaccination strategies, including recommendations for specific sub-populations (children, pregnant women, older adults, and international travellers).

The Dutch FMS 2023 guideline also addresses vaccination, delivering a similar but more concise message concerning the screening before initiating treatment and the immunization strategy.

The FR MS Pregnancy 2022 guideline focuses on pregnant women and includes recommendations not only for this population, but also for vaccination during breastfeeding and in infants.

NICE refers exclusively to the *Green Book*, which outlines the UK vaccination schedule; therefore, its details are not reproduced here. However, in the chapter “*Additional Safety Information*”, reference is made to the Advisory Report 9158 of the Superior Health Council (CSS)(11), which provides scientific advice underpinning the Belgian vaccination policy, and specifically addresses vaccination in immunodeficient or chronically ill children and adults.

Other guidelines did not address vaccination.

ECTRIM/EAN 2023

Safety and efficacy of vaccines

Live-attenuated vaccines can be safely used in MS patients without DMTs or in those receiving immunomodulatory treatments (interferons [IFNs] or glatiramer acetate [GA]) but should be avoided in patients receiving the following therapies: dimethyl fumarate [DMF]; teriflunomide; sphingosine-1-phosphate [S1P] modulators; natalizumab; cladribine; alemtuzumab; or anti-CD20 monoclonal antibodies.

People with MS receiving some immunosuppressive therapies (S1P modulators, or anti-CD20 monoclonal antibodies or alemtuzumab and cladribine before immune reconstitution) should receive counseling about the risk of diminished protection after vaccination and the need to follow other protective strategies against infections.

General immunization strategy

Recommendation 1. An evaluation of the immunization status is recommended for all MS patients, regardless of initial therapeutic plans, as part of the disease management strategy to minimize risks.

Recommendation 2. Care providers should inform patients about the importance of immunization and the risks of not vaccinating. Patients' opinions, values, and preferences should be considered, including the possibility of declining vaccination, to define a personalized immunization plan for each patient.

Recommendation 3. Vaccination should be performed at the time of diagnosis or in the early stages of the disease to prevent future delays in the initiation of therapies.

Recommendation 4. In order to define the vaccination plan, it is essential to:

- (i) document the patient's past, current, and, if planned, future therapies and

(ii) establish vaccination needs based on the patient's natural immunity, vaccine history, as well as the results of the pre-vaccine serological tests: varicella, measles, mumps, rubella (MMR), tetanus, hepatitis B, and other infections according to the local epidemiological context.

Recommendation 5. The specific vaccination guidance according to the prescribing instructions for each of the DMTs should be followed, considering the treatment-specific infectious risks, the epidemiological context and the local immunization requirements.

Recommendation 6. In MS patients who are experiencing a relapse, vaccination should ideally be delayed until clinical resolution or stabilization.

Recommendation 7. Physicians should reassess the vaccination status of pwMS before prescribing any immunosuppressive therapy (DMF, teriflunomide, S1P modulators, natalizumab, cladribine, alemtuzumab, or anti-CD20 monoclonal antibodies).

Recommendation 8. For non-treated MS patients or those receiving immunomodulatory treatment (IFNs or GA) who are planning to start any immunosuppressive therapy (DMF, teriflunomide, S1P modulators, natalizumab, cladribine, alemtuzumab, or anti-CD20 monoclonal antibodies) timing of vaccination should be adjusted:

- (i) Inactivated vaccines can be administered any time, but ideally at least 2 weeks before treatment onset to ensure a complete immune response;
- (ii) Live-attenuated vaccines should be administered at least 4 weeks before treatment onset, and 6 weeks before for ocrelizumab and alemtuzumab.

Recommendation 9. For MS patients planning to start any immunosuppressive therapy, accelerated vaccination schedules can be proposed when available and if needed.

Recommendation 10. Live-attenuated vaccines:

- (i) can be safely used in MS patients without DMT or those receiving immunomodulatory treatments (IFNs or GA);
- (ii) should ideally be avoided in MS patients receiving DMF and natalizumab because of the potential risk of developing vaccine-related infections. In very exceptional cases, such as a high risk of infection, vaccination with live-attenuated Vaccines could be considered if the potential risk of acquiring the infection is superior to the risk of developing vaccine-related infections;
- (iii) should be avoided in MS patients receiving DMF* (*If absolute lymphocyte counts < 800/mm³ (Grades 2 and 3 lymphopenia)), teriflunomide, S1P modulators, anti-CD20 monoclonal antibodies, and before immune restoration for cladribine and alemtuzumab because of the potential risk of developing vaccine-related infections.

Recommendation 11. MS patients receiving immunosuppressive therapies that are non-immune against measles and/or VZV should be informed that, in case of a risk exposure to measles and/or chickenpox, they should seek medical advice immediately, and a post-exposure prophylaxis with Ig should be offered.

Recommendation 12. For MS patients who are treated with anti-CD20 immunosuppressive therapies every 6 months, inactivated vaccines should ideally be administered, if the clinical situation allows it, at least 3 months after the last anti-CD20 treatment and 4–6 weeks before the next infusion to optimize vaccine responses.

Recommendation 13. For MS patients who receive vaccines before initiation or during treatment with immunosuppressive therapies:

- (i) Measurement of vaccine-induced antibody titers in an optimal interval of 1–2 months after the last dose of the vaccine is suggested for hepatitis B, tetanus, measles, mumps, and varicella to check whether they have mounted a protective immune response, according to accepted cut-off levels;
- (ii) In the case of attenuated live vaccines, the serological response should be confirmed before starting the immunosuppressive therapy;
- (iii) In case of insufficient response, consider administering a booster dose of the vaccine. For hepatitis B, a complete revaccination with an adjuvanted or high antigenic load vaccine is recommended.

Recommendation 14. MS patients who do not mount a protective immune response to hepatitis B after two complete courses of vaccination should be informed that, in the situation of a risk exposure to the virus, they should seek medical advice immediately, and post-exposure prophylaxis with Ig should be offered.

Recommendation 15. In MS patients who receive a short-term pulse of high-dose steroid treatment, live-attenuated vaccines should be postponed for 1 month. Ideally, inactivated vaccines should also be delayed for 1 month but can be administered any time.

Recommendation 16. In MS patients who stop receiving immunosuppressive therapies, inactivated vaccines can be administered any time, but preferably after immune restoration to maximize vaccine responses.

Recommendation 17. In MS patients who stop receiving immunosuppressive therapies, live-attenuated vaccines should only be administered after a safety interval that ensures immune restoration is met.

Recommendation 18. Adult patients with MS should receive those vaccines included in the routine vaccination schedule for the general population unless there is a specific contraindication.

Recommendation 19. MS patients, especially those who are candidates for/or on immunosuppressive therapies or those with a significant disability, should receive yearly influenza vaccination, following general recommendations.

Recommendation 20. MS patients who are candidates for/or on immunosuppressive therapies or those with a significant disability should receive pneumococcal vaccination, following general recommendations for immunosuppression (following guidelines applicable in each country; age and/or comorbidities should also be considered in the indication of pneumococcal vaccination).

Recommendation 21. In MS patients who are candidates for/or on immunosuppressive therapies, other vaccines with more restrictive indications should be considered:

- (i) Human papillomavirus (HPV) vaccine in women and men with MS who are scheduled to receive treatment with alemtuzumab, S1P modulators, cladribine, or anti-CD20 monoclonal antibodies, and have not already received the vaccine previously, independently of their age (in some countries, there can be limitations regarding age);
- (ii) Herpes zoster recombinant vaccine in patients over 18 years of age * (*With a background of chickenpox disease or live-attenuated varicella vaccination (otherwise consider varicella immunization)) who are scheduled to receive any treatment with a high risk of herpes infections such as cladribine, alemtuzumab, S1P modulators, natalizumab,

and anti-CD20 monoclonal antibodies (in some countries, there can be limitations regarding age);
(iii) Hepatitis B in non-immune high-risk patients, especially those who are scheduled to receive treatment with anti-CD20

Recommendation 22. In people with MS receiving immunosuppressive therapies vaccination for household and healthcare professional contacts should be recommended:

- (i) with influenza vaccines for all and
- (ii) with MMR and/or varicella vaccines for those non-immune to measles and/or varicella (through vaccination or natural immunity) and if the patient is not adequately protected against these infections.

Note from the bibliography group: Tables 1 and 2 as well as figure 1, reported in the appendix of the full document (chapter 8.4.2), provide detailed information on the recommended vaccines for people with MS, schemes, and indications as well as the timing of live-attenuated vaccines for the different DMTs.

Vaccination strategy in pediatric patients with MS

Recommendation 1. Care providers must remain vigilant in maintaining children's vaccination status following local vaccination guidelines and complete vaccinations ideally before the start of any immunosuppressive therapy. In case of non-vaccinated children or missed doses, a catch-up vaccination program following local guidelines should be conducted.

Recommendation 2. The same general precautions and timings with respect to the DMTs for immunization in adults should be applied to pediatric patients, taking into account the authorized age for the administration of each vaccine, specified in Table 1.

Recommendation 3. The safety and timing of vaccination should be discussed with the infant's physician/family doctor.

Vaccination strategy in pregnant women with MS

Recommendation 1. In women with MS with childbearing potential, a complete review of vaccination status should be performed. If needed, immunization with live-attenuated vaccines should be completed at least 1 month before pregnancy, unless there is a specific contraindication.

Recommendation 2. In pregnant women with MS, vaccination is recommended, as in the general population, to prevent potential infections with a high impact on maternal and infant morbidity and mortality.

Recommendation 3. Pregnant women with MS should be vaccinated with an inactivated influenza vaccine in any trimester at the beginning of the influenza season.

Recommendation 4. Pregnant women with MS should be advised to receive vaccination against diphtheria, tetanus, and pertussis (Tdap) during the end of second or third trimester of pregnancy, preferably between weeks 20 and 36* (*Unless national recommendations state otherwise.) to allow the greatest materno-fetal transfer of anti-pertussis antibodies. This vaccination should be performed during each pregnancy, regardless of whether the Tdap vaccine has been previously administered.

Recommendation 5. Pregnant women with MS should be evaluated for evidence of immunity to rubella and varicella and be tested for the presence of hepatitis B surface antigen (HBsAg). Women

without evidence of immunity to rubella or varicella should be vaccinated in the post-partum period before initiating DMT.

Recommendation 6. In women with MS, the timing of vaccines post-partum should be adjusted to treatment plans to obtain fast protection and adequate vaccine responses:

- Immunizations with live-attenuated vaccine should be completed after delivery, regardless of breastfeeding (except for yellow fever vaccine), and 4–6 weeks before initiation of immunosuppressive DMT.
- Inactivated vaccines can be administered at any time after delivery and during immunosuppressive treatment but, ideally, should be completed at least 2 weeks before the start of immunosuppressive DMT.

Recommendation 7. In newborns who have been exposed to anti-CD20 therapies during pregnancy or for some time before pregnancy, CD19-positive B-cell levels should be measured, and live-attenuated vaccines (i.e., rotavirus) should be delayed until B-cell levels have recovered.

Recommendation 8. In women with MS who are breastfeeding, vaccines are considered safe except for the yellow fever vaccine.

Vaccination strategy for elderly with MS

Recommendation 1. Elderly people with MS, similarly to the general elderly population, should be informed about the higher risk of severe infections and the altered immune response to vaccines (i.e., antibody titer, antibody diversity, protective immunity).

Recommendation 2. In elderly people with MS, the same general vaccination strategy as in the adult MS population should be applied in terms of timings, recommended vaccines, and precautions according to DMTs.

Recommendation 3. Elderly people with MS should receive the influenza vaccine annually as well as pneumococcal and inactivated herpes zoster vaccines.

Vaccination strategy for patients with MS planning to undertake international travel

Recommendation 1. Care providers should discuss potential travel plans with MS patients as early as possible, especially with those patients who will start immunosuppressive therapies.

Recommendation 2. MS patients planning to travel to a tropical or subtropical destination should be advised to consult a specialist travel clinic or a vaccination expert in coordination with the MS specialist for a specific evaluation and individualized indication of pretravel immunizations, considering the risk–benefit balance.

Recommendation 3. Care providers should consider travel details about timing and destination to advise on the best immunization strategy before travel.

Recommendation 4. Immunizations needed to travel should ideally be started 2–3 months before departure. Accelerated vaccination schedules can be applied whenever available.

Recommendation 5. For pwMS receiving immunosuppressive therapies, post-vaccination serology for those vaccines with accepted antibody cut-off levels, such as hepatitis A, hepatitis B, rabies, tetanus and/or polio should be verified, and additional booster doses may be required if negative responses.

Recommendation 6. Care providers should discuss the risks/benefits of stopping treatment for receiving a live-attenuated vaccine for traveling.

Dutch FMS 2023

Recommendation 1

Screening Prior to Initiating Disease-Modifying Treatment

Actively inform patients who are already being treated with immunomodulatory agents (and their other healthcare providers) about the increased risk of infections, and educate them on the potential risk reduction offered by vaccination prior to immunosuppressive therapy.

Check whether the patient has received a live attenuated vaccine within the past 6 weeks or a non-live vaccine within the past 2–4 weeks. Assess whether vaccinations are required (see Table 2, Module 1). Emphasize adherence to age-based vaccination programs (influenza, pneumococcal, COVID-19) and facilitate the provision of information about and the administration of vaccines for other age groups or other recommended vaccines.

Evaluate whether there are specific risk factors (e.g. frequent changes in sexual partners, travel plans, region of origin, comorbidities) and perform additional screening as needed (see Table 1, Module 1).

Investigate whether there are (anamnestically derived) indications of an active infection or malignancy. Treat these, where possible, before initiating disease-modifying therapy.

Recommendation 2

Complete the full National Immunisation Programme before initiating disease-modifying treatment in cases of incomplete participation. Pay attention to the additional vaccinations recommended for vulnerable individuals (pneumococcal vaccination, influenza, COVID-19), as well as the HPV vaccination in patients receiving S1P receptor modulators.

Determine VZV IgG serostatus if it is unknown whether the individual has had chickenpox. If VZV IgG is negative, vaccination against varicella is recommended, except in cases where live-attenuated virus vaccines are contraindicated due to disease-modifying therapy.

Consider vaccination against herpes zoster in patients with a prior history of shingles or in those over 50 years of age, and consider it prior to initiating disease-modifying therapy that increases the risk of herpesvirus (re-)activation.

Consult a vaccination clinic specialised in immunising patients receiving immune-modulating therapy if the patient requires specific travel vaccinations.

FR MS Pregnancy 2022

Vaccination and pregnancy

Before pregnancy:

- it is recommended to **update the vaccination schedule** in women with MS of childbearing age, according to recommendations for the general population and those specific for MS.
- It is recommended to update vaccination before pregnancy, especially for **measles, mumps, rubella (MMR), chickenpox and pertussis vaccines**.

During pregnancy:

- **Live attenuated vaccines are contraindicated** during pregnancy. It is recommended not to administer live attenuated vaccines in the month before conception.
- The **inactivated injectable influenza vaccine is recommended** before or at the start of the epidemic season, regardless of the trimester of pregnancy.
- **Vaccination against COVID-19 is possible** regardless of the trimester of pregnancy

After delivery:

- It is recommended to **update** vaccination after delivery, mainly **live attenuated vaccines, before resuming immunosuppressive treatments**.
- **Vaccination against yellow fever is contraindicated during breastfeeding**. All other vaccines are allowed, including other live attenuated vaccines.

Vaccination of neonates

The Dutch FMS guideline recommends that newborns of mothers treated with a monoclonal antibody during pregnancy **SHOULD NOT receive live attenuated vaccines** in their first year of life.

NICE 2022

Recommendation

Offer vaccinations in line with advice from the Joint Committee on Vaccinations and Immunisation and the Green Book: Immunisation against infectious disease for people with MS and their carers. [2014, amended 2022]

5.5 Managing bladder, bowel, pain, and fatigue symptoms of MS in primary care

5.5.1 General information

NICE 2022 formulates recommendations based on diagnostic accuracy and recommends to not routinely suspect MS based solely on non-specific symptoms, such as fatigue, depression, dizziness, or vague sensory changes, unless there is a history or evidence of focal neurological signs.

NICE 2022 **also recommends to be aware of the wide range of symptoms** that multiple sclerosis (MS) can present with, affecting various systems:

- loss or reduction of vision in 1 eye with painful eye movements
- double vision
- ascending sensory disturbance and/or weakness
- altered sensation or pain travelling down the back and sometimes into the limbs when bending the neck forwards (Lhermitte's sign)
- progressive difficulties with balance and gait.

On the other hand, German AWMF provide recommendations for ongoing symptom monitoring and multidisciplinary care. German AWMF formally states (strong consensus) that symptom-based treatment represents an important and indispensable pillar of therapy in the care of people with MS and includes medication-based and non-pharmacological interventions.

They recommend (strong consensus) that MS symptoms should be regularly assessed, preferably using a standardized checklist. In cases of limited functioning, appropriate treatment should be offered, taking into account the side effect profile.

Furthermore, therapy goals (Consensus) should be agreed through shared decision-making jointly, formulated in a patient-centered manner, and regularly reviewed during the course of treatment, if necessary according to the SMART principle. The goals should follow a biopsychosocial approach according to the International Classification of Functioning, Disability and Health (ICF).

German AWMF (strong consensus) also recommends that MS sufferers are informed early on about the support available through self-help services.

5.5.2 Bladder dysfunction

For bladder dysfunctions, 2 specific guidelines were used: NICE URINARY which discusses neurological disease in general and FR URINARY. The German AWMF 2024 general guideline also

formulated recommendations on Neurogenic Lower Urinary Tract Dysfunction (NLUTD). No recommendations on bladder functions were issued by NICE 2022 or Dutch FMS.

Diagnosis and assessment

German AWMF 2024 recommends (strong consensus) that all people with MS should be actively asked about bladder dysfunction (NLUTD), especially frequency/nocturia, urgency symptoms, incontinence episodes, slowed urination/urinary retention, and the frequency of urinary tract infections in the last six months.

NICE urinary formulated a full range of recommendation on the assessment of lower urinary tract dysfunction in a person with neurological disorder. Some points are also discussed by the German AWMF without formulating formal recommendations.

- Clinical history

NICE URINARY recommends to take a clinical history including neurological, urinary, bowel, sexual symptoms; diagnosis and progression of the neurological disease; comorbidities and other medications.

Similarly, German AWMF notices (not formal recommendation) to ask targeted questions about micturition problems (e.g., urgent urgency, pollakiuria, nocturia, incontinence, urinary stream).

Both German AWMF and NICE URINARY consider the value of using urinary journal (at least 3 days). While not formulated as formal recommendation AWMF 2024 mentions completing a three-day voiding diary even in the absence of subjective symptoms. NICE URINARY formally recommends to ask people and/or their family members and carers to complete a 'fluid input/urine output chart' to record fluid intake, frequency of urination and volume of urine passed for a minimum of 3 days.

- Functional impact

NICE URINARY recommends to assess the impact of the neurological disease on factors influencing the management, such as mobility, hand and cognitive functions, social support and lifestyle.

- Physical examination

NICE URINARY recommends to undertake a general physical examination that includes blood pressure, abdominal and external genital exam, and if clinically indicated (for example, to look for evidence of pelvic floor prolapse, faecal loading or alterations in anal tone) vaginal or rectal examination.

- Neurological examination

NICE URINARY recommends to carry out a focused neurological examination, assessing cognition, mobility, hand use, lumbar/sacral nerve function.

- Urine test

According to NICE URINARY, dipstick test using an appropriately collected sample is recommended to test for the presence of blood, glucose, protein, leukocytes and nitrites. Appropriate urine samples include clean-catch midstream samples, samples taken from a freshly inserted intermittent sterile catheter and samples taken from a catheter port. **DO NOT** take samples from leg bags.

If the dipstick test result and person's symptoms suggest an infection, arrange a urine bacterial culture and antibiotic sensitivity test before starting antibiotic treatment. Treatment need not be delayed but may be adapted when results are available.

NICE URINARY warns that bacterial colonisation will be present in people using a catheter and so urine dipstick testing and bacterial culture may be unreliable for diagnosing active infection. Similarly, German AWMF also mentions (not formal recommendation) laboratory tests (urinary status, microbiology, antibiogram) if necessary.

See also below additional recommendations specifically on urinary tract infection and bacteriuria from the FR URINARY guideline.

- Measures

NICE URINARY recommends to:

- measure the post-void residual urine volume by ultrasound, preferably using a portable scanner. Consider taking further measurements on different occasions to establish how bladder emptying varies at different times and in different circumstances.
- consider measuring the urinary flow rate in people who are able to void voluntarily.

German AWMF mentions the following to diagnose NLUTD but does not formulated this as formal recommendation:

- residual urine (≥ 70 ml)
- micturition frequency (> 13 per day)
- occurrence of UTIs in the last six months and
- the presence of incontinence.
-

According to them, voided volume less than 250 ml is an indication of NLUTD in MS.

- Urodynamic investigations

NICE urinary recommends to:

- **NOT offer** urodynamic investigations (such as filling cytometry and pressure-flow studies) routinely, in case of low risk of renal complications (for example, most people with multiple sclerosis)

- offer urodynamic investigations before surgery
- offer **video**-urodynamic investigations only in case of high risk of renal complications (for example, people with spina bifida, spinal cord injury or anorectal abnormalities).

Similarly, German AWMF 2024 notices (not formal recommendation) that urodynamics is not mandatory for every patient to initiate treatment. They add that this decision can **only be made IF** the residual urine is known and a voiding diary is available.

- Referral and additional investigation

NICE URINARY recommends to:

- consider to refer for a renal ultrasound scan people with high risk of renal complications (spina bifida or spinal cord injury).
- refer for urgent investigation if there are **red flag signs**: haematuria, recurrent urinary tract infections (three or more infections in the last 6 months) , loin pain, recurrent catheter blockages (within 6 weeks of being changed), hydronephrosis or kidney stones on imaging, biochemical evidence of renal deterioration.
- refer if there are changes in urinary function that may be due to new or progressing neurological disease needing specialist investigation (for example, syringomyelia, hydrocephalus, multiple system atrophy or cauda equina syndrome).
- consider further urinary tract investigation and treatment if urinary-caused changes in neurological symptoms (for example, confusion or worsening spasticity) is suspected.

German AWMF mentions (not formal recommendation) that depending on the findings and response to treatment, further diagnostics may be performed by a urologist: uroflowmetry, urodynamics.

- Support family and carers

NICE urinary recommends to assess the impact of lower urinary tract symptoms on the person's family members and carers and consider ways of reducing any adverse impact. If it is suspected that severe stress is leading to abuse, follow local safeguarding procedures.

Treatment

German AWMF specifies that the treatment of NLUTD in MS is carried out by a **urologist** experienced in the diagnosis and treatment of lower urinary tract dysfunction or a **neuourologist**. This should be done in close cooperation with the treating neurologist (especially with regard to medication coordination). The neurologist should also be informed about current treatment options.

- Patient information and support

NICE URINARY formally recommends **to offer patients, along with their families and carers information** (including on how to access further support) **and training**. Those using bladder management systems including catheters, pads, or appliances should also

- receive training, support and review from trained healthcare professionals,
- have access to a range of products that meet their needs
- have their products reviewed, at a maximum of 2 yearly intervals.

NICE URINARY also recommends that the information and training are tailored to the person's physical condition and cognitive function to promote their active participation in care and self-management.

Healthcare professionals are also expected to follow NICE guidance on patient experience and shared decision making (NICE clinical guideline 138).

- Behavioral management

NICE URINARY formally recommends to consider behavioral management program (e.g. timed voiding, bladder retraining, habit retraining) after assessment by a trained professional and in conjunction with education for the patient and/or carers. They add to take into account that prompted voiding and habit retraining are especially useful in patients with cognitive impairment. Similarly, German AWMF proposed, but does issued this as formal recommendation, some basic interventions including:

- informing about the symptoms and possible complications, adequate and evenly distributed fluid intake, individually planned urination intervals, and no delay in urination
- urination calendar, toilet training
- intensive training and implementation of aseptic single-use catheterization
- advice on any necessary aids: pads, liners, drip guards, diapers, and external urinary diversion devices such as self-adhesive condom urinals and urinals with adhesive strips or glue

They added that structured urological rehabilitation with detailed urological diagnostics (type of neurogenic dysfunction, residual urine measurement, urosonography and urodynamics, urine and blood analysis, micturition diary, fluid balance), bladder training, pelvic floor exercises, bladder emptying training, and, if necessary, intermittent self-catheterization (ISC) training, as well as infection prophylaxis options, also lead to a significant improvement in bladder function and quality of life.

- Non pharmacological therapies

German AWMF mentions that non-pharmacological therapies include pelvic floor muscle training with or without electrical stimulation without formulating recommendation.

For stress incontinence, NICE URINARY recommends considering pelvic floor muscle training for people with lower urinary tract symptoms **due to MS** or stroke. This may be combined with biofeedback or electrical stimulation. Patients are selected **after specialist pelvic floor assessment**.

- Pharmacological treatment

To improve bladder storage NICE URINARY recommends to offer antimuscarinics to patients with spinal cord disease (e.g. spinal cord injury, MS) and overactive bladder symptoms (frequency, urgency, incontinence). In this case it is recommended to monitor residual urine if the patient is not catheterized.

NICE URINARY further recommends to take into account that antimuscarinics that cross the blood-brain barrier (e.g. oxybutynin) have the potential to cause central nervous system-related side effects (such as confusion); and that antimuscarinics may reduce bladder emptying (which may increase the risk of urinary tract infections) and precipitate or exacerbate constipation.

Similarly, in cases of symptoms of an overactive bladder, high levels of suffering, and a lack of residual urine, German AWMF recommends that a **neurologist** may initiate a trial with an antimuscarinic agent. If there is insufficient improvement or side effects, a urological consultation should be made (consensus recommendation).

In cases of treatment-resistant urge symptoms, according to German AWMF, intermittent treatment with nasal desmopressin can be initiated, strictly observing contraindications (cardiac and/or renal insufficiency) (consensus recommendation).

In cases of insufficient efficacy, side effects from, or contraindications to antimuscarinic drugs, German AWMF says without formulating this as recommendation that the use of the β 3-adrenoceptor agonist mirabegron is a possible second-line treatment (dose 1x50 mg/day; side effects: particularly hypertensive blood pressure, tachycardia), possibly in combination with antimuscarinic.

Note from the bibliography group: Recommendations on treatment with botulinum toxin type A injections were made by NICE URINARY. They are available in the full document (Appendix chapter 8.5.2.2) but were not included in this summary, as we have considered this treatment reserved for specialist use only.

In case of neurogenic detrusor underactivity, German AWMF states without issuing a formal recommendation that alpha-receptor blockers such as tamsulosin can be used (off-label) for women and men.

In contrast, the NICE URINARY recommends against the use of alpha-blockers for managing bladder emptying problems caused by neurological disease.

- Catheterization, neuromodulation and surgical procedures

Note from the bibliography group: Additional recommendations from German AWMF and NICE URINARY on several surgical procedures, use of urethral tape or catheterization are reported in the full length document. Similarly, discussion from German AWMF about use and efficacy of some catheterization, neuromodulation and surgical procedures are reported in the appendix documents in chapter 8.5.2.1.

As this information was considered relevant only for specialist practice, it was not included in the summary.

Urinary tract infections (UTIs)

According to AWMF 2024, UTIs in MS are always considered complicated, due to neurogenic bladder, recurrent infections, polymicrobial etiology, and immunosuppressive treatments.

FR URINARY provides specific recommendations regarding the potential impact of urinary tract infections on the risk of relapse and disability progression in patients with multiple sclerosis and concludes that urinary tract infections are not associated with an increased risk of relapse or long-term disability progression in patients with multiple sclerosis (Level C, Appropriate; Relative to strong agreement). However, febrile infections are linked to a transient worsening of disability, whereas non-febrile infections are not (expert recommendation, Appropriate strong agreement).

- Clinical symptoms and diagnosis

AWMF 2024 emphasizes that clinical symptoms may be non-specific or absent; urine culture with pathogen testing is the gold standard for diagnosis.

- Management of Symptomatic UTIs

Both the German AWMF and FR URINARY agree on the need to treat symptomatic urinary tract infections. German AWMF does not provide a formal recommendation, but notes that infections should be treated for a sufficient duration following microbiological confirmation.

FR URINARY explicitly recommends treating symptomatic bacteriuria in all MS patients, regardless of the presence of neurogenic bladder or the mode of voiding. Treatment should follow the general population guideline (Level A, Appropriate, strong agreement).

- Management of Asymptomatic Bacteriuria (colonisation)

FR URINARY **does NOT recommend** routine screening or treatment of asymptomatic bacteriuria in patients with multiple sclerosis even before treatment with immunosuppressors or when intermittent or indwelling catheters are used.

Exceptions apply

- in situations where such management is indicated for the general population (e.g. pregnancy, invasive urological procedures) (Level C, Appropriate, strong agreement)
- in cases of hypogammaglobulinemia before immunosuppressive therapy (expert recommendation, Appropriate, strong agreement)
- or prior to urodynamic studies **only** when specific infection risk factors are present (e.g. recurrent UTIs, vesico-ureteral reflux, high detrusor pressure) (Level C, Appropriate, strong agreement).

- Prevention and Prophylaxis

All three guidelines advise against the routine use of antibiotic prophylaxis in patients with MS. However, only NICE URINARY has issued a formal recommendation against routine antibiotic prophylaxis. German AWMF acknowledges the absence of a gold standard for prophylaxis and notes that the value of long-term antibiotic therapy remains controversial.

Both NICE URINARY and FR URINARY recommend considering targeted prophylaxis in selected patients with recurrent UTIs:

- For NICE urinary, this applies to individuals with a **recent history of frequent or severe** infections, after evaluating reversible causes, discussing risks and benefits with the patient, and consulting microbiology protocols. In such cases, regular reassessment is recommended.
- For FR URINARY, the use of **weekly oral cycling antibiotics** is an established approach in patients with spinal cord injury. By analogy, this strategy may apply in MS patients in case of **recurrent infections and under specialist supervision** (expert recommendation) (Appropriate, strong agreement)

FR URINARY also emphasizes that the effectiveness of alternative preventive strategies is unproven. While German AWMF highlights the frequent use of non-antibiotic approaches such as methionine, D-mannose, or cranberry preparations.

Besides, NICE URINARY also specifically addresses patients with long-term indwelling catheters. It does not recommend routine prophylactic antibiotics when changing the catheter but suggests considering prophylaxis in patients who have a history of symptomatic UTI following catheter change or who experience trauma during catheterisation.

- Monitoring and surveillance protocols

NICE URINARY recommends **NOT relying solely** on serum creatinine or eGFR to monitor renal function in patients with NLUTD. **Routine** use of plain abdominal X-rays, cystoscopy, or renal scintigraphy is **NOT** recommended as well. Instead, **high-risk patients** should receive lifelong kidney ultrasound surveillance, annually or every two years. Urodynamic testing should also be considered in these patients. When an accurate measurement of glomerular filtration rate is required NICE URINARY recommends considering **isotopic GFR**.

Risks related to urinary tract dysfunctions

NICE URINARY recommends informing patients with NLUTD and their caregivers about the increased risk of kidney complications (e.g. stones, hydronephrosis, scarring), the warning signs to watch for (such as loin pain, UTIs, or haematuria), and when to seek medical attention.

Indwelling catheters carry a higher renal risk than intermittent self-catheterisation. It is recommended to use renal imaging if upper tract disease is suspected.

NICE URINARY recommends discussing with persons with NLUTD and their carers about the higher risk of bladder stones. They should be told which symptoms mean they need to see a healthcare professional, such as recurrent infections, catheter blockages, or haematuria.

Indwelling catheters are associated with a higher risk than other bladder management options. It is recommended to refer for cystoscopy if symptoms suggest bladder stones.

NICE URINARY recommends discussing with persons with NULTD and their carers the possible increased risk of bladder cancer, especially those with a long history of the condition and recurrent complicating factor (e.g. urinary tract infections). They should be told to watch for symptoms (especially haematuria) that mean they should see a healthcare professional.

It is recommended to arrange urgent (within 2 weeks) investigation with urinary tract imaging and cystoscopy for people with visible haematuria, increased frequency of urinary tract infections or other unexplained lower urinary tract symptoms.

Interaction between services

NICE URINARY notes that, due to the wide range of neurological conditions linked to NLUTD and the variable way in which patients' urinary tracts can be affected, it is not possible to design rigid referral pathways. Nevertheless, they add that "red flag" symptoms, signs, or test results can help guide appropriate referral.

They recommend to share specialist contact details with the person, their carers, and any non-specialist healthcare professionals involved in their care. Patient with NULTD and/or their family members and carers should be given a list of key healthcare professionals involved, their roles, and contact details; copies of all clinical correspondence; a list of prescribed medications and equipment. This information should also be sent to the person's GP.

NICE URINARY refers healthcare professionals to the guidance on good patient experience in adult NHS services (NICE guideline 138).

In addition, NICE URINARY issues recommendations to guide the transition of care from paediatric to adult services for people with neurogenic lower urinary tract dysfunction:

- Plan a clear care pathway early, involving the person their parents and their carers.

- Involve the young person's parents and carers when preparing transfer documentation with the young person's consent
- Provide a full summary of medical history, investigations, and treatments
- Include information from the multidisciplinary team.
- Identify and plan ongoing urological services needed after transition.
- Formally transfer care to a named individual(s).

When receiving someone from paediatric to adult services:

- Review transfer documents and coordinate with other adult care teams.
- Give the person details and contacts of the adult service and key staff.
- Ensure urological care continues after transition.

NICE URINARY recommends to consider regular multidisciplinary meetings between paediatric and adult teams during the years leading up to transition and after entering adult services.

5.5.3 Bowel dysfunction

Dutch FMS and NICE 2022 do not provide recommendation on bowel dysfunction

German AWMF 2024 recommends (consensus) to actively ask about bowel dysfunction. If present, initiate a stool diary including stool consistency (which supports both diagnosis and monitoring of treatment effectiveness).

According to them, if constipation persists despite laxatives the patient should be informed about transanal irrigation as a treatment option (strong consensus).

In cases of neurogenic bowel dysfunction, the following measures should be considered (consensus):

strengths of recommendation in the table: A = must; B = should; O = can

For Constipation:

- Adequate hydration (1.5–2 L/day) (A) if necessary additionally fruit juice (B).
- High-fiber diet (B)
- Exercise, physiotherapy, standing frame, power-assisted leg trainers (A).
- Pelvic floor exercises, colonic massage, biofeedback, foot reflexology (O).
- If ineffective, transanal irrigation (B); manual evacuation (B), return-flow enema (O).
- For hard stools: Lactulose or Macrogol (caution: stools too soft) (A).
- For rectal emptying: Glycerin suppositories, if necessary enemas (B), if necessary stimulant laxatives every 3–4 days (O).
- For painful sphincter spasticity: botulinum toxin (B). **No** antispasmodics (B).

- For severe meteorism: dimethicone (B).

For Incontinence

- Individual dietary changes, no irritants such as coffee, alcohol, and carbonated drinks, gas- or bowel-stimulating foods (B).
- Avoiding excessively soft stools (caution: laxatives in cases of constipation) (A).
- Targeted, regular bowel movements, e.g., transanal irrigation (B).
- If necessary, pelvic floor exercises and/or neurostimulation (Percutaneous Tibial Nerve Stimulation -PTNS) (B).
- If necessary, adequate provision of aids: for patients who are able to walk, e.g., intraanal tampons (A).
- If necessary, loperamide after each bout of diarrhea (caution: subsequent constipation) or anticholinergics (e.g., butylscopolamine, amitriptyline) (O).

5.5.4 Pain

Both NICE 2022 and the German AWMF issue formal recommendations on the management of pain in people with MS, while the Dutch FMS guideline does not.

They both recognize that pain in people with MS is heterogeneous and may arise from various causes, including neuropathic, musculoskeletal, and treatment-related pain. However, only NICE 2022 issues a formal recommendation to assess and investigate the cause of pain in order to provide targeted treatment.

While they both highlight the negative impact of pain on quality of life, NICE 2022 explicitly recommends being mindful of the mental health impact and refers to existing guidance on depression in the context of chronic illness.

German AWMF formulates recommendations for the management of neuropathic pain, spasticity-related pain, and headaches in MS.

- For neuropathic pain, it refers to the WHO stepwise pain management scheme, the National Care Guideline for Non-Specific Low Back Pain, and the DGN Guideline on chronic neuropathic pain (strong consensus).
- Musculoskeletal pain management is recommended (strong consensus) according to the chapter on spasticity treatment within the AWMF guideline (not detailed in the current document).
- Headaches management in MS should be based on the AWMF DGN guidelines on migraine and tension-type headache treatment (strong consensus).

Although this is not a formal recommendation, German AWMF notes that non-pharmacological treatment should be considered part of the overall therapeutic strategy.

NICE 2022 recommends treating neuropathic pain and referring individuals to pain services, in line with its guideline on neuropathic pain in adults. It also highlights the high prevalence of musculoskeletal pain in MS, often secondary to immobility, spasticity, or posture-related issues and recommends assessment and targeted treatment with reference chapters on mobility problems and spasticity (not detailed in the current document) and NICE's guideline on low back pain and sciatica in over 16s.

5.5.5 Fatigue

Assessment of fatigue

All three guidelines acknowledge the importance of identifying the nature and potential causes of fatigue in people with MS, although their approaches differ in scope and depth.

Dutch FMS recommends distinguishing between primary and secondary fatigue.

German AWMF (consensus) also recommends assessing fatigue symptoms and their impact.

Only NICE 2022 recommends asking people with MS whether they experience fatigue, sudden tiredness, or changes in energy levels that affect daily life, and not assuming that fatigue is always caused by MS.

While both Dutch FMS and NICE 2022 provide formal recommendations for a comprehensive assessment of potential contributing factors to fatigue in MS, German AWMF also highlights, without issuing a formal recommendation, that a detailed symptom description is essential to rule out secondary fatigue. Relevant factors include:

- Sleep disorders
- Medication side effects
- Comorbidities: anemia, thyroid dysfunction
- MS symptoms: pain, spasticity, bladder dysfunction
- Loss of fitness
- Over- or underexertion
- Infections
- Depression and anxiety
- Cognitive problems

NICE 2022 and German AWMF (although not formal) further recommends managing (or refer for management) these other possible causes of fatigue.

In addition, NICE 2022 issues a recommendation asking to explain patients that MS-related fatigue may be triggered by heat or by biological, physical, or emotional stress. The German AWMF mentions heat as well, though without a formal recommendation.

German AWMF also notes that fatigue may occur as a prodromal symptom of MS, appear early in the disease course or as an isolated symptom, and is independent of physical disability.

Both Dutch FMS and German AWMF recommends the use of standardized questionnaires, but only Dutch FMS provides structured guidance recommending choosing questionnaires based on the aspect of fatigue and the time period to be determined:

- FSS: fatigue severity and frequency
- MFIS: physical, cognitive, and psychosocial functioning
- CIS20R: subjective fatigue, motivation, activity level, concentration.

The use of multiple questionnaires in parallel can be considered.

German AWMF also recommends that a neuropsychological examination with attention intensity testing should be attempted for objectification.

Nonpharmacological interventions

Although all three guidelines recommend offering non-pharmacological interventions to manage primary fatigue (Dutch FMS), disabling fatigue (German AWMF), or fatigue more generally (NICE 2022), they differ in the specific interventions they support.

Dutch FMS recommends discussing CBT and physical training as treatment options for MS-related fatigue. Patients should be informed about the nature and burden of these interventions, and their effect should be evaluated after 3 to 4 months. The possibility of maintaining long-term benefits should also be addressed during and after the intervention.

Conversely, the Dutch FMS recommends **not using** energy management or multidisciplinary rehabilitation to treat MS-related fatigue. The principles of energy management may be discussed only if the patient raises questions about daily activity planning.

Concerning the evaluation of the evidence, Dutch FMS concludes that:

- CBT and physical training appear to have a clinically relevant effect on fatigue symptoms. Although the data are limited and not always conclusive, CBT likely carries a low absolute risk, and physical training appears relatively safe.
- Energy management and multidisciplinary outpatient rehabilitation do not appear to have a clinically relevant effect on fatigue symptoms. It is not possible to draw conclusions about adverse events related to multidisciplinary rehabilitation, while the absolute risk of adverse events associated with energy management is probably low.

German AWMF recommends offering non-pharmacological interventions such as energy management training, CBT, mindfulness training, and, when possible, attention training should be offered, possibly with the help of a digital health application (DiGA: elevida©). Patients should also be informed about the positive effects of physical activity (strength and endurance training) and cooling measures.

NICE 2022 recommends offering people with MS and fatigue a personalised discussion to support self-management, which may include goal setting, energy conservation, lifestyle review (diet and exercise), and stress management techniques such as mindfulness and CBT. It is also recommended:

- advising that aerobic, resistance, and balance exercises (e.g. yoga, pilates) may help manage fatigue;
- considering vestibular rehabilitation for fatigue or mobility issues associated with balance problems;
- considering supervised exercise program with moderate progressive resistance and aerobic training treat people with MS who have mobility problems or fatigue,
- If multiple interventions are suitable, offering treatment based on patient preference and whether the activity can be continued after the program ends,
- not offering hyperbaric oxygen therapy.

NICE 2022 also notes (not formal recommendation) that a fatigue diary may be a useful tool in the management of fatigue.

Dietary interventions

All three guidelines recon that there is no or insufficient evidence. However, German AWMF decides to not formulate any recommendation for a specific diet, while Dutch FMS formally recommends against using dietary intervention to treat MS-related fatigue. NICE 2022 rather formally recommends to explain people that there is no evidence that a specific diet will improve fatigue in people with MS, but that a healthy diet will benefit their general health.

Pharmacological treatment

Only NICE 2022 provides formal recommendations regarding diverse pharmacological treatments for MS-related fatigue. The Dutch FMS issues formal recommendations for non-pharmacological interventions, but does evaluate the efficacy and safety of several pharmacological treatments.

German AWMF only makes a brief recommendation, specifying that antidepressants (particularly SSRIs) may be used in cases of depressive mood, but not for fatigue alone.

Concerning the evidence evaluation of the pharmacological efficacy **Dutch FMS** concludes that:

- alfacalcidol and retinyl palmitate appear to have a beneficial effect on fatigue symptoms. However, adverse event data are insufficient to confirm safety of retinyl palmitate. For alfacalcidol, it is uncertain whether it causes headaches or dizziness.
- the effects of acetyl-L-carnitine, amantadine, and acetylsalicylic acid (aspirin) on MS-related fatigue are uncertain. No conclusions can be drawn about safety of acetyl-L-carnitine and amantadine. For aspirin, it also remains unclear whether it causes nausea or epigastric pain.
- american ginseng and modafinil do not have a clinically relevant effect on fatigue symptoms in MS patients. Safety data are also insufficient to draw conclusions for ginseng. It is uncertain whether modafinil causes nausea and restlessness.

NICE 2022 recommends:

- discussing with the person with MS whether a medicine to treat fatigue may be an option, explaining the potential benefits, risks, and safety concerns;
- if the person wishes to try a medicine, referring to a specialist for full discussion of the treatment options;
- using shared decision-making to choose whether to initiate pharmacological treatment and which option would be most appropriate, considering the individual's needs, preferences, and the risk–benefit profile.
- Medicines that may be considered include:
 - amantadine: follow BNF dosage guidelines
 - modafinil except in people who are pregnant or planning pregnancy
 - Follow **MHRA safety advice** regarding monitoring (including cardiovascular monitoring before and during treatment), caution for use, and pregnancy precautions (including the use effective contraception and explaining that **modafinil may reduce the effectiveness of steroidal contraceptives**).
 - Use the **lowest effective dose**.
 - selective serotonin reuptake inhibitors (SSRIs)
 - Use the lowest recommended dose for licensed indications.
 - Follow NICE guidance on prescribing medicines associated with dependence or withdrawal symptoms.
- To **not use** vitamin B12 injections to treat fatigue in people with MS.

NICE 2022 further recommends to regularly review treatment to assess effectiveness, safety, and acceptability, adjust the dose as needed, and decide whether to continue or stop treatment. The frequency of review should be agreed with the person, taking into account the medicine used, the need of dose adjustments, and person's preference.

Collaboration between prescribers

While NICE specifies that if a person with MS wishes to try a medicine for fatigue, they should be referred to a specialist. NICE also recommends that, once a person is on a stable dose,

prescriptions may be continued by another prescriber under a shared-care agreement with the specialist.

5.6 Managing MS across the life course: focus on specific patient groups

5.6.1 Managing MS in children and adolescents

None of the selected guidelines provide recommendations about the management of MS in children and adolescents.

The German AWMF 2024 guideline mentions that the diagnosis and treatment follow the principles and recommendations for adults and refers to a specialist guideline for pediatric multiple sclerosis for details. (out of scope)

Note from the bibliography group: For recommendations on vaccination strategy in children with MS, see chapter 5.4 “Vaccination considerations with MS Treatment”.

5.6.2 MS and family planning

for the topic MS and family planning, an additional guideline was consulted: **FR MS Pregnancy 2022*

MS and family planning

The French MS Pregnancy guideline states that **pregnancy is not contraindicated** in women with MS.

All guidelines (Dutch FMS 2023, German AWMF 2024, NICE 2022, FR MS Pregnancy 2022) emphasize the importance of **proactively discussing reproductive plans** early (soon after diagnosis and particularly when starting DMT).

The FR MS Pregnancy guideline recommends to **consider the pregnancy plan** of women with MS **when choosing a disease-modifying treatment**.

The NICE guideline emphasizes to make sure the patient understands that they should discuss this with their healthcare provider **as soon as they are planning** to become pregnant, **especially if treated with DMT**.

The NICE guideline recommends to offer the opportunity to **speak with a healthcare professional with knowledge of MS**.

NICE provides examples of topics or information to discuss:

“For example, this may include discussing the following:

- *that fertility is not affected by MS*
- *that pregnancy can be well managed in people with MS*
- *the risk of the child developing MS*

- *taking vitamin D and folic acid supplements before and during pregnancy*
- *possible changes to medicine use before and during pregnancy*
- *that pregnancy does not increase the risk of disease progression*
- *that relapses may decrease during pregnancy and may increase 3 to 6 months after childbirth before returning to pre-pregnancy rates*
- *that birth options and pain relief choices available (including epidurals) should not be affected by MS*
- *that breastfeeding is safe unless the person with MS is taking certain disease-modifying treatments*
- *support that may be available with caring for and supporting children. “*

NICE recommends to **proactively discuss caring for a child** and the possible impact of MS symptoms, such as fatigue, and how these could be managed.

Three guidelines (Dutch FMS, German AWMF and FR MS Pregnancy) recommend **planning pregnancy during a stable phase** of the disease. FR MS Pregnancy specifies that planning a pregnancy during a disease inactivity of at least 12 months should be favoured.

Both the Dutch and German guideline recommend **making a management plan preconceptionally** if on DMT, together with the treating **neurologist and gynaecologist**. This plan should involve discussing the risks of temporarily stopping DMT, and planning the restart of DMT after birth. The FR MS Pregnancy guideline recommends that the **neurologist** discusses adjustment of essential and symptomatic treatments, discussion of other disease management, and update of vaccinations.

The Dutch FMS guideline recommends to consider involving a **revalidation physician** for advice regarding functional problems during pregnancy and postpartum.

Referral and specialist care during pregnancy

The FR MS Pregnancy guideline recommends to carry out the **obstetric follow-up recommended for the general population** in women with MS, with at least one **neurological consultation** dedicated to the interactions between pregnancy and MS during the pregnancy.

In women with MS and disability, The FR MS Pregnancy guideline recommends to organize **multidisciplinary care** adapted to the disability from the start of the pregnancy.

The Dutch FMS guideline provides **specific referral criteria** for when to involve specialist care (**gynaecologist**). Referral to the second line is advised when:

- The woman requests it,
- The patient continues disease-modifying therapy during pregnancy,
- Physical impairments might interfere with labor or delivery,
- Symptomatic medications may pose risks during pregnancy,

- Or for any other reason that suggests specialist monitoring is appropriate.

The FR MS Pregnancy guideline recommends to **NOT** perform **routine MRI** during pregnancy, but it **can be performed if warranted**. If gadolinium is essential, its administration is possible during pregnancy regardless of the term, avoiding linear gadolinium salts.

MS relapses during pregnancy

The Dutch FMS, French MS Pregnancy and German AWMF guidelines support the use of **high-dose corticosteroids** during pregnancy when clinically indicated.

Both agree the **severity of the attack** must be weighed against **fetal risk of treatment**.

The German AWMF guideline makes a distinction between relapse **after the first trimester**, after which high-dose corticosteroids can be initiated as a standard practice, and relapse **in the first trimester**, when both the German AWMF and the French MS Pregnancy guideline recommend that high-dose corticosteroids be used only in exceptional cases and after explicit explanation of the specific risk.

The Dutch FMS guideline offers the possibility of giving dexamethasone (instead of methylprednisolone), only in consultation with the gynaecologist.

The German AWMF and the French MS Pregnancy guidelines recommends to consider immunoadsorption or plasmapheresis in case of severe refractory relapse or contraindication to corticoids.

The French MS Pregnancy guideline recommends to NOT USE IV immunoglobulins to treat relapse.

Other pharmacological treatments and pregnancy

The French MS Pregnancy guideline makes several statements regarding other pharmacological treatments and pregnancy in women with MS:

- The recommendations regarding **antenatal vitamin supplementation** for the **general population** apply to women with MS
- A table with recommendations and precautions regarding the use of **DMTs** (and gadolinium) during conception, pregnancy and breastfeeding is provided, but out of scope of this document.
- It is recommended NOT to administer preventive treatment for postpartum relapses.
- If they have been stopped, **early resumption of disease-modifying treatments after childbirth** is recommended in women with MS.

Delivery modalities, analgesia/anaesthesia in MS

The French MS Pregnancy guideline recommends that women with MS should **receive the same care and delivery modalities as the general population**, in particular regarding:

- Referral to a particular level of maternity department
- Planned induction of labor
- Indications for caesarean delivery
- Postpartum perineal rehabilitation
- Analgesia/anesthesia procedures for childbirth

Breastfeeding and MS

The French MS Pregnancy guideline states that **breastfeeding is not contraindicated** in women with MS.

In women who are **not treated with DMT**:

The German AWMF guideline recommends to support exclusive breastfeeding.

In women who are treated with DMT:

The Dutch FMS guideline recommends an individualized decision taking into account the **benefits of breastfeeding for the child** against the **risks of delaying DMT or drug transfer through breastmilk**. The French MS Pregnancy guideline recommends discussing breastfeeding and when to resume DMTs during a consultation with the neurologist, taking into account **the patient's choice** and **disease activity**.

The Dutch FMS and French MS Pregnancy guidelines provide a table with recommendations on the use of individual drugs during breastfeeding. (out of scope)

The German AWMF guideline recommends evaluating the **indication for resuming DMT** postpartum based on disease activity before and during pregnancy.

The German AWMF guideline provides specific recommendations on the use of some individual drugs during breastfeeding:

- Beta-interferons and glatiramer acetate may be used after risk-benefit assessment.
- Monoclonal antibodies can be used in high disease activity, preferably starting 1–2 weeks postpartum.

MS relapse treatment during breastfeeding

The German AWMF and French MS Pregnancy guideline recommend to treat relapses with **high-dose corticoids** in women who breastfeed. The French MS Pregnancy guideline recommends to **wait 4 hours** after treatment to resume breastfeeding.

According to the French MS Pregnancy guideline, the use of immunoadsorption or plasmapheresis in lactating women is possible in case of severe relapse that does not respond to methylprednisolone.

Vaccination and pregnancy

The French MS Pregnancy guideline makes several recommendations concerning vaccination before pregnancy, during pregnancy and after delivery, and concerning the vaccination of neonates.

Note from the bibliography group: For recommendations on vaccination strategy in pregnant women with MS, see chapter 5.4 "Vaccination considerations with MS Treatment".

MS and Fertility treatment

The Dutch FMS guideline recommends to inform the patient that there is **no reason to withhold IVF** if needed. The French MS Pregnancy guideline states that assisted reproductive technology can be offered to women with MS and recommends to **inform about the increased risk of relapse** in the weeks following the procedure.

The French MS Pregnancy guideline recommends to favour assisted reproductive technology **after at least 12 months of clinical and radiological inactivity of MS**, with or without disease-modifying treatment.

The French MS Pregnancy guideline states that all assisted reproductive technologies can be offered to women with MS, with no limit to the number of attempts because of the diagnosis of MS itself.

The French MS Pregnancy guideline recommends to discuss the planning of these procedures during a consultation with the **neurologist, in coordination with the assisted reproduction specialist**.

The German AWMF and French MS Pregnancy guidelines recommend **to continue DMT during fertility treatments** (taking into account disease activity and specific contra-indications). The French MS Pregnancy guideline adds to continue DMTs at least during the first trimester of pregnancy.

5.6.3 Employment and Work Disability Considerations

Only the Dutch FMS 2023 guideline makes recommendations regarding employment and work disability in patients with MS.

The guideline emphasizes the importance of **proactive monitoring** to support continued employment among people with MS. **Throughout the disease course**, healthcare professionals should **actively inquire** about:

- The person's current work situation,
- Presence of **cognitive difficulties**,
- **Fatigue**,
- Progressive **functional limitations**, and
- Any concerns related to work or job retention.

The guideline recommends that patients at higher risk of early work disability, such as those who are **older, female**, or have a **lower educational level**, should be monitored more closely.

If any of the above issues are identified, the guideline recommends following the relevant recommendations on managing cognitive problems, fatigue, and functional decline.

***Note from the bibliography group:** only the recommendations on fatigue were summarized in this report, as managing cognitive problems and functional decline were considered out of scope.*

The guideline recommends to **refer** patients early to an **occupational physician** if there are any concerns about work participation, even in the absence of sick leave.

If an occupational physician is not available, referral to a **vocational rehabilitation service** should be considered.

5.6.4 Managing MS in Older Adults / Cardiovascular comorbidities

***Note from the bibliography group:** Although formulated as separate jury questions, older age and cardiovascular comorbidities are grouped here because none of the reviewed guidelines address cardiovascular comorbidities as a distinct category. However, cardiovascular risk is sometimes considered implicitly within recommendations for older adults with MS.*

All three guidelines (Dutch FMS 2023, German AWMF 2024, NICE 2022) take a different approach formulating recommendations for older people with MS.

The Dutch FMS guideline focuses on the **long-term treatment with DMT** (in relapsing remitting MS, secondary progressive MS and primary progressive MS).

It provides specific criteria for considering **first-line DMT discontinuation in rrMS**, including **age over 45 or 55 years**, the absence of relapses and radiological disease activity for at least five years and no EDSS progression.

These recommendations are based on the observation that inflammatory disease activity decreases with increasing age and that older individuals may be more vulnerable to adverse effects of DMT.

The German AWMF guideline focuses on **late-onset MS** (typically defined as MS with onset after the age of 50). It emphasizes the importance of **differential diagnosis**, particularly in individuals with vascular risk factors.

The guideline states that **DMT should not be withheld solely on the basis of older age** in patients with active MS. However, it recommends that **when starting DMT** in individuals older than 55 years, closer **monitoring for tolerability, risks and adverse effects** is necessary due to immunosenescence and altered pharmacokinetics and pharmacodynamics.

Additionally, it highlights the need to **identify and treat cardiovascular comorbidities** that are more prevalent in this population.

The NICE 2022 guideline focuses on **advanced MS**, which is defined not by age but by the progressive burden of disease and increasing disability. It recommends providing tailored support, including information about mobility aids, social services, and advance care planning, and emphasizes the importance of addressing emotional well-being, functional capacity, and palliative needs.

Note from the bibliography group: For recommendations on vaccination strategy in elderly people with MS, see chapter 5.4 “Vaccination considerations with MS Treatment”.

5.7 The Role of Lifestyle, Exercise, and Rehabilitation in MS Care

Exercise

All three guidelines (Dutch FMS, German AWMF and NICE) encourage regular exercise for people with MS, underlining its beneficial effects on health and disease management.

- Dutch FMS

Recommendation 1

Ask regularly during consultations about physical activity, the patient's motivation to be active, and any barriers they may face.

Explain the positive effects of physical activity on health.

Encourage the patient to start or continue engaging in physical activity.

Recommendation 2

Consider referring patients with MS who are unable to maintain an active lifestyle independently for support in starting and maintaining a physical activity program.

Inform the patient that:

- exercise does not negatively affect the progression of MS;
- physical activity can temporarily worsen existing symptoms, which may increase the risk of injury or falling;
- continued physical activity is necessary to maintain its positive effects.

Evaluate the patient's approach to physical activity and discuss the importance of performing it in a responsible and safe manner. Ensure that physical activity becomes a sustained part of the patient's routine.

-German AWMF 2024

Recommendation C1 (strong consensus): From the time of diagnosis, every person with MS should be informed about the benefits of strength and endurance training as well as current recommendations for physical activity. Up to EDSS 7.0, the WHO recommends a minimum of 75 minutes of intensive or 150 minutes of moderate endurance training per week. Ideally, fitness status should be assessed regularly. The level of physical activity should be regularly assessed to provide motivational support.

-NICE

Recommendation. Help the person with MS continue to exercise, for example, by referring them to a physiotherapist with expertise in MS or to exercise referral schemes.

Encourage people with MS to exercise. Advise them that regular exercise may have beneficial effects on their MS and does not have any harmful effects on their MS.

Nutrition

All three guidelines recognize the relevance of a balanced diet for general health, though their emphasis varies: the Dutch FMS and German AWMF explicitly promote healthy eating, while NICE supports this only indirectly by advising against ineffective dietary treatments. Each guideline recommends some form of vitamin D assessment or intervention, though with differing aims and thresholds. The importance of patient education and referral is acknowledged (Dutch FMS, German

AWMF). Finally, the guidelines advise caution regarding unproven dietary approaches, such as the Wahls and Jelinek diets (Dutch FMS) or omega-3/omega-6 supplementation (NICE).

-Dutch FMS

Recommendation

Advise the patient to follow the guidelines for healthy eating. Refer them to the following webpage:

<https://www.voedingscentrum.nl/nl/gezond-eten-met-de-schijf-van-vijf.aspx>

Vitamin D

Check the patient's vitamin D status at the start of treatment or guidance. Supplement with vitamin D3 (5600 IU/week) if the vitamin D level is below 75 nmol/L. Reassess the status after 3 to 6 months. Increase the dose to 2000–4000 IU/day if levels remain insufficient.

Discuss the negative consequences of vitamin D deficiency.

Wahls and Jelinek

If the patient expresses interest in following the Wahls or Jelinek diets (or other diets), discuss the potential adverse effects. Consider referring the patient to a dietitian.

-German AWMF 2024

Recommendation C2 (strong consensus): MS patients should be advised to follow a balanced diet according to current nutritional standards and a diet that is preventively effective in terms of cardiovascular health. This diet should be based on the current food-related recommendations of the German Nutrition Society (DGE). Nutritional counseling should be prescribed if necessary to support the change of unhealthy eating habits.

Recommendation C3 (strong consensus): MS patients should be informed about the negative impact of overweight, obesity, and cardiovascular risks. Patients should be informed about the options for treating obesity.

Recommendation C4 (strong consensus): Vitamin D levels should be checked in patients with multiple sclerosis. If a deficiency exists, it should be corrected, ideally through daily or weekly drug supplementation.

Recommendation C5 (strong consensus): Even in patients with multiple sclerosis and vitamin D levels within the normal range, further vitamin D supplementation to the high-normal range of 50-125 nmol/L can be considered. In this case, the patient should be informed that a positive effect of this treatment has not been proven. Long-term daily intake via supplements should not exceed 4,000 IU (< 100 µg).

Recommendation C6 (strong consensus): Ultra-high-dose vitamin D therapies should not be administered, as a health risk cannot be ruled out.

-NICE

Recommendation. Do not offer vitamin D solely for the purpose of treating MS.

Recommendation. Do not offer omega-3 or omega-6 fatty acid compounds to treat MS. Explain that there is no evidence that they affect relapse frequency or progression of MS.

Other lifestyle factors

Other lifestyle factors than exercise and nutrition are mentioned here. Both AWMF and NICE address smoking as a significant, modifiable risk factor in MS. Beyond smoking, the German AWMF also

includes two additional lifestyle considerations: bone health and osteoporosis, and stress and psychological well-being.

-German AWMF 2024

Recommendation C7 (consensus): In MS patients, bone density measurements should be performed from menopause onwards in women and from age 50 onwards in men for the early detection of osteoporosis, especially in cases of longer disease duration, higher EDSS, and a lifetime dose of steroid equivalents of > 15g. Depending on the findings, osteological consultation, lifestyle modification, and drug therapy should then be initiated.

Recommendation C8 (Consensus): The importance of stress factors should be repeatedly addressed with people with MS, and access to individually tailored counseling and therapy services should be provided.

Recommendation C9 (strong consensus): MS patients should be informed about the negative impact of smoking and passive smoking. Patients should also be informed about specific options (e.g., "smoke-free" from the Federal Center for Health Education, including web-based group training) and approved digital health apps (e.g., "Non-Smoker Heroes") for smoking cessation.

-NICE

Recommendation. Advise people with MS not to smoke and explain that it will increase the progression of disability. (See NICE's guideline on tobacco: preventing uptake, promoting quitting and treating dependence.)

Rehabilitation

As part of the broader non-pharmacological approach to MS, the Dutch FMS guideline presents rehabilitation as a goal-oriented, multidisciplinary process tailored to the individual's functional limitations, personal goals, and life context. Rehabilitation should be considered when people with MS experience limitations in activity or participation, with the scope of care adapted to the complexity of these limitations and the patient's social situation and preferences. Coordination across disciplines—such as physiotherapy, occupational therapy, and rehabilitation medicine—is recommended. The guideline addresses rehabilitation targets including fatigue, physical fitness, gait disturbances, and arm and hand function.

Participation restrictions - Recommendation

Multidisciplinary rehabilitation is recommended for people with MS who experience difficulties with activities and participation. Treatment goals should preferably be coordinated among the different professionals involved.

The scope and complexity of the activity and participation limitations—as well as the patient's social situation, preferences, and personal goals—determine the appropriate setting and intensity of the rehabilitation program.

In cases of limited mobility, exercise therapy is preferably provided under the supervision of a physiotherapist.

Fatigue - Recommendation

Determine whether the fatigue in MS is primary or secondary.

Discuss with the patient the use of cognitive behavioral therapy or physical training as treatment options for MS-related fatigue. Inform the patient about the content and demands of the proposed interventions. Evaluate the effectiveness of the chosen treatment after 3 to 4 months.

During and after completion of the selected intervention, pay attention to maintaining its effects in the long term.

Do not use dietary interventions, energy management strategies, or multidisciplinary rehabilitation to treat MS-related fatigue. Consider applying energy management principles only if the patient specifically asks for guidance on how to distribute activities throughout the day.

Treatment of Physical Fitness – Recommendation

It is recommended that patients with MS, within their physical capabilities, strive to maintain good physical fitness due to its positive effects on overall health.

Patients with limited physical capacity should be supported in finding (adapted) opportunities for physical activity. Such options are available for a large proportion of people with MS.

Physical activity is also recommended as a tool to achieve disease-related goals, such as reducing spasticity, re-establishing physical boundaries and body awareness, alleviating perceived fatigue, and enhancing self-confidence.

When developing a physical activity program, the following factors should be considered: gradual progression, avoiding peak exertion, alternating between periods of effort and rest, and managing heat intolerance by ensuring body heat can dissipate and the environment is not too warm. It is likely that people with MS benefit more from frequent, shorter bouts of activity rather than one longer session at submaximal intensity.

If the person does not experience any issues during physical activity, regular evaluation is not immediately necessary. However, if problems do arise, the frequency of evaluations should be increased.

Gait disturbances

Recommendation 1

Regular exercise programs as an intervention to reduce gait problems can be safely prescribed following proper information and instruction.

Inform the patient about the possibility of temporary worsening of pre-existing symptoms and how to manage them.

Inform the patient that reduced muscle strength or impaired sensation may affect stability and thus the safety of training.

Encourage continuation of healthy physical activity after completion of rehabilitation. See the module [Leefstijl - Beweging](#).

Recommendation 2

Consider treating **gait impairments** with progressive strength training and/or combined exercise interventions.

Consider improving **walking speed** through strength training or whole-body vibration.

Consider improving **reduced functional exercise capacity** with ergometer training and Pilates.

Consider improving **balance** with balance training, strength training, hippotherapy, or Pilates.

Treatment of dysarthria

The recommendation advises involving physiotherapists and occupational therapists as needed to support the patient in a multidisciplinary treatment plan.

Arm and hand function

Recommendation 1

Preferably refer patients with MS who have arm and hand complaints to a therapist (occupational therapist and/or physiotherapist), and/or a physician (rehabilitation specialist, geriatric specialist, and/or neurologist) who is familiar with central neurological disorders and preferably knowledgeable about treatment options for arm/hand problems in patients with MS.

Consider collaborating with specialized MS centers or MS networks where MS-specific expertise is not available.

Recommendation 2

Perform diagnostics to determine the following aspects:

- The neurological impairments (motor, sensory, coordination);
- The impact of these impairments on daily life (functioning, participation);
- Secondary consequences (e.g., disuse, deconditioning, contracture formation) of MS.

Based on the findings, initiate treatment:

- Physical sensorimotor training and/or training focused on the functional use of the arm/hand in daily activities, for example to address disuse and deconditioning;
- Prevention, for example regarding contracture formation and preservation of function;
- Compensation for experienced hand function problems, such as enabling activities that cannot be trained.

Recommendation 3

Aim for a tailored progressive program with a high dosage (duration, frequency, sessions, intensity [number of repetitions]) to build function or, where not possible, maintain function.

Consider offering arm exercises multiple times per week, provided the patient can tolerate the dosage.

6 Additional safety information from other sources

6.1 Corticoids (Treatment of exacerbations)

6.1.1 Contraindications

- Do not use in untreated systemic infections (tuberculosis and other bacterial infections; viral (e.g. herpes), parasitic or mycotic infections), except as adjuvant therapy in life-threatening infections and in patients with adrenal insufficiency.(1)

6.1.2 Adverse events

In the case of systemic administration, adverse effects are frequent and sometimes serious, especially when physiological daily doses (20 to 30 mg hydrocortisone or equivalent) are exceeded for prolonged periods.(1)

Short courses at high dosage for emergencies appear to cause fewer adverse effects than prolonged courses with lower doses.(2)

- Fluid retention, sometimes responsible for oedema, hypertension and congestive heart failure; the severity of these effects depends on the mineralocorticoid activity of the substance used, potassium loss with muscle weakness, arrhythmias(1) and the possibility of hypokalaemic alkalosis.(2)
- Disturbances of electrolyte balance are common with the naturally occurring corticosteroids, such as cortisone and hydrocortisone, but are less frequent with many synthetic glucocorticoids, which have little or no mineralocorticoid activity. (2)
- Cushing's syndrome with weight gain, moon face, acne, skin atrophy and fragility, stretch marks and muscle atrophy. Euphorie, agitation, insomnie, réactions psychotiques, dépression.(1)
- Myopathy, especially in children and the elderly, and in the case of high doses.(1)
- Hyperglycaemia, sometimes with the onset of diabetes or an increased need for insulin.(1) Increased appetite is often reported. (2)
- Osteoporosis with possible fractures, especially in the case of prolonged treatment with daily doses equivalent to at least 7.5 mg of prednisolone; bone loss is greatest during the first six months of treatment. Cataracte, glaucome à angle ouvert.(1)
- Increased susceptibility to all kinds of infection, including septicaemia(2). Reduced resistance to infections, especially Mycobacterium tuberculosis, Candida albicans and viral infections; in addition, clinical symptoms of infection may be masked(1) by the anti-inflammatory, analgesic, and antipyretic effects of glucocorticoids. The increased severity of varicella and measles may lead to a fatal outcome in non-immune patients receiving systemic corticosteroid therapy. (2)
- Secondary adrenal insufficiency(1)
- Rarely: aseptic osteonecrosis, particularly of the femoral head, tendon rupture.(1)
- Other adverse effects include menstrual irregularities, amenorrhoea, hyperhidrosis, benign intracranial hypertension, acute pancreatitis, and avascular necrosis of bone. (2)
- An increase in the coagulability of the blood may lead to thromboembolic complications. (2)
- Peptic ulceration has been reported but reviews of the literature do not always agree that corticosteroids are responsible for an increased incidence. (2)

With prolonged use of oral corticosteroids, depending on the dose, duration of treatment and patient characteristics: (14);(15)

- fractures (especially vertebral and femoral neck fractures),
- muscle wasting,
- increased glycaemia,
- increased blood pressure,
- heart failure,
- open-angle glaucoma,
- cataracts,
- mental disorders
- and increased susceptibility to infections.

Rapid intravenous injection of massive doses of corticosteroids may sometimes cause cardiovascular collapse and injections should therefore be given slowly or by infusion. (2)

6.1.3 Interactions

- Increased risk of tendon rupture due to quinolones.
- Increased risk of gastrointestinal ulceration due to NSAIDs.
- Increased effect of vitamin K antagonists when combined with high-dose corticosteroids.
- Increased risk of bleeding when combined with low molecular weight heparins.
- Disturbance of glycaemic control achieved by antidiabetic drugs.
- Increased risk of hypokalaemia when combined with other drugs that cause hypokalaemia (e.g. diuretics that increase potassium loss).
- Corticosteroids (except beclometasone) are substrates of CYP3A4, with an increased risk of systemic effects when combined with strong CYP3A4 inhibitors. Dexamethasone, methylprednisolone and prednisone are also P-gp substrates. (1)

Oral corticosteroids: increased risk of gastrointestinal bleeding when combined with direct oral anticoagulants.(1)

6.1.4 Particular precautions

- Given the adverse effects of corticosteroids, doses should be kept as low as possible and the duration of treatment as short as possible.(1)
- Caution is especially advised in patients with obesity, diabetes, osteoporosis, severe hypertension, heart failure, peptic ulcer disease, psychiatric history and in patients at risk of infection. The same applies to patients concomitantly taking a low-molecular-weight heparin or a direct oral anticoagulant.(1)
- In patients without osteoporosis when corticosteroid therapy is started, there is no consensus regarding follow-up with bone densitometry nor preventive treatment with bisphosphonates. (14);(15)
- Non-pharmacological preventive measures (physical activity, avoidance of smoking and alcohol, diet/UV exposure for calcium and vitamin D) and pharmacological measures (calcium-vitamin D), usually recommended to slow bone loss, have not been shown to be beneficial in preventing fractures. (14);(15)

- PPIs for the prevention of corticosteroid-related peptic ulcers are rarely justified. The risk of ulcers associated with corticosteroid therapy is low, and prolonged use of PPIs can have adverse effects, including an increased risk of fractures. However, they are recommended for patients at risk, such as those receiving NSAIDs at the same time. (14);(15)

Before starting corticosteroid therapy scheduled for more than 3 weeks,

it is useful to: (14);(15)

- Identify situations where there is an increased risk of adverse effects from corticosteroid therapy. This mainly concerns the presence of risk factors for osteoporotic fracture, diabetes, heart failure, cardiovascular accidents, glaucoma and psychological disorders.
- Review any medications taken by the patient that are likely to interact with corticosteroid therapy.
- Review vaccinations and plan for any useful live attenuated vaccines (see chapter 5.4 on vaccinations)

During treatment scheduled for more than 3 weeks,

the following are suggested(14);(15):

- healthy lifestyle measures: sufficient physical exercise, avoidance of smoking and alcohol, a balanced diet rich in calcium and protein, and avoidance of severe calorie restrictions. There is evidence of the benefits of physical exercise in maintaining muscle strength and bone density in patients on prolonged corticosteroid therapy.
- clinical and biological monitoring from the start of treatment and periodically thereafter (e.g. monitoring of blood pressure and weight, ophthalmological examination at least every 6 to 12 months if there is a risk of chronic glaucoma, monitoring of glycaemia and kalaemia, etc.).
- do not vaccinate with live attenuated vaccines, carry out seasonal vaccinations (influenza, covid 19 and pneumococcus), and check basic vaccinations (see chapter 5.4)

After

- corticosteroid treatment lasting more than 3 weeks, or
- high doses for more than 1 week (≥ 32 mg methylprednisolone or equivalent/day) or
- repeated treatment (> 3 courses/year),

secondary adrenal insufficiency may occur. This is particularly the case when treatment is stopped, but can also occur months later, in a stressful situation (infection, trauma or surgery). Insufficiency is generally reversible, but may persist for several months. Educating patients about this risk is useful and important. A gradual reduction in dose may be necessary (see Dosage section). Temporary resumption (or increase) of the corticosteroid dose may also be necessary in the event of stress or surgery.(1)

6.1.5 Specific population

6.1.5.1 Pregnancy

- If justified, corticosteroids can be used during pregnancy. Predniso(lo)ne and hydrocortisone are preferable during pregnancy, as the foetus has little exposure to them.(1)
- A slight risk of cleft palate cannot be excluded, although most studies do not show an increased risk.(1)
- Intrauterine growth retardation in the event of prolonged use, especially at high doses.
- Adrenal insufficiency in newborns whose mothers have been treated during pregnancy with high doses of corticosteroids.(1)
- In women with adrenal insufficiency or congenital adrenal hyperplasia, existing treatment with corticosteroids should certainly be continued during pregnancy.(1)
- If there is a risk of premature delivery, corticosteroids are introduced to stimulate lung maturation in the foetus. Future parents should be informed of the risk of serious infections and advised to be vigilant during the first year of life.(1)

6.1.5.2 Children

Children may be at increased risk of some adverse effects; (2)

- Statural growth arrest in the event of prolonged use in children(1)
- Myopathy, especially in children and the elderly, and in the event of high doses.(1)

6.1.5.3 Elderly

Elderly patients are generally more vulnerable to the side-effects of corticosteroids, especially if they have multiple medications and comorbidities (in particular heart failure and fluid retention, peptic ulcer disease, myopathy, osteoporosis, cataracts, glaucoma and susceptibility to infections). (1)

As with younger patients, the use of corticosteroids should be carefully assessed on the basis of the individual benefit-risk balance and should be limited in time. (1)

6.1.5.4 Patients with CV comorbidities

- Care should be taken in patients with severe hypertension or heart failure. The same applies to patients concomitantly taking a low-molecular-weight heparin or a direct oral anticoagulant. (1)
- Patients taking a vitamin K antagonist should have their INR monitored when corticosteroid treatment is started or stopped. (1)

6.1.6 Implication for vaccination

6.1.6.1 Impacts of exacerbations on vaccination

There is no evidence that vaccinations are a trigger for the aggravation of chronic immune diseases or exacerbations. Where possible, the CSS advises against vaccinations during the acute phase of an exacerbation, as a precautionary measure.(16); (17)

6.1.6.2 Implication of corticotherapy on vaccination

Since corticosteroids increase the risk of infection, seasonal vaccination against influenza, pneumococcus and COVID-19 is recommended. However, live vaccines are contraindicated in patients treated with corticosteroids. In anticipation of prolonged systemic treatment, it may be

useful to ensure that the patient is immunized against varicella, and to propose vaccination where appropriate. (1)

Before starting corticosteroid therapy scheduled for more than 3 weeks(14);(15)

- Review vaccinations, in particular varicella immune status (also in the patient's close contacts), as this infection can sometimes be severe in immunocompromised patients. (14);(15)
- Schedule any useful live attenuated vaccinations several weeks before starting corticosteroid therapy. (14);(15)
- •where possible, carry out vaccination with non-live vaccines at least 2 weeks before the start of immunosuppressive treatment. (1)

During treatment scheduled for more than 3 weeks,(14);(15)

There is a risk of a reduced immune response. (1)

The following are suggested(14);(15):

- do not vaccinate with live attenuated vaccines (wait at least 3 months after the end of corticosteroid therapy).

The “Conseil Supérieur de la Santé” in its opinion 9158 of September 2019 on the vaccination of immunodeficient or chronically ill children and/or adults recommends a delay of 1 month before giving a live vaccine to patients exposed to high-dose corticosteroid therapy (more than 14 days of treatment at a dose of prednisone or equivalent > 1mg/kg/d (in children) and > 20 mg/d in adults).

- proceed with seasonal vaccination (influenza, covid 19 and pneumococcus), and check basic vaccination (DTP).

6.1.6.3 Implication of vaccination for particular population exposed to corticoids (mars 2021)

Vaccination of infants exposed in utero

With dexamethasone, the data do not indicate immunosuppression in neonates: these drugs will therefore not influence the vaccine response in infants. (14);(15)

6.2 Disease-Modifying Therapies

6.2.1 General information

6.2.1.1 Adverse events

Treatment is personalised according to certain individual parameters (co-morbidities, desire for pregnancy, etc.) or parameters specific to the disease (prognostic factors, etc.), and according to the side effects that the patient is prepared to accept. (1)

With most treatments, side effects are frequent and sometimes very serious, and there is an increased risk of infections.(1)

Alemtuzumab, cladribine, fingolimod, natalizumab and mitoxantrone are alternative treatments for RRMS. The risk of serious adverse events is greater than with first-line treatments. (1)

Ocrelizumab, ofatumumab, ublituximab and siponimod are also alternative treatments. Their exact role is not yet clear. (1)

First-line treatments:

- interferons β -1a and β -1b
- glatiramer acetate
- teriflunomide
- dimethyl fumarate
- ozanimod and ponesimod

6.2.1.2 Specific population

6.2.1.2.1 Pregnancy

- The safety of these drugs during pregnancy is generally poorly documented. Some drugs are contraindicated or not recommended from the 3rd trimester onwards, while for others there is limited but reassuring data. (1)

See the SPC to find out how long contraception should be continued after stopping a contraindicated drug. (1)

- To date, there is no evidence of a teratogenic effect with monoclonal antibodies (they do not cross the placental barrier during the first trimester), but many drugs have not been sufficiently documented in pregnant women (16);(17)
- Transplacental passage of monoclonal antibodies increases progressively from the 2nd trimester of pregnancy. If these drugs are used during this period, they are still present for some time in the plasma of the newborn, which entails a risk of immunosuppression. (1)

If treatment has been continued beyond the 22nd week of pregnancy, vaccination of the infant with a live vaccine should be postponed until after 6 months of age (for infliximab, until after 1 year of age) (1)

6.2.1.2.2 Breast-feeding

- For several drugs, there is little or no data on safety in humans. (1)
- For a number of drugs, it is stated that harmful effects cannot be excluded in children exposed via breast milk (e.g. teriflunomide). (1)

6.2.1.3 Implication for vaccination

6.2.1.3.1 Impacts of exacerbations on vaccination

There is no evidence that vaccinations are a trigger for the aggravation of chronic immune diseases or exacerbations. Where possible, the CSS advises against vaccinations during the acute phase of an exacerbation, as a precautionary measure. (16);(17)

6.2.1.3.2 Vaccination of patients on immunosuppressive therapy

See also the « Conseil Supérieur de la Santé »'s advice ([Avis 9158, 2019](#)). (11)

- The advisory gives recommendations on which vaccines are (strongly) recommended or contraindicated in these conditions, the most appropriate vaccination period, the most appropriate vaccination schedule and the possible need for serological monitoring.
- The decision to vaccinate these patients, and all the details involved, is often a matter for the specialist.
- The CSS recommends that the vaccination status of immunodeficient and chronically ill patients should be checked at least once a year in consultation between the specialist and the GP(16);(17)
- If possible, carry out vaccinations before the start of immunosuppression:
 - For live vaccines, at least 4 weeks before
 - For non-live vaccines, at least 2 weeks before. (1)
- Vaccination with live vaccines is contraindicated in patients undergoing immunosuppression(1), due to the risk of replication of the vaccine virus, with a risk of invasive infection(16);(17).
- Vaccination with non-live vaccines is safe, but the immune response may be reduced (weaker immune response, shorter duration of protection and/or slower onset of protection). (1)

However, it is assumed that even with partially reduced vaccine efficacy, vaccination remains associated with benefit in this vulnerable patient population. When vaccination takes place during treatment, the immune response is probably less affected if a first dose of vaccine has already been administered prior to immunosuppression. (16);(17)

At the time of publication of the HSC opinion, COVID-19 was not yet available. A few vaccines against COVID-19 have since become available. Experience with COVID-19 vaccines in immunocompromised patients is not sufficient to determine their safety and efficacy profile. Since mRNA vaccines are non-live vaccines and the viral vector vaccine is non-replicative, it is assumed that immunocompromised patients can be vaccinated safely. However, the immune response may be reduced. It is therefore preferable here too to administer vaccines at least two weeks before the start of immunosuppressive treatment (16);(17)

- There is no consensus on the need for serological monitoring after vaccination of immunodeficient patients. The CSS recommends monitoring antibody titres after the following vaccinations: hepatitis B vaccination, yellow fever vaccination and, in certain cases, rabies vaccination as 'post-exposure prophylaxis'. (11)

After stopping immunosuppressive drugs:

- wait several weeks, or even several months, before vaccinating with live vaccines. (1)

This time interval varies from one drug to another and depends on the half-life of the drug and the duration of the immunosuppressive effect (see the table in CSS Advice 9158, 2019) (Avis 9158, 2019)(11). This immunosuppressive effect may still be present even if the drug is no longer detectable in the blood (16);(17)

- Inactivated vaccines can be administered immediately after stopping treatment. (1)

If the patient plans to travel (even in the future):

It is important to refer the patient in good time to a vaccination centre to plan the necessary vaccinations, especially as regards vaccination against yellow fever (which uses a live vaccine). (16);(17)

Vaccination of infants exposed in utero to biological agents (16);(17)

- There are still many uncertainties about the effects, in terms of safety and immune response, of biological agents, and in particular monoclonal antibodies, on the infant's developing immune system, and for many of these agents, experience in pregnant women is very limited.
- It is also known that some of these agents can circulate in the child for several months after birth.
- If the administration of the biological agent has been interrupted before the 22nd week of pregnancy, all vaccines (inactivated and live vaccines) can be administered according to the usual vaccination calendar.
- if the biological agent was continued after the 22nd week of pregnancy, vaccination with live vaccines should be postponed until after 6 months of age. Inactivated vaccines can be administered according to the usual vaccination calendar
- When live vaccines are administered during the first few months of life to infants who have been exposed in utero to monoclonal antibodies, it should be borne in mind that these vaccines may cause serious infections.
- Any vaccine administered (live or non-live) may be less effective in these infants.

Vaccination of children breastfed by mothers treated with monoclonal antibodies (16);(17)

- Few monoclonal antibodies pass into breast milk, and the small quantities that do are destroyed in the digestive tract of the breastfed child. Breast-fed children whose mothers are treated with such agents (e.g. TNF inhibitors, interleukin antagonists) can therefore be vaccinated with inactivated and live vaccines according to the usual vaccination calendar.

Measures if people in the immediate environment or close contacts of the immunodeficient patient have received live vaccines (16);(17)

The following precautions should be followed to avoid the risk of transmission of the vaccine virus to the immunodeficient patient:

- o For measles-mumps-rubella vaccines, varicella vaccine and live shingles vaccine: contact with the immunodeficient patient should only be avoided if a rash occurs after vaccination, until the rash has disappeared; there are no other precautions to be taken.
- o For rotavirus vaccines: the immunodeficient patient should avoid all contact with the faeces of the vaccinated infant until 4 weeks after vaccination.

6.2.2 Interferons (β -1a and β -1b)

6.2.2.1 Contraindications

- Severe depression or suicidal ideation.
- For interferon beta-1b, also severe hepatic impairment (RCP). (1)

6.2.2.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Haematological disorders; rare: thrombotic microangiopathy (sometimes fatal). (1)
- Hyperkalaemia and increased urea; rare: nephrotic syndrome (even after several years of treatment). (1)
- Flu-like syndrome(1), infection(2).
- Skin rashes, hypersudation, alopecia. (1)
- Gastrointestinal disorders. (1)
- Headache, spasticity, hypoesthesia. (1)
- Musculoskeletal pain(1). In addition transient episodes of hypertonia and/or severe muscular weakness may occur at any time during treatment. (2)
- Thyroid disorders. (1)
- Psychiatric disorders (depression, insomnia). (1)
- Hepatotoxicity. (1)
- Injection site reactions. (1)
- Menstrual irregularities have been associated with interferon beta use. (2)
- On injection, transient neurological symptoms that may mimic an exacerbation of multiple sclerosis have been reported. (2)

6.2.2.3 Particular precautions

- Beware of suicidal ideation or behaviour. (1)
- Beware of early clinical signs of thrombotic microangiopathy: thrombocytopenia, new-onset hypertension, fever, neurological symptoms (e.g. paresis or confusion) and impaired renal function. (1)
- Regular monitoring for early signs or symptoms of nephrotic syndrome, such as oedema, proteinuria and impaired renal function. (1)
- Caution in the presence of cardiac pathology. (1)
- Concerning vaccination of patients on immunosuppressive therapy: see 5.4

6.2.2.4 Specific population

6.2.2.4.1 Pregnancy

Use is probably safe during the first trimester. Experience with exposure during the second and third trimester is very limited. (1)

6.2.2.4.2 Breast-feeding

Use is probably safe. (1)

6.2.3 Glatiramer acetate

6.2.3.1 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Increased risk of infections(1)
- Immediate post-injection reactions are common with glatiramer acetate and include chest pain, palpitations or tachycardia, dyspnoea, throat constriction, urticaria, flushing (vasodilatation), and anxiety. (2)
- Rare incidents of skin lipoatrophy and necrosis. (1)
- Severe (systemic) hypersensitivity reactions. Potentially fatal anaphylactic reactions may occur, even months or years after the start of treatment. (1)
- Liver disorders. Rare cases of serious liver damage a few days or a few years after the start of treatment. (1)
- Other common adverse effects include asthenia, nausea, vomiting, constipation, rash, arthralgia, back pain, and dizziness. Convulsions and anaphylactoid reactions have been reported rarely. (2)

6.2.3.2 Particular precautions

- The initial symptoms of anaphylaxis may resemble those of a post-injection reaction, which may delay their recognition. (1)
- Caution should be exercised in patients with pre-existing cardiac disease (in the context of cardiac symptoms during hypersensitivity reactions). (1)
- Renal function must be monitored in accordance with the prescribing information for patients with renal insufficiency (theoretical risk of immune complex deposition in the renal glomeruli). (1)

6.2.3.3 Specific population

6.2.3.3.1 Pregnancy

Limited but reassuring data. (1)

6.2.3.3.2 Breast-feeding

Use if probably safe. (1)

6.2.4 Teriflunomide

The benefit/risk balance of teriflunomide is unfavourable given its serious, sometimes fatal, side effects and its uncertain clinical efficacy. (1)

6.2.4.1 Contraindications

- Pregnancy and breast-feeding. (1)
- Severe hepatic impairment (SPC). (1)

6.2.4.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Increased risk of infections. (1)
- Haematological disorders, hepatotoxicity, gastrointestinal disorders (including diarrhoea, nausea). (1)
- Hypertension, hair loss, rare: severe skin reactions. (1)
- Peripheral neuropathy. (1)
- Respiratory problems (including interstitial lung disease, rare). (1)
- Hyperkalaemia has also been reported in patients given teriflunomide. (2)

6.2.4.3 Interactions

- Reduces the effect of vitamin K antagonists. (1)
- Acceleration of teriflunomide excretion by colestyramine, which may be useful in cases of toxicity or desire for pregnancy. (1)
- Teriflunomide is an inducer of CYP1A2(1)

6.2.4.4 Particular precautions

Screening for latent tuberculosis (anamnesic signs, tuberculin skin test or IGRA test and chest X-ray) must be carried out before treatment is initiated. If screening is positive, latent tuberculosis must be treated for 6 months. (1)

- Concerning vaccination of patients on immunosuppressive therapy: see 5.4

6.2.4.5 Specific population

6.2.4.5.1 Pregnancy

- Teriflunomide is contraindicated during pregnancy due to a possible risk of teratogenicity. (1)
- Reliable contraception must be used during treatment and for up to 2 years after it has been discontinued. (1)
- Even before the desire to become pregnant, plasma concentrations of teriflunomide must be less than 0.02 mg/l, measured on 2 consecutive occasions at least 14 days apart. (1)

6.2.4.5.2 Breast-feeding

- Teriflunomide is contraindicated during breast-feeding. (1)

6.2.5 Dimethyl fumarate

6.2.5.1 Contraindications

- Pregnancy. (1)
- Lactation(1)
- Severe gastrointestinal disorders. (1)
- Severe hepatic impairment (RCP). (1)

6.2.5.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Increased risk of infections. (1)
- Reactivation of latent viruses, e.g. herpes zoster and progressive multifocal leukoencephalopathy (PML). (1)
- Skin flush, flushing, skin reactions, burning sensation. (1)
- Gastrointestinal disorders, lymphopenia, liver function disorders. (1)
- Kidney disorders. (1)

- Raised hepatic transaminases and proteinuria may occur with the fumarates, and hepatic and renal function should be assessed before starting, and then every 3 to 12 months throughout therapy as needed. (2)

- Anaphylactic reactions. (1)
- Hair loss (18); (19)

6.2.5.3 Specific population

6.2.5.3.1 Pregnancy

- Dimethyl fumarate is contraindicated during pregnancy. (1)

6.2.5.3.2 Breast-feeding

It is not possible to make a statement about the safety of using these preparations during breastfeeding (no or insufficient information available). (1)

6.2.6 Sphingosine-1-phosphate (S1P) receptor modulators (ozanimod, ponesimod, fingolimod, siponimod)

According to the SPC, ozanimod and ponesimod can only be used in patients with active disease of RRMS.

6.2.6.1 Contraindications

- Pregnancy. (1)
- Active infection. (1)
- Congenital or acquired immunodeficiency. (1)
- Active malignant diseases. (1)
- Severe hepatic impairment (RCP).
- Severe cardiovascular events in the previous 6 months (e.g. infarction, stroke, heart failure).
- Cardiac conduction disorder (e.g. atrioventricular block); risk factors for QT interval prolongation. (1)

Fingolimod: also severe cardiac rhythm disorder. (1)

Ponesimod: also moderate hepatic impairment (RCP).

Siponimod: also peanut or soy allergy; slow metabolizers of CYP2C9; history of progressive multifocal leukoencephalopathy or cryptococcal meningitis(1)

6.2.6.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Increased susceptibility to infections. (1)
- Reactivation of latent viruses, e.g. herpes infections and progressive multifocal leukoencephalopathy (PML). (1)
- Increased risk of cancer (especially skin cancer). (1)
- Hematological disorders (especially lymphopenia); liver function disorders. (1)
- Macular edema, peripheral edema, convulsions. (1)

- Back pain, (2)
- Cough, (2)

- Hypertension; early bradycardia and atrioventricular block; rare reversible posterior encephalopathy syndrome. (1)
Reduction in heart rate occurs within one hour of starting fingolimod treatment; the effect is usually maximal within 6 hours, followed by recovery and a second decrease within 24 hours. Similar reductions in heart rate occur after subsequent doses but are usually of smaller magnitude, and with continued fingolimod treatment the heart rate generally returns to baseline levels within one month. Most patients are asymptomatic, but hypotension, dizziness, fatigue, palpitations, and chest pain may occur in some. (2)

Fingolimod: also diarrhea, depression, migraine, dyspnea, eczema, alopecia, pruritus, increased triglyceridemia, acute liver failure(1)

Ponesimod: also depression, insomnia, anxiety, vertigo, hypoesthesia, migraine, dyspnea, dyspepsia, musculo-articular pain, elevated cholesterol and CRP, abnormal respiratory function tests. (1)

Siponimod: also diarrhea, musculo-articular pain, abnormal respiratory function tests. (1)

Ozanimod: also abnormal respiratory function tests. (1)

6.2.6.3 Interactions

- Caution is advised in the case of concomitant use of certain antiarrhythmics, bradycardiac drugs and QT-interval prolongers. (1)

Fingolimod:

- CYP3A4 substrate. (1)

Ozanimod:

- CYP2C8 substrate. (1)
- Avoid concomitant use of BCRP (Breast Cancer Resistance Protein) and MAO-B (monoamine oxidase type B) inhibitors. (1)

Siponimod:

- CYP2C9 and CYP3A4 substrate(1)
- The risk of interactions also depends on the patient's CYP2C9 genotype (see RCP).

6.2.6.4 Particular precautions

Parameters to be monitored before and/or during treatment include :

- CYP2C9 genotyping (for siponimod),
- pregnancy test,
- varicella virus antibodies,
- ophthalmological examination,
- ECG,
- skin examination,
- blood pressure. (1)

Pour plus de détails, voir le RCP.

On treatment discontinuation: risk of severe exacerbation of multiple sclerosis. It may take several weeks for the lymphocyte count to return to normal. (1)

Concerning vaccination of patients on immunosuppressive therapy: see 5.4

6.2.6.5 Specific population

6.2.6.5.1 Pregnancy

- Use during pregnancy is contraindicated due to the possible teratogenic risk. (1)
- Reliable contraception is necessary during and after treatment:
 - fingolimod: up to 2 months after treatment,
 - ozanimod: up to 3 months after treatment,
 - ponesimod: up to 1 week after treatment,
 - siponimod: up to 10 days after treatment. (1)

6.2.6.5.2 Breast-feeding

There are limited data in humans. Use during breastfeeding is not recommended.

6.2.7 Anti CD-20 monoclonal antibodies (ocrelizumab, ofatumumab et ublituximab)

6.2.7.1 Contraindications

- Active infection (including hepatitis B). (1)
- Severe immune deficiency. (1)
- Active malignant disease. (1)

6.2.7.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Increased risk of infections. (1)
- Reactivation of latent viruses, e.g. progressive multifocal leukoencephalopathy (PML) and hepatitis B. (1)
- Infusion or injection-related reactions. (1)

Infusion reactions associated with a cytokine release syndrome, which commonly occur at the start of an infusion. Symptoms are typically flu-like and can include fever, chills, nausea, headache, flushing, rash, urticaria, and pruritus; more serious effects occur rarely and include hypotension, bronchospasm, and cardiac adverse effects. Serious hypersensitivity reactions, including anaphylaxis, can occur. (2)

6.2.7.3 Particular precautions

All patients should be screened for hepatitis B prior to treatment. (1)

Concerning vaccination of patients on immunosuppressive therapy: see 5.4

6.2.7.4 Specific population

6.2.7.4.1 Pregnancy

- Very few data in humans: avoid during pregnancy. (1)
- Reliable contraception is necessary during and after treatment:
 - ocrelizumab, up to 12 months after treatment;
 - ofatumumab, up to 6 months after treatment;
 - ublituximab, up to 4 months after treatment. (1)

6.2.7.4.2 Infants born from mothers treated with ofatumumab

Vaccination of infants born to mothers treated with ofatumumab during pregnancy: consultation between the neurologist and vaccinator is necessary. (1)

6.2.7.4.3 Breast-feeding

It is not possible to make a statement about the safety of using these preparations during breastfeeding (no or insufficient information available). (1)

6.2.8 Natalizumab

6.2.8.1 Contraindications

- Progressive multifocal leukoencephalopathy (PML). (1)
- Patients at increased risk of opportunistic infections, including immunocompromised patients. (1)
- Combination with other disease-modifying therapies. (1)
- Progressive malignancies (except basal cell carcinoma of the skin). (1)

6.2.8.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Hematologic disorders, increased risk of infections, hepatotoxicity. (1)
- Reactivation of latent viruses, e.g., herpes infections and progressive multifocal leukoencephalopathy (PML). The risk of PML appears to increase with treatment duration, particularly over 2 years. (1)
- Rare cases of acute retinal necrosis caused by herpes viruses(1). Life-threatening and fatal cases of herpes encephalitis and meningitis have been reported with natalizumab. (2)
- Gastrointestinal disorders, dyspnea, arthralgia, pruritus, rash, urticaria(1), headache, dizziness, gastrointestinal disturbances, arthralgia, and fatigue.
- Hepatotoxicity, including liver failure requiring transplantation, has been reported and treatment should be stopped if there is evidence of jaundice or other significant liver injury. (2)
- Infusion-related reactions; hypersensitivity reactions. (1)

Infusion reactions associated with a cytokine release syndrome, which commonly occur at the start of an infusion. Symptoms are typically flu-like and can include fever, chills, nausea, headache, flushing, rash, urticaria, and pruritus; more serious effects occur rarely and include hypotension, bronchospasm, and cardiac adverse effects. Serious hypersensitivity reactions, including anaphylaxis, can occur(2)

6.2.8.3 Particular precautions

- Patient materials containing important safety information regarding progressive multifocal leukoencephalopathy (PML) are available. (1)
- If symptoms of acute retinal necrosis, such as decreased visual acuity, redness, and eye pain, occur, the patient should be referred to a specialist. (1)
- Beware of symptoms of thrombocytopenia. (1)
- Concerning vaccination of patients on immunosuppressive therapy: see 5.4

6.2.8.4 Specific population

6.2.8.4.1 Pregnancy

Use during pregnancy: limited but reassuring data. (1)

6.2.8.4.2 Infants born from mothers treated with natalizumab

If the mother has been exposed for most of her pregnancy, it is not recommended to vaccinate her child with a live vaccine before the age of one. (1)

6.2.8.4.3 Breast-feeding

It is not possible to make a statement about the safety of using natalizumab during breastfeeding (no or insufficient information available).

6.2.9 Alemtuzumab

6.2.9.1 Contraindications

- HIV infection. (1)
- Active infection. (1)
- Uncontrolled hypertension. (1)
- History of stroke, angina, or myocardial infarction. (1)
- Coagulopathy, use of antiplatelet or anticoagulant therapy. (1)
- Other associated autoimmune diseases, other than MS. (1)

6.2.9.2 Adverse events

Adverse events are frequent and sometimes very serious. (1)

- Reactivation of latent viruses, which can lead to progressive multifocal leukoencephalopathy (PML), reactivation of cytomegalovirus and Epstein-Barr virus. (1)
- Hematologic disorders. (1)
- Infusion-related reactions, usually 1-3 days after infusion: hemorrhagic stroke, myocardial infarction, myocardial ischemia, thrombocytopenia, and pulmonary alveolar hemorrhage. (1)

Infusion reactions associated with a cytokine release syndrome, which commonly occur at the start of an infusion. Symptoms are typically flu-like and can include fever, chills, nausea, headache, flushing, rash, urticaria, and pruritus; more serious effects occur rarely and include hypotension, bronchospasm, and cardiac adverse effects. (2)

- Serious hypersensitivity reactions, including anaphylaxis, can occur. (2)
- Autoimmune diseases: immune thrombocytopenic purpura, thyroid disorders, nephropathy, hepatitis, hemophagocytic lymphohistiocytosis (up to 4 years after treatment), pneumonitis (up to 1 month after infusion), cholecystitis (up to 2 months after infusion). (1)
- Severe cardiovascular reactions (including myocardial infarction, stroke). (1)
- Anxiety, depression, paraesthesia, tremor, eye disorders, vertigo, cough, oropharyngeal pain, abdominal pain, vomiting, diarrhoea, myalgia, arthralgia, back pain, pain in extremities, and menstruation disorders. Lymphopenia occurs in most patients given alemtuzumab and may be severe and profound; recovery of lymphocyte counts may take 6 months or longer after stopping treatment. (2)
- Serious, sometimes fatal, auto-immune disorders have been reported with alemtuzumab. These include thrombocytopenia, neutropenia, and other cytopenias, immune thrombocytopenic purpura, thyroid disorders, hepatitis, nephropathies, and haemophagocytic lymphohistiocytosis. Stroke, myocardial infarction, pulmonary alveolar haemorrhage, and tears in the lining of arteries in the head and neck (cervicocephalic dissection) have occurred and may be fatal. Alemtuzumab may increase the risk of acute acalculous cholecystitis. In common with other immunomodulating therapies, alemtuzumab may increase the risk of malignancies including thyroid cancer, melanoma, and lymphoproliferative disorders. (2)

6.2.9.3 Particular precautions

- Screening for latent tuberculosis (anamnesic signs, tuberculin skin test or IGRA test and chest X-ray) should be carried out before treatment is initiated. If screening is positive, latent tuberculosis must be treated for 6 months. (1)
- In women: annual screening for human papillomavirus. (1)

- Screening for hepatitis B and hepatitis C is sometimes recommended prior to initiation of treatment. (1)
- Dietary advice to prevent listeriosis is important: avoid raw meat, unpasteurised dairy products and soft cheese. (1)
- Monitor laboratory tests and clinical symptoms to detect the appearance of new autoimmune pathologies. (1)
- Inform the patient of the possibility of late reactions and complications (see adverse reactions). (1)
- Concerning vaccination of patients on immunosuppressive therapy: see 5.4
- Unprotected patients should be vaccinated against shingles prior to treatment. (1)

6.2.9.4 *Specific population*

6.2.9.4.1 Pregnancy

- It is not possible to make a statement about the safety of using alemtuzumab during pregnancy (no or insufficient information available). (1)
- Reliable contraception is necessary during treatment and for 4 months afterward. (1)

6.2.9.4.2 Breast-feeding

- It is not possible to make a statement about the safety of using alemtuzumab during breastfeeding (no or insufficient information available). (1)

6.2.9.4.3 Infants born from mothers treated with alemtuzumab

- If the mother has been exposed for most of her pregnancy, it is not recommended to vaccinate her child with a live vaccine before the age of one year. (1)

6.2.10 Cladribine

6.2.10.1 Contraindications

- HIV infection. (1)
- Active infection. (1)
- Immunodeficiency, immunosuppression. (1)
- Progressive malignant disease. (1)
- Moderate or severe renal impairment. (1)
- Pregnancy and breastfeeding. (1)

6.2.10.2 Adverse events

- Increased risk of infections (e.g., herpes zoster). (1)
- Possible increased risk of cancer. (1)
- Blood disorders (lymphopenia). (1)
- Hepatotoxicity, risk of serious liver damage (20); (21)
- Hypersensitivity reactions. (1)
- Skin rashes, alopecia. (1)

When used orally for the treatment of multiple sclerosis, the most clinically significant adverse effects reported with cladribine were lymphopenia and herpes zoster; other common adverse effects include alopecia and rash(2)

6.2.10.3 Particular precautions

- Before initiating treatment: screening for tuberculosis and hepatitis B and C. A baseline MRI should also be performed, the SPC specifies. (1)
- Pregnancy should be ruled out before initiating treatment. (1)
- Advise patients to follow cancer screening recommendations. (1)
- Concerning vaccination of patients on immunosuppressive therapy: see 5.4
- Shingles vaccination is recommended before treatment in non-immune patients. (1)
- Cladribine should not be initiated within 4 to 6 weeks of receiving a live vaccine. Live vaccines should not be administered during and after treatment until the white blood cell count has returned to normal. (1)

6.2.10.4 Specific population

6.2.10.4.1 Pregnancy

- Cladribine is contraindicated during pregnancy. (1)
- Contraception is recommended for women during treatment and for up to 6 months afterward. (1)
- **Men** must use a condom during treatment and for up to 6 months afterward. (1)

6.2.10.4.2 Breast-feeding

- Breastfeeding is contraindicated during treatment and up to 1 week after the last dose of cladribine. (1)

6.2.11 Mitoxantrone

6.2.11.1 *Contra indication*

- Pregnancy and breastfeeding. (1)
- Severe heart failure; recent myocardial infarction; severe arrhythmias. (1)

6.2.11.2 *Adverse events*

- Significant cardiotoxicity can occur up to several years after treatment discontinuation and is generally irreversible. Cardiotoxicity depends, among other things, on the total cumulative dose. (1)
- Stomatitis, esophagitis. (1)
- High fever within 24 hours of administration. (1)
- Significant tissue necrosis in the event of extravasation (antidote: dexrazoxane). (1)
- Nail dystrophy and onycholysis can occur. (2)
- Blue coloration of the sclera(1) (which can also occur after extravasation) (2)and urine(1).
- Elevation in liver enzyme values may occur; there are occasional reports of severe hepatic impairment in patients with leukaemia, in whom doses are generally higher and adverse effects of mitoxantrone may be more frequent and severe. (2)
- Treatment with mitoxantrone, either alone or with other antineoplastics and/or radiotherapy, has been associated with an increased risk of development of secondary acute myeloid leukaemia(2)

6.2.11.3 *Particular precautions*

- Regular monitoring of cardiac ejection fraction is necessary. (1)
All patients should be assessed for cardiac signs and symptoms. (2)
The risk of symptomatic congestive heart failure is higher after a cumulative dose of 140 mg/m², multiple sclerosis patients should not receive a total cumulative dose greater than this. (2)
- Care is also required in patients with hepatic impairment. (2)
- Regular blood counts should be performed during treatment. (2)

6.2.11.4 *Specific population*

6.2.11.4.1 Patients with CV comorbidities

Multiple sclerosis patients with a baseline LVEF below the lower limit of normal should not be treated with mitoxantrone. (2)

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