MSIF Essential Medicines Panel (MEMP)

Guidelines for essential disease-modifying therapies for multiple sclerosis for low-resource settings

There are 2.8 million people living with MS but many people do not have access to disease modifying therapies (DMTs). The DMTs may simply not be available or too expensive for the person with MS. In 7 out of 10 countries people face barriers in accessing treatment. There is an urgent need to make MS treatments available in all health systems.

To ensure an evidence-based approach for advocacy, MSIF convened an international multi-disciplinary panel, the MSIF Essential Medicines Panel (MEMP), which made recommendations on essential MS DMTs for low-resource settings. The Cochrane MS Group systematically retrieved and evaluated the evidence and the panel made judgments using the GRADE evidence-to-decision (EtD) framework, facilitated by the GRADE McMaster Centre. These MEMP recommendations were considered together with MSIF's Off-Label Treatments (MOLT) guidelines to propose MS DMTs on the World Health Organization essential medicines list.

These recommendations are now open for public comment using https://www.surveymonkey.co.uk/r/MEMP_GL until **27 January 2023.**

In addition, we have prepared

- A scope document explaining the purpose of the recommendations: http://www.msif.org/wp-content/uploads/2023/01/MEMP-scope_110123.pdf
- A Frequently Asked Questions (FAQs) document to give more context to the recommendations: http://www.msif.org/wp-content/uploads/2023/01/FAQs_MEMP_GLs_201222.pdf

Please note that due to the potential large number of comments, we are unable to provide individual replies. We will aim to consider all potential errors in the evidence reviews.

Background

The Cochrane systematic review protocols can be found here:

Relapsing forms of MS (RMS): Forthcoming updated version of https://doi.org/10.1002/14651858.CD011381

Progressive forms of MS (PMS): https://doi.org/10.1002/14651858.CD015443

Rapid systematic review protocol for acceptability, equity, feasibility, and values: https://osf.io/w9gs8/

We are using the GRADE Evidence-to-Decision (EtD) framework which includes 12 criteria for making a recommendation. We added availability as an additional criteria for the purpose of essential medicines. The EtD framework also defines the certainty of the evidence considered in relation to treatment outcomes and their level of importance. Certainty then forms part of the recommendations, in particular the strength of the recommendations that can be made. You can

view the GRADE evidence profile, Summary of Findings table, Evidence to Decision framework, multi-comparison tables and recommendations using the links below.

Recommendations for Relapsing forms of MS (RMS)

The MEMP RMS documents can be accessed here and the full RMS EtD here.

Full wording and justification of MEMP recommendations for Relapsing forms of MS

- The MEMP suggests ***for*** in priority order (conditional recommendation): 1. cladribine (low certainty ⊕⊕◯◯), 2. dimethyl fumarate (low certainty ⊕⊕◯◯), 3. fingolimod (low certainty ⊕⊕◯◯), 4. ocrelizumab (very low certainty ⊕◯◯◯), 5. interferon beta 1b (very low certainty ⊕◯◯◯), 6. interferon beta 1a (low certainty ⊕⊕◯◯), 7. glatiramer acetate (very low certainty ⊕◯◯◯), for the treatment of active and/or worsening relapsing forms of MS. Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: Cladribine is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), short treatment period, low maintenance for screening and monitoring, low discontinuation rate, easy storage, and favourable cost-effectiveness. Dimethyl fumarate is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), low maintenance for screening and monitoring, and easy storage, but has a higher discontinuation rate compared to other oral treatments. Fingolimod is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, e.g., due to unreliable supply of medicine. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, less frequent administration, but requires infusion facilities and cold storage at the healthcare facility. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by person with MS, and type of adverse events. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of administration (injection), and requirement of cold-storage by the person with MS.

- The MEMP suggests **either for or against** in priority order (conditional and neutral recommendation, dependent on setting) the use of 1. natalizumab (low certainty ⊕⊕◯◯), 2. alemtuzumab (low certainty ⊕⊕◯◯), for the treatment of active and/or worsening relapsing forms of MS. Remark: Feasibility of pre-tests, monitoring requirements, cost and affordability are concerns limiting the application of these DMTs in some low-resource settings. The panel felt a recommendation either for or against these medicines for low-resource settings was appropriate, despite evidence of clinical benefit. In settings where the feasibility challenges related to costs and long-term monitoring (and surety of supply for natalizumab) are surmountable, these treatments may be considered and have an important role to play.

Justification: The panel noted that the evidence on balance of the effects clearly favours the use of natalizumab and alemtuzumab. Despite the demonstrated benefit, the panel noted variable feasibility issues for low-resource settings in the access to and cost of pre-screening and monitoring required (including monthly blood tests and three-monthly urine tests), regular JCV testing and MRI monitoring for PML. These tests are essential for the safe use of these DMTs and not currently available in many low-resource settings. High cost of medicines was also noted for budget impact, although cost-effectiveness studies favoured alemtuzumab. The two DMTs had very similar net balance of effects, but the safety profile of natalizumab was considered better as the risk of PML can be prognosticated and minimised. Alemtuzumab is associated with the broader suite of less severe but more frequent side effects.

- The MEMP suggests **against** (conditional recommendation) the use of mitoxantrone (very low certainty ⊕◯◯◯) for the treatment of active and/or worsening relapsing forms of MS.

Justification: The panel noted significant post-marketing surveillance safety concerns and long-term monitoring requirements with mitoxantrone, creating barriers to feasibility and acceptability. This recommendation was against mitoxantrone despite balance of effects probably favouring the intervention based on included studies, which did not include these post-marketing surveillance and safety concerns.

Recommendations for Progressive forms of MS (PMS)

The MEMP PMS documents can be accessed here and the full PMS EtD here.

Full wording and justification of MEMP recommendations for Progressive forms of MS

- The MEMP suggests **for,** in priority order (conditional recommendation): 1. rituximab (very low certainty ⊕◯◯◯), 2. glatiramer acetate (very low certainty ⊕◯◯◯), 3. ocrelizumab (very low certainty ⊕◯◯◯) 4. interferon beta 1a (low certainty ⊕⊕◯◯), 5. fingolimod (low certainty ⊕⊕◯◯), 6. interferon beta 1b (very low certainty ⊕◯◯◯) for active and/or progressing progressive forms of MS. Remark: The recommendation is conditional due to low and very low certainty of evidence.

Justification: Rituximab is a feasible and acceptable option in low-resource settings due to balance of effects, mode of administration (6-monthly infusions), low maintenance for screening and monitoring with low risk of rebound effect if treatment is discontinued, and low discontinuation rate, but requires infusion facilities and cold storage at the healthcare facility. Glatiramer acetate is a feasible and acceptable option in low-resource settings due to balance of effects, very low maintenance for screening and monitoring, but is less acceptable due to mode and frequency of administration (injection), and requirement of cold-storage by persons with MS. Ocrelizumab is a feasible and acceptable option in low-resource settings due to balance of effects, low maintenance for screening and monitoring, low discontinuation rate, mode of administration (6-monthly infusions), but requires infusion facilities and cold storage at the healthcare facility. It is less acceptable than rituximab due to significant cost of the medication. Interferons beta 1a and 1b are feasible and acceptable options in low-resource settings due to balance of effects, low maintenance for screening and monitoring, but are less acceptable due to mode and frequency of administration (injection), requirement of cold-storage by persons with MS and type of adverse events. Fingolimod is a feasible and acceptable

option in low-resource settings due to balance of effects, mode of administration (oral), easy storage, but requires more maintenance for screening and monitoring, and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, e.g., due to unreliable supply of medicine.

- The MEMP suggests **either for or against** in priority order (conditional and neutral recommendation, dependent on setting): 1. siponimod (low certainty ⊕⊕◯◯), 2. natalizumab (very low certainty ⊕◯◯◯), 3. immunoglobulins (very low certainty ⊕◯◯◯) for active and/or progressing progressive forms of MS. Remark: Feasibility of pre-tests, monitoring requirements, cost and affordability are concerns limiting the application of these DMTs in some low-resource settings. The panel felt a recommendation either for or against these medicines for low-resource settings was appropriate, despite evidence of clinical benefit. Immunoglobulin use was noted to be rare even in high-income settings, with efforts to reduce demand for immunoglobulin in many countries.

Justification: The panel noted that the evidence on balance of the effects clearly favours siponimod and natalizumab. Despite the demonstrated benefit, the panel noted variable feasibility issues for low-resource settings in the access to and cost of pre-screening and monitoring required, e.g., for siponimod CYP2C9 genotyping and for natalizumab regular JCV testing and MRI monitoring for PML. These tests are essential for the safe use of these DMTs and not widely available in low-resource settings. It was noted that the high cost of medicines resulted in a significant budget impact. Natalizumab and siponimod were noted to be used routinely in high-income settings, whereas the use of immunoglobulin was rare.

- The MEMP suggests **for** in priority order (conditional recommendation): 1. azathioprine (very low certainty ⊕◯◯◯), 2. methotrexate (very low certainty ⊕◯◯◯) in clinical settings where no alternative treatments are accessible for active and/or progressing progressive forms of MS. Remark: This recommendation is conditional to other treatment options not being accessible due to the very low evidence-base available. Use in research settings may also be appropriate due to the need for higher quality evidence for these medicines, although trials with placebo would be considered unethical.

Justification: Azathioprine and methotrexate have a conditional recommendation for with a condition of no alternative DMTs being accessible, where the alternative would be no treatment. This condition was due to the evidence-base being very limited and more research would be required to ascertain effects of these DMTs in progressive forms of MS. The DMTs are oral treatments, widely available in health systems with a low cost, not requiring cold-chain, making them a feasible option in low-resource settings. The ranking is based on balance of effects.