A.28	Ocrelizumab – multiple sclerosis – EML
Draft recommendation	☒ Recommended ☐ Not recommended Justification: Ocrelizumab is indicated in (highly) active RMS, SPMS with relapses, PPMS with clinical/MRI activity. For PPMS, ocrelizumab is the only currently approved treatment. Some studies have compared the effectiveness and safety of rituximab and ocrelizumab in the treatment of MS, and while the results are generally favorable for both drugs, there is no clear consensus on their clinical equivalence. Some studies have suggested that ocrelizumab may be more effective than rituximab in reducing MS disease activity, while others have found no significant difference between the two drugs. Benefit has been further confirmed in real-world observational studies on both RMS and PPMS. In terms of safety, both drugs have been shown to have similar side effect profiles, with the most common adverse events being infusion-related reactions such as itching, rash, flushing, or fever. However, specialized tests such as magnetic resonance imaging (MRI) for diagnosis and follow-up of MS, as well as specialized care for management of adverse events such as infusion related reactions (IRRs), inclusion in the complementary list may be considered. However, potential issue with ocrelizumab is the high cost of the medication, which may impact access and reimbursement by national health systems. Pricing and reimbursement decisions are made by individual countries and may be influenced by a variety of factors, including the cost-effectiveness of the medication, the availability of alternative treatments, and budget constraints.
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: In two phase III clinical trials (OPERA I and II), ocrelizumab was found to significantly reduce the number of relapses and slow the progression of disability compared to a placebo and interferon beta-1a in patients with relapsing-remitting MS. Additionally, in a separate clinical trial (ORATORIO), ocrelizumab was found to significantly reduce disability progression and the number of brain lesions compared to a placebo in patients with primary progressive MS. Another trial was the ASCLEPIOS I and II studies, ocrelizumab reduced the annualized relapse rate and the number of new or enlarging brain lesions compared to teriflunomide in patients with RRMS. Additionally, ocrelizumab was associated with a significantly greater reduction in disability progression compared to teriflunomide. However, more research is needed to confirm these findings and to determine the optimal treatment approach for patients with PPMS, updated analyses of efficacy and safety for patients who have continued in the open-label extension (OLE) phase of the three pivotal studies for up to nine years have confirmed continued benefit after the controlled treatment phase. No new safety signals have been identified. The available evidence suggests that ocrelizumab may be more effective than interferon beta-1a in reducing disease activity and disability progression in patients with PPMS.
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: Contraindications, and warnings and precautions include infusion related reactions (IRRs), hypersensitivity reactions, infection, progressive multifocal leukoencephalopathy (PML), hepatitis B reactivation, late neutropenia, malignancies, treatment of severely immunocompromised patients, vaccinations, use with other immunosuppressants, and use in pregnancy and lactation.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: In principle risk of progressive multifocal leukoencephalopathy (PML), and infections like TB, upper respiratory tract infection, nasopharyngitis, influenza, herpes infection. Ocrelizumab administration should be delayed, in patients with an active infection until the infection is resolved.

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: To be administered by specialized physicians/neurologists experienced in the diagnosis and treatment of neurological conditions. Before therapy blood count and diff. blood picture; recommended: immune status. During therapy diff. blood picture every 3 months, immune status 3 months after first dose, and recommended every 6 months thereafter. Before therapy: IgG and IgM in serum; liver count, kidney count; infection status (TB, HBV, HCV, HIV, lues, VZV, Tbc), pregnancy test, urine status, CRP, vaccination status including pneumococcal vaccination; baseline MRI of the skull with contrast medium < 3 months old. Ocrelizumab administration should be delayed in patients with an active infection until the infection is resolved. During and up to 1 h after infusion: monitoring for infusion reactions. During therapy: Serum IgG and liver, kidney values every 6 months. Annual cMRI. Staff also needs to be trained to eliminate infusion related reactions by premedication. Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. It is feasible to plan a conception 4 months after treatment with ocrelizumab.
Are there any issues regarding cost, cost-effectiveness, affordability and/or access for the medicine in different settings?	☒ Yes ☐ No ☐ Not applicable Comments: Recommended for a specific subset of MS (PPMS or high relapsing MS). The potential issue with ocrelizumab is the high cost of the medication, which may impact access and reimbursement by national health systems. Pricing and reimbursement decisions are made by individual countries and may be influenced by a variety of factors, including the cost-effectiveness of the medication, the availability of alternative treatments, and budget constraints. The applicant has proposed a differential pricing approach tailored to country individual needs and affordability balancing the need of the healthcare systems and patients, and sufficient market incentives for industry to invest in future innovation.

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 has been approved by regulatory authorities in several countries, including the United States, the European Union, Canada, Australia, and Switzerland, for the relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adult. However, the regulatory approval process can vary by country, and some issues may arise during the registration process. One potential issue with ocrelizumab is the risk of serious infections, including opportunistic infections such as progressive multifocal leukoencephalopathy (PML), a rare and potentially fatal brain infection. These risks have been addressed by the inclusion of appropriate warnings and precautions in the product labeling, and the requirement for post-marketing monitoring and reporting of adverse events. Ocrevus® is marketed by Roche in many countries where a registration was granted. There are no pharmacopeial standards specific for ocrelizumab. The drug product does comply with the European Pharmacopoeia monographs, “Pharmaceutical Preparations (2619)”, “Parenteral Preparations (0520)”, and “Substances for Pharmaceutical Use (2034)”.
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: There are several guidelines which recommend ocrelizumab as a first-line treatment option for patients with relapsing-remitting MS (RRMS) or primary progressive MS (PPMS), based on its efficacy and safety profile. Ocrelizumab as an alternative treatment option for patients who have not responded to or are intolerant of other disease-modifying therapies [National Multiple Sclerosis Society's Clinical Practice Guidelines for the Use of Disease-Modifying Therapies in Multiple Sclerosis, The European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS), The American Academy of Neurology (AAN)].