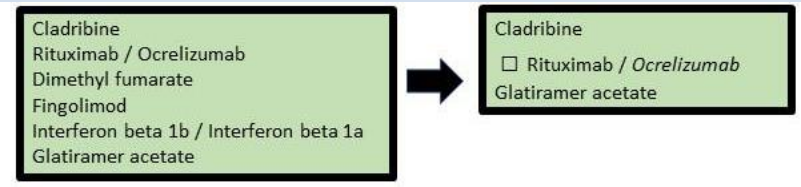
A.10	Cladribine, glatiramer and rituximab – multiple sclerosis – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: This Application refers to the inclusion of rituximab [□ listed representative medicine of square box grouping with ocrelizumab], cladribine and glatiramer acetate for the treatment of multiple sclerosis (MS). This Application is supported by several international organisations representing all six WHO world regions, including upper-middle and lower-middle income countries. An application to include glatiramer acetate, fingolimod, and ocrelizumab on the WHO Model List of Essential Medicines was submitted in 2019 by the Multiple Sclerosis International Federation (MSIF), also co-author of the current Application. At that time, the Committee noted that there was no clear-cut superiority of these drugs over other MS medicines in terms of safety, efficacy, and affordability, and commonly used agents (e.g., natalizumab) and off-label medications (e.g., rituximab) were excluded from that Application. Therefore, this Reviewer carefully considered the selection of the most promising agents among several pharmacological options available for MS (at least in its relapsing and remitting forms). The Application reports a robust and detailed process of selection, summarising the body of evidence and transparently reporting the decision-making process, based on the work done by two specific initiatives - MSIF Off-Label Treatments (MOLT) and MSIF Essential Medicines (MEMP) guidelines. In line with the MEMP and MOLT recommendations, rituximab, cladribine and glatiramer acetate emerged as effective, feasible and acceptable options for the treatment of MS. **Rituximab** is already listed on the WHO Model List of Essential Medicines, is widely available and listed on many national EMLs. The magnitude of benefit was judged large to moderate, however the certainty of evidence supporting its benefit risk profile was judged low or very low. Overall, the balance of effects, mode of administration (6-monthly infusions), possibility to use it without screening and monitoring, its availability and low cost support the inclusion in the EML for the treatment of MS, both relapsing and progressive forms. Rituximab is contraindicated during pregnancy, but may be used with careful timing of treatment. Harms are considered small to trivial. There are no direct comparisons between ocrelizumab and rituximab, the latter being less costly, available as biosimilars, but used off label. In those setting where off-label prescribing is limited, ocrelizumab may offer an alternative to rituximab. Therefore, this Reviewer support the inclusion of rituximab as the representative of the square box grouping, including ocrelizumab. Please, also refer to Application A28 Application for the addition of ocrelizumab on the WHO Model List of Essential Medicines. **Cladribine** is considered the oral agent with the best benefit risk profile. Its benefit in relapsing forms of MS was judged large, while no data from RCTs are available on progressive forms. **Glatiramer acetate** offers several advantages in low-resourced settings, including its lack of pre-test and on-therapy monitoring requirements, good safety profile without risk of opportunistic infections, and safety in women of childbearing age, pregnant and breastfeeding women. Its benefit was judged large in relapsing MS and moderate in progressive forms. Harms were judged trivial.

	In conclusion, this Reviewer supports the inclusion of rituximab, cladribine and glatiramer acetate on the WHO Model List of Essential Medicines. However, beyond the availability of treatment options, people with MS should have access to adequate medical expertise and facilities to support diagnosis, monitoring, appropriate treatment choices and regular monitoring of effectiveness and potential side-effects. The inclusion of new section for MS on the WHO Model List of Essential Medicines should be seen as a potential tool to increase global advocacy efforts to reduce the global burden of MS, especially in low and middle-income countries where access is a greater unmet need.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: MS is the most common non-traumatic cause of neurological disability in young adults. Approximately 2.8 million people are living with MS worldwide, with women affected 2-3 times more than men. The most common form is relapsing-remitting MS (RRMS), characterised by relapses and remissions of neurological symptoms. Over time, most people with RRMS develop a secondary-progressive course of the disease (SPMS) marked by gradual worsening with or without additional inflammatory events. An estimated 15% of people with MS have a progressive course from disease onset, known as primary progressive MS (PPMS), without clearly defined relapses. Since many resource-limited settings lack both neurologists and neuroimaging facilities, the precise, modern diagnosis of MS remains suboptimal for several people with MS worldwide. Similarly, access to disease-modifying therapies (DMTs) is variable and not always guaranteed, despite the increased number of relapses and progression highly impact usual activities and increase the risk for serious morbidity.

Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: The application includes extensive systematic reviews and clinical guidelines gathering comprehensive evidence on health effects (benefits and harms) of DMTs. After a complex process of selection among the 30 treatments used for the treatment of MS, either licensed or off-label, only the most positively recommended DMTs from each guideline project were proposed for inclusion on the WHO Model Lists of Essential Medicines.  **Relapsing Forms of MS** **Recommendation "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). **Progressive Forms of MS** **Recommendation "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). **RITUXIMAB** ***Relapsing forms of MS*** Large benefit vs no DMT (switching from another DTM); relapse at 12 months: 198 fewer per 1000 (very low certainty, RCT) Large benefit vs other DMTs (treatment naïve); relapse at 24 months: 84 to 227 fewer per 1000 (low certainty, non-RCT) Based on the balance of effects and the wider Evidence to Decision framework, both rituximab and azathioprine were recommended over no treatment. However, rituximab was considered superior to azathioprine, and an appropriate treatment when switching from another DMT. The desirable effects of rituximab were judged as 'large' compared to interferon and glatiramer acetate and 'moderate' compared to natalizumab and dimethyl fumarate. ***Progressive forms of MS*** Moderate benefit vs no DMT (treatment naïve), disability at 24 months: 85 fewer per 1000 (very low certainty of evidence, RCT) Rituximab was recommended over no treatment for active progressive MS, both for treatment-naive patients and when switching from another DMT.

	CLADRIBINE ***Relapsing forms of MS*** Large benefit vs no DMT; relapse at 24 months: 240 fewer per 1000 (high certainty); disability at 24 months: 53 fewer per 1000 (low certainty, RCT); QoL SMD 0.19 SD higher (moderate certainty, RCT) ***Progressive forms of MS*** No data **GLATIRAMER ACETATE** ***Relapsing forms of MS*** Large benefit vs no DMT; relapse at 24 months: 82 fewer per 1000 (moderate certainty, RCT); disability at 24 months: 49 fewer per 1000 (very low certainty, RCT); QoL SMD 0.19 SD higher (moderate certainty, RCT) ***Progressive forms of MS*** Moderate benefit vs no DMT; disability at 24 months: 68 fewer per 1000 (very low certainty, RCT) --- Despite the large number of studies, the certainty of the supporting evidence is often low or very low.
Does adequate evidence exist for the safety/harms associated with the proposed medicine? (this may be evidence included in the application, and/or additional evidence identified during the review process)	☒ Yes ☐ No ☐ Not applicable Comments: **Rituximab** (small harm): the evidence for adverse reactions showed a significant level of short-term infusion reactions (high certainty of evidence). Mortality risk may be low, while the risk of infections may be high. Limited evidence for long-term adverse events of rituximab is available. **Cladribine** (trivial harm): mortality not affected, serious adverse events were few and did not affect treatment adherence. **Glatiramer acetate** (trivial harm): mortality not affected, serious adverse events were few and did not affect treatment adherence.
Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☒ No ☐ Not applicable Comments:

Are there any special requirements for the safe, effective and appropriate use of the medicines? (e.g. laboratory diagnostic and/or monitoring tests, specialized training for health providers, etc)	☐ Yes ☒ No ☐ Not applicable Comments: Overall, these treatments require very low screening and monitoring. Rituximab/ocrelizumab require infusion facilities and cold storage at the healthcare facility. Glatiramer has the disadvantage of frequent injections and requires refrigeration. Cladribine is an oral agent, with few monitoring requirements, short duration of treatment, and no refrigeration requirements. A point that deserves attention is the global differences in access to MRI and technical/clinical capacity and human/physical resources needed in its application. This may affect the likelihood of receiving a MS diagnosis and proper monitoring of the disease.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: According to the Application, several economic analyses are available on recently marketed drugs, most funded by the company producing the DMT assessed in the economic analysis. Most studies are performed in high-income countries. Several studies suggest a superiority of cladribine over other DMTs in terms of cost effectiveness, but their results should be interpreted with caution. Similar considerations can be made for glatiramer acetate and ocrelizumab. The price of rituximab was the lowest, followed by glatiramer acetate. The price of cladribine and ocrelizumab were significantly higher. Apart from the cost of the medicines, cost of screening, monitoring and administration should also be considered in comparison among DMT.

Are there any issues regarding the registration of the medicine by national regulatory authorities? (e.g. accelerated approval, lack of regulatory approval, off-label indication)	☐ Yes ☒ No ☐ Not applicable Comments: Ocrelizumab, cladribine and glatiramer acetate are approved by all "stringent" regulatory authorities. Rituximab is off-label but has regulatory approval for other indications. This does not appear to be a major issue for availability as off-label rituximab is widely used to treat MS and listed on 40% of the national EMLs, including in low-income countries, according to the Application. Ocrelizumab square box grouping ensures availability to an anti-CD20 therapy when off-label prescribing is not possible. Availability of glatiramer acetate and oral cladribine is more limited globally. The inclusion on the WHO EML would enable focused activities to make these agents more widely available. Biosimilars are available for rituximab and generics for glatiramer acetate. According to the analysis by Medicines Patent Pool (MPP) and MSIF ocrelizumab is protected by a product patent expiring in 2023 in many jurisdictions, but secondary patents will expire in 2029 or possibly as late as 2036. It is unclear whether these represent a true block to biosimilar market entry. (https://www.msif.org/?s=Overview+of+the+patent+status+of+MS+treatments) According to the Application, cladribine has the potential for being prioritised for voluntary licensing by the Medicines Patent Pool (MPP) due to its clinical relevance, feasibility in low and middle-income countries, and patent status.
Is the proposed medicine recommended for use in a current WHO guideline? (refer to: https://www.who.int/publications/who-guidelines)	☐ Yes ☒ No ☐ Not applicable Comments: Currently there are no WHO guidelines on MS. In 2022 WHO recognised neurological disorders as a major global health priority and committed to prioritise brain health