A.10	Cladribine, glatiramer and rituximab – multiple sclerosis – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Cladribine – This oral DMD for MS has adequate indication for use in RRMS. Due to its safety profile, cladribine is recommended for patients who are unresponsive or intolerant to an alternate drug indicated for the treatment of MS. Cladribine offers several advantages especially in low-resourced settings. First, it is an oral regimen, requiring only 16-20 days of total treatment distributed over 2 years, and further retreatment is not needed for at least another two years. This significantly reduces pill burden. Also, the ease of administration, no requirement for specialised training to use and cost effectiveness favour its recommendation. However, it cannot be used in pregnancy & breast feeding but it therapy with cladribine can be planned around pregnancies given its infrequent dosing. Other infections such as HIV, TB, hepatitis B and C, must be excluded. Glatiramer – It is the only drug which can be safely administered in the pregnant and lactating women with MS. Further, there is adequate evidence on efficacy, safety, and cost effectiveness of the drug in MS. Also, no requirement for on-therapy laboratory monitoring, good safety profile without risk of opportunistic infections, safety in women of reproductive age, pregnant and breast feeding and paediatric populations, no specialised training to use and cost effectiveness favour its recommendation. The requirement for refrigeration and non-preferred administration route are some of its limitations which can be managed given its cost-effectiveness. Rituximab – It has been shown to have efficacy in treatment of various subset of MS patients like treatment naïve patients in RMS, SPMS and also as a switch over drug for aggressive/active MS and has a better safety profile than other DMDs.
Does the proposed medicine address a relevant public health need?	☒ Yes ☐ No ☐ Not applicable Comments: MS is a relevant health issue worldwide. MS is a chronic neurological disease that affects the central nervous system and can lead to a wide range of symptoms, including difficulties with movement, coordination, and cognition. Onset is commonly seen between 20-40 years of age. MS can have a significant impact on individuals, families, and communities. 2.8 million people currently live with MS where 85% of these patients have a relapsing type of MS leading to substantial disability and expenditure per capita. The disease can lead to disability, reduced quality of life, and increased healthcare costs. In addition, MS can also have broader social and economic impacts, including reduced workforce participation and productivity. The WHO Intersectoral Global Action Plan on epilepsy and other neurological disorders was adopted by the Seventy-fifth World Health Assembly in May 2022, endorsed by 194 countries, making neurological disorders a major global health priority and committing WHO to prioritize brain Health.

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: Cladribine: Evidence exists on the efficacy of Cladribine in RRMS patients. As per a RCT conducted in 2010 (CLARITY trial), the drug had benefit in efficacy, relapse rates and disability when compared to placebo. Cladribine reduced the risk of relapse and slowed disease progression in patients with relapsing-remitting MS. The efficacy of cladribine varies depending on the type and severity of MS. In addition, cladribine can have side effects, including an increased risk of infections, which may limit its use in some patients. Glatiramer: Adequate evidence is available on the Glatiramer in patients of RRMS. Some evidence is also available in patients of PMS. The RCT's show benefit in efficacy, safety, relapse rates when compared to placebo in both these subset of MS patients. Further, it is a recommended drug by the US-FDA in pregnant and lactating women. Rituximab: Though evidence is available on Rituximab towards efficacy, relapse rates, and disability in RRMS particularly those with relapsing-remitting MS who have not responded to other treatments, and PMS patients. The evidence exists in form of RCT with placebo as well as comparison with other DMDs. However, these studies have limitations, including small sample sizes, lack of control groups, and short follow-up periods. There have also been some larger clinical trials evaluating the effectiveness of B-cell targeting therapies like rituximab in MS. Ocrelizumab versus placebo in Primary Progressive Multiple Sclerosis (ORATORIO) trial, which showed that ocrelizumab was effective in slowing disease progression in patients with primary progressive MS, a type of MS that has been particularly challenging to treat. While this trial did not specifically evaluate rituximab, it provides some evidence for the effectiveness of B-cell targeting therapies in MS. Despite these promising results, the use of rituximab in MS is still considered off-label, as it has not been approved by regulatory agencies for this indication. All three proposed DMTs have been studied in adults with RRMS. Rituximab, ocrelizumab and glatiramer acetate have also been studied in PMS. Glatiramer acetate is licensed in patients with RRMS aged 12 years or older (in Europe, decision has not been issued by EMA, but by individual national regulatory agencies). Off-label use of anti-CD20s such as rituximab is common in both adults and pediatric MS. Ocrelizumab use is on-label in adults but off-label in pediatric MS.

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: The overall safety profile of cladribine appears to be manageable, and it is generally well-tolerated by most patients. Although only one RCT on safety/ harms of this drug has been done but it suggests that harm was not higher than placebo. CLARITY and CLARITY Extension studies demonstrated that cladribine significantly reduced the risk of relapse and disability progression in patients with relapsing-remitting MS. However, they also reported some potential safety concerns, including an increased risk of infections, lymphopenia, and malignancies. Glatiramer (GA): GA is generally considered to have a favorable safety profile, with most adverse events being mild to moderate in severity and reversible. These include injection site reactions, such as pain, redness, swelling, and itching, as well as systemic reactions, such as flushing, chest pain, and shortness of breath. However, these reactions are usually mild and resolve on their own without the need for treatment. Rarely, serious adverse events associated with GA use are (severe allergic reactions, such as anaphylaxis, and immune-mediated disorders, such as thrombocytopenia and autoimmune hepatitis). Rituximab is used widely both for MS and for other conditions such as non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, etc. The safety profile and harms of RTX in other conditions has been well documented. It is generally safe and well-tolerated by most patients but may be associated with a higher risk of certain adverse events (such as an increased risk of infections, infusion reactions, and malignancies) compared to other DMDs. RCTs in patients of MS shows lower rates of SAEs, and lesser opportunistic infections compared to other DMDs (including Natalizumab). In terms of efficacy, both rituximab and ocrelizumab have shown similar benefits in reducing disease activity and disability progression in MS. However, ocrelizumab has been FDA-approved specifically for the treatment of relapsing and primary progressive MS, while rituximab is used off-label for MS treatment. Both rituximab and ocrelizumab carry risks of serious infections, infusion reactions, and other potential adverse effects. However, more research is needed to fully understand the comparative safety and efficacy of rituximab and other treatments for MS.

Are there any adverse effects of concern, or that may require special monitoring?	☐ Yes ☐ No ☐ Not applicable Comments: Cladribine – Patients should be monitored for signs of following disorders during and after treatment: lymphopenia and infections (such as herpes and pneumonia), malignancy, teratogenicity, and autoimmune disorders (such as thyroid disease or autoimmune hepatitis). Glatiramer acetate: It is generally well-tolerated oral therapy, but there are some adverse effects of concern injection site reactions, systemic allergic reactions (rare), some patients may experience systemic allergic reactions to glatiramer acetate. Monitoring required for immune system effects and increase the risk of infections. Rituximab: Some adverse effects of concern that may require monitoring during treatment include infusion reactions, infections, progressive multifocal leukoencephalopathy (PML) though is rare but serious brain infection that has been reported in patients treated with rituximab and cardiac adverse events (heart failure and myocardial infarction).
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: Cladribine: There are no special laboratory diagnostic or monitoring tests required except some routine laboratory tests that may be needed before and during treatment including complete blood count, liver function tests, and kidney function tests every 2–3 months; pregnancy test before each treatment cycle. Annual cMRI. Infection prophylaxis for grade 3 and 4 lymphopenia. Discontinue medication in second year of treatment if lymphocyte levels are below 800/µl. Glatiramer: There are no special laboratory diagnostic or monitoring tests required for the use of glatiramer in the treatment of multiple sclerosis. However, patients should undergo regular clinical evaluations to monitor their disease status and response to treatment. Before therapy blood count and diff. blood picture. During therapy diff. blood. picture every 3 months in the first year of therapy. Before therapy: liver count, kidney count, vaccination status. cMRI < 3 months old. During therapy: liver and kidney count checks every 3 months in the first year of therapy. Annual cMRI. Rituximab: Acceptability is good, infrequent infusion requirements (every 6 months) with low monitoring requirement which include baseline routine laboratory tests (complete blood count (CBC), liver function tests, and serum immunoglobulin levels) and regular laboratory monitoring during treatment including CBC and liver function tests, to detect potential adverse effects of the medication. Off label but familiarity of use from other conditions favors its acceptability. It should be administered under the guidance and supervision of experienced healthcare providers who are trained in the proper dosing, administration, monitoring and managing potential infusion-related reactions, such as anaphylaxis and cytokine release syndrome. It is safer to avoid rituximab in pregnancy but can be managed with careful timing.

Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☐ Yes ☒ No ☐ Not applicable Comments: Cladribine: Studies have shown that cladribine is cost-effective compared to other disease-modifying therapies for MS. Cost-effectiveness favors glatiramer compared to ocrelizumab, alemtuzumab, natalizumab and fingolimod. The cost and access to cladribine may vary depending on the healthcare system and insurance coverage in different settings. but overall has low monitoring costs and oral mode of administration. Access to cladribine may also be limited in some areas due to the availability of healthcare resources and specialized healthcare providers. On-label, oral medicine with few monitoring requirements, short treatment periods favorable. Glatiramer: The cost and access may vary depending on the healthcare system and insurance coverage in different settings. Cost-effectiveness variable compared to fingolimod, interferon beta 1b but not dimethyl fumarate, peg-interferon beta 1a or teriflunomide. Low monitoring requirement and safe for use in pregnancy. Frequent injections requiring cold chain but can be managed at home. Listing both Cladribine and glatiramer on WHO EML would reduce costs and increase health equity. Rituximab: Though it is a high-cost medication, the cost varies depending on the country and healthcare system, therefore, affordability may be an issue, but it is used in many other conditions as well. As far as equity is concerned its cost is lower compared to other DMTs listed on WHO EML, and other national EML, therefore, there is a high probability to improve health equity. Though there are not many systematic studies on cost-effectiveness of rituximab in MS. Norwegian HTA found it to be cost effective compared to other disease-modifying drugs and ocrelizumab and fingolimod in treatment-naïve RMS. Both glatiramer and rituximab require storage at temperatures between 2-8°C (36-46°F) and protected from light.

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: Cladribine: Cladribine use is on-label as is approved by several regulatory authorities, including the US FDA and the European Medicines Agency (EMA), for the treatment of multiple sclerosis. Regulatory approval may vary between countries and may be subject to change. Glatiramer: It is a well-established and widely used medication for multiple sclerosis that has been approved by regulatory authorities in many countries. However, there may be specific issues related to its registration and availability in certain countries, depending on their individual regulatory processes and healthcare systems. Rituximab: Rituximab is used off-label for the treatment of MS, particularly in cases where other disease-modifying therapies have been ineffective but widely available and listed on WHO EML. Product patents have expired, and several follow-on products are available. It is a Who pe-qualification product. Rituximab has been approved by regulatory authorities in many countries for various indications but has not been approved specifically for the treatment of MS including US FDA. Off-label could be likely due to a variety of factors, including the need for additional clinical studies and data on the safety and efficacy of the drug for MS, as well as potential concerns regarding its cost and affordability for patients.
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: Cladribine: No WHO guidelines on MS. The other guideline on "Management of Multiple Sclerosis" includes cladribine as a therapeutic option for relapsing-remitting and active secondary progressive multiple sclerosis. Glatiramer: It is recommended as a first-line treatment option, along with interferon beta-1a and interferon beta-1b. Rituximab: Several disease-modifying therapies for the treatment of relapsing-remitting MS are recommended, including interferon beta, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, alemtuzumab, and natalizumab.