A.28	Ocrelizumab – multiple sclerosis – EML
Draft recommendation	☐ Recommended ☒ Not recommended* Justification: This Application refers to the inclusion of ocrelizumab as an individual medicine for the treatment of multiple sclerosis (MS). The possible benefits of ocrelizumab in the management of relapsing and primary progressive forms of MS (RMS and PPMS) is clearly reported by the Application. However, this Reviewer suggests considering this Application in the light of the request of including other disease-modifying therapies (DMTs) in WHO Model List of Essential Medicines. Please, see Application A10 "Proposal for inclusion of multiple sclerosis disease-modifying therapies (DMTs) on the complementary WHO Model Lists of Essential Medicines" for further details. Ocrelizumab may be offered to people with MS in certain settings, given its regulatory status in PPMS and where off-label prescribing is limited. However, overall, there is no compelling evidence of its superiority over other alternatives, specifically the cheapest and widely used rituximab. Therefore, this Reviewer cannot support the inclusion of ocrelizumab, as an individual medicine, on the complementary list of the WHO Model List of Essential Medicines for the treatment of adult with MS *but would consider its listing as an alternative option to rituximab.
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: ***Relapsing forms of MS*** Ocrelizumab was shown to be safe and effective in two pivotal double-blind, double-dummy randomised phase 3 trials on relapsing forms of MS, OPERA I (WA21092; n=821) and OPERA II (WA21093; n=835). • Annualized Relapse Rate was lower with ocrelizumab than with IFNβ1a in OPERA I (0.16 vs. 0.29; 46% lower rate with ocrelizumab) and in OPERA II 2 (0.16 vs. 0.29; 47% lower rate) over a period of 96 weeks. • Proportion of patients with 12-week Confirmed Disability Progression (pooled analysis) lower with ocrelizumab than IFNβ1a (9.8% vs. 15.2%, 40% lower rate with ocrelizumab). • Proportion of patients with 42-week Confirmed Disability Progression (pooled analysis) lower with ocrelizumab than IFNβ1a (7.6% vs. 12%, 40% lower rate with ocrelizumab) • QoL not significantly different Open label extensions of OPERA I and II demonstrated that the benefits of earlier initiation of ocrelizumab were maintained compared with patients switching from IFNβ1a. Other studies: CHORDS (NCT02637856) and CASTING (NCT02861014) single-arm studies evaluating ocrelizumab effectiveness and safety in patients with RRMS who had suboptimal response with prior DTM (switch). ***Progressive forms of MS*** Ocrelizumab was shown to lower rates of clinical and MRI progression compared to placebo in the double-blind, parallel-group, multicenter pivotal phase 3 clinical trial in primary progressive MS, ORATORIO (WA25046; n=732). • Proportion of patients with 12 weeks - Confirmed Disability Progression lower with ocrelizumab than placebo (30.2% vs. 34%, 24% lower rate with ocrelizumab) • Proportion of patients with 24 weeks - Confirmed Disability Progression lower with ocrelizumab than placebo (28.3% vs. 32.7%, 25% lower rate with ocrelizumab) • QoL not significantly different Ongoing: CONSONANCE trial (NCT03523858), a single arm phase 3b trial, designed to evaluate the effectiveness and safety of ocrelizumab across the spectrum of progressive MS (i.e., in patients with either PPMS or SPMS). The Application also lists about 50 other studies, mainly cohort studies in clinical practice, assessing ocrelizumab. A few address the issue of comparative effectiveness over other DMTs. A recent review, sponsored by Roche, including only observational studies assessing ocrelizumab in clinical practice, reported only six studies capturing data on ocrelizumab and other treatments, i.e., rituximab, cladribine, fingolimod, dimethyl fumarate, natalizumab, and teriflunomide. Data were not conclusive, and the review calls for prospective comparative cohort studies with matched pairs to generate evidence on the comparative effectiveness of the available therapies (Montalban et al., Ann Clin Transl Neurol. 2023; 10(3): 302–311).

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: Safety data for ocrelizumab has been continuously collected via multiple data sources, including, but not limited to, the pivotal trials, long-term OLEs of clinical trials, phase 3b/4 trials, non-interventional studies, and spontaneous AE reports to the post-marketing safety database. Typical adverse effects of ocrelizumab includes infusion-related reactions, hypersensitivity reactions, infection, progressive multifocal leukoencephalopathy (PML), hepatitis B virus reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, late neutropenia. Ocrelizumab should be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus.
Are there any adverse effects of concern, or that may require special monitoring?	☒ Yes ☐ No ☐ Not applicable Comments: Infusion-Related Reactions are frequently described, especially after the first infusion (34.3%, 40.1% in RMS and PPMS, respectively). Premedication should be used prior to each ocrelizumab infusion to reduce the frequency and severity of infusion-related reactions, as methylprednisolone and antihistamine agents.
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: Ocrelizumab is administered by intravenous infusion as 600 mg dose every six months. Treatment should be initiated and supervised by specialised physicians experienced in the diagnosis and treatment of neurological conditions and who have access to appropriate medical support to manage severe reactions such as serious infusion-related reactions.

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 submitted by the marketing authorisation holder, in France, Germany, Italy, Spain, and the United Kingdom (UK) ex-factory prices for ocrelizumab range from €5'125 – €6'250 per vial, or €20'500 – €25'000 per patient per year. In upper-middle, lower middle, and low-income countries, the average ocrelizumab list price is €4'450 per vial with the lowest list price starting at €1'495 per vial. Although the company states that the International Differential Pricing (IDP) allows price adjustment to reflect a country's relative income and ability to pay, the costs for treatment appears to be unsustainable for most of the countries. Ocrelizumab is more costly than off-label rituximab.
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 is licensed in over 100 countries worldwide for the treatment of people with RRMS and PPMS. According to the analysis by Medicines Patent Pool and Multiple Sclerosis international federation (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)
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.