Cladribine

Section: 5. Medicines for neurological disorders > 5.1. Medicines for central nervous system disorders > 5.1.2. Medicines for multiple sclerosis

ATC codes: L04AA40

Indication	Multiple sclerosis ICD11 code: 8A40
INN	Cladribine
Medicine type	Chemical agent
List type	Complementary
Formulations	**Oral > Solid > tablet:** 10 mg
EML status history	First added in 2023 (TRS 1049)
Sex	All
Age	Adolescents and adults
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Main patents have expired but secondary patents might remain active in some jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org Read more about patents.
Wikipedia	Cladribine
DrugBank	Cladribine

Expert Committee recommendation

The Expert Committee noted that MS is the most common non-traumatic cause of neurological disability in young adults. About 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, characterized by relapses and remissions of neurological symptoms. Over time, most people with relapsing-remitting MS develop a secondary progressive course of the disease (secondary progressive MS) marked by gradual worsening with or without additional inflammatory events. Currently, there are no medicines specifically for the treatment of MS included on the Model List. However, rituximab is included for other conditions, is widely available and is listed on many national essential medicines lists. The Committee acknowledged the availability of a large number of disease-modifying medicines for MS (particularly for the treatment of relapsing and remitting forms of the disease) and the need to prioritize the most effective, best tolerated, and most affordable options. In 2019, the Committee considered an application to include glatiramer acetate, fingolimod and ocrelizumab and noted that there was no clear-cut superiority of these drugs over other options in terms of safety, efficacy and affordability. Moreover, commonly used agents (e.g. natalizumab) and off-label medications (e.g. rituximab) were excluded from that application. The Committee considered that the approach taken in the current application submitted by the Multiple Sclerosis International Federation, based on the work done by two specific initiatives – MSIF Off-Label Treatments (MOLT) and MSIF Essential Medicines (MEMP) guidelines – to identify which medicines to prioritize for EML listing from among the many available was comprehensive, up-to-date, transparent, robust and evidence-based. The Committee recognized the value of involving different organizations and stakeholders at the global level, including

consultation with people living with MS. The Committee considered that the application's selection of cladribine, glatiramer acetate and rituximab as priority medicines for EML inclusion was well justified and supported by evidence of clinical benefit and safety across different settings, as well as suitability for use in different patient populations (e.g. pregnant women) and feasibility. The inclusion on the EML of three medicines, with different routes of administration, different prices (including the availability of generic and biosimilar products) and different recommended uses, would provide valuable options for patients and national selection decisions and could facilitate improved access to treatment for people living with MS. The Committee noted that, 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. The addition of multiple medicines allows options with different price, routes of administration and potential use in pregnancy. Generics of glatiramer acetate and rituximab biosimilars are available at lower cost than branded products, which could facilitate access to treatment. The Committee considered that inclusion of a new section for medicines for the treatment of MS in the WHO Model List of Essential Medicines could increase global advocacy efforts to reduce the global burden of MS, especially in low- and middle-income countries where the unmet need for access is greater. This would also raise awareness of the need for specialized care and diagnostics, as well as monitoring of the disease response and progression. The Committee recognized that rituximab did not have regulatory approval for the indication of MS but is widely used in clinical practice, is supported by evidence of efficacy and safety, and is reimbursed for MS in several countries. The Committee acknowledged the benefits of ocrelizumab in the management of relapsing/remitting and primary progressive forms of MS. However, there was no compelling evidence of its superiority over alternative treatments, specifically rituximab, which has the same molecular target (CD20). The Committee considered the option of listing ocrelizumab as alternative to rituximab, but also recognized the difference in current prices of the two products and the fact that off-label use of medicines is allowed in many countries, when robust evidence exists. The Committee concluded that including ocrelizumab as a therapeutic alternative to rituximab could result in considerable additional expenditure at the country level for patients and health systems, without offering additional clinical benefit. The Committee considered that inclusion only of the less expensive rituximab on the EML might serve to facilitate its use (albeit off-label) for MS. The Committee recalled and reiterated the views expressed by the 2015 Expert Committee on consideration of medicines for inclusion on the Model Lists for off-label uses or indications: that is, labelling is the responsibility of national regulatory authorities and there may consequently be different labels for the same product in different countries, and there is thus no global standard for what is considered off-label. Furthermore, updating approved labels for older products may not be pursued by market authorization holder(s) if doing so is not considered commercially viable, and there are many examples of older products whose regulatory labels are inconsistent with current clinical evidence and current clinical practice. Consequently, the Expert Committee reaffirmed that off-label status of a medicine need not be a reason to exclude it from the Model Lists if it otherwise meets the criteria for inclusion. The Committee considered that the Model List can play an important role in identifying those medicines for which off-label use is supported by convincing evidence, complementing the assessment and labelling by jurisdictional authorities. Therefore, the Committee recommended the inclusion of cladribine, glatiramer acetate and rituximab as individual medicines on the complementary list of the EML in a new section dedicated to medicines for MS. The recommendation was based on the important public health need, and evidence of efficacy, safety and feasibility of use of the medicines proposed. The Committee did not recommend the inclusion of ocrelizumab as an alternative under a square box listing for rituximab for the reasons outlined above.

Background

In 2019, the Expert Committee reviewed an application from the Multiple Sclerosis International Federation requesting the addition of glatiramer acetate, fingolimod and ocrelizumab on the Model Lists for use in the treatment of MS. The Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments. However, the Committee noted that the superiority of the proposed medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge from the application. The Committee noted that some commonly used treatments were not included in the application (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine), or were not given full consideration (e.g. rituximab),

with reasons for their exclusion being unclear. In particular, the Committee noted the evidence presented in the application in relation to rituximab and considered that rituximab could have a relevant clinical role in the treatment of MS and recommended that any future application include evidence for rituximab versus active comparators, not just placebo. The Committee therefore did not recommend listing of glatiramer acetate, fingolimod or ocrelizumab at the time, and requested a revised application which comprehensively reviewed the relative roles of relevant available medicines for MS (2).

Public health relevance

Public health relevance MS is a chronic autoimmune disease characterized by inflammation of the central nervous system that leads to demyelination, axonal loss and progressive neuronal degeneration, resulting in irreversible disability and cognitive impairment (3, 4). Common symptoms include pain, fatigue, mood and cognitive changes, mobility and sensory impairment, visual disturbances, and elimination dysfunction. Symptoms can vary in severity and can result in significant disability, and reduction in quality and length of life. Data on the global prevalence of MS vary. The Global Burden of Disease study reported that globally, about 1.8 million people (23 per 100 000) had MS in 2019. Age-standardized prevalence per 100 000 population shows large variability across WHO regions, ranging from 4 cases per 100 000 in the Western Pacific Region to 60 per 100 000 in the European Region (5). The atlas of MS estimated that globally, about 2.8 million people (36 per 100 000) had MS in 2020 (6). The number of people with MS per 100 000 population also showed large variability across WHO regions, ranging from 5 per 100 000 in the African and Western Pacific regions to 133 per 100 000 in the European Region (6). MS is most often diagnosed between the ages of 20 and 50 years, but the disease may also first manifest in older adults and children. Women are affected 2–3 times more than men (7, 8). MS is broadly divided into relapsing and progressive forms, classified in three different clinical phenotypic patterns based on the presence of transient attacks of neurological symptoms and/or a progressive worsening of the neurological function: relapsing-remitting MS, secondary progressive MS and primary progressive MS (9). Relapsing-remitting MS is characterized by relapses and remissions of neurological symptoms, with relapses associated with new areas of inflammation in the central nervous system. Over time, most people with relapsing-remitting MS will transition to secondary progressive MS, marked by gradual worsening of neurological function with or without additional inflammatory events. Primary progressive MS is characterized by the absence of clearly defined relapses (9, 10). The course of MS is highly variable and unpredictable, and patients may have a broad range of neurological symptoms or signs, depending on the location and degree of central nervous system inflammation. Life expectancy for patients with MS is 5–10 years shorter than for the general population (3, 11, 12). Exposure to any disease-modifying therapy for MS is associated with a lower risk of death compared with no exposure (13). MS has a substantial negative impact on health-related quality of life (14-16). People with MS have significantly lower health-related quality of life scores than people who have other chronic diseases, such as chronic ischaemic heart disease, gastro-oesophageal reflux disease, non-insulin-dependent diabetes mellitus, or inflammatory bowel disease (17). People with MS are less likely to be employed, more likely to take time off work when they are employed, and more likely to retire early than the general population (18-20). Globally, an estimated 1 million people (unpaid spouses, partners, children, family members or friends) are involved in the overall care of people living with MS (21). Caregivers often stop working to care for the person with MS, further increasing the societal burden of the disease (22). Caregivers of people with MS also experience high levels of distress and reduced quality of life (23, 24).

Benefits

The application described the detailed process undertaken by the applicants to prioritize the medicines being proposed for EML listing from among 30 medicines used in the treatment of MS. The EML application was planned as part of a comprehensive guideline coordinated by the Multiple Sclerosis International Federation. The evidence synthesis informing the guideline process was supported by a Cochrane network meta-analysis on treatments for both progressive (25) and relapsing/remitting MS (26). The network meta-analyses were conducted with placebo as the common comparator. The network meta-analyses are in later stages of preparation for publication in the Cochrane Library. The guideline followed the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method. The guideline panel and the supporting methodological team first generated all

questions following the patient, intervention, comparison and outcome (PICO) framework and prioritized outcomes using a structured approach which included health outcome descriptors and definitions, establishing a priori all important and critical outcomes. Absolute effects were estimated across all outcomes. A summary table demonstrating the desirable and undesirable effects, net balance of effects and certainty of the evidence was created. The medicines evaluated in the network meta-analyses were ranked based on a numeric coefficient summing the values calculated for the desirable and undesirable effects. Based on the relevance of the outcomes and associated net benefit, the guideline panel was then requested to prioritize the 10 medicines with the largest net benefit, and then prioritize among these medicines those that would offer the greatest benefits taking into account the needs of special populations, such as adolescents, and pregnant or breastfeeding women. Short-listed medicines were cladribine, rituximab/ocrelizumab, dimethyl fumarate, fingolimod, interferon beta 1b/1a and glatiramer acetate. Four medicines were ultimately proposed for addition to the EML by the guideline panel. The justification for the selection of rituximab (with ocrelizumab as a therapeutic alternative), cladribine and glatiramer acetate, and summaries of evidence for benefit for each medicine are described below. Rituximab/ocrelizumab Rituximab (with ocrelizumab as a square box alternative) was considered a feasible and acceptable option in resource-constrained settings due to balance of effects, mode of administration (6-monthly infusions), and low requirements for screening and monitoring. These medicines have a low risk of rebound effect if treatment is discontinued and low discontinuation rates by people with MS. They require infusion facilities and cold storage at the health care facility. Rituximab and ocrelizumab, while contraindicated during pregnancy, may be used in pregnant women with careful timing of treatment. Rituximab and ocrelizumab have been extensively used off-label in paediatric MS. Clinical trials of ocrelizumab in children and adolescents with relapsing-remitting MS are ongoing. On-label ocrelizumab is more costly than off-label rituximab, but off-label prescribing is limited in some settings, making ocrelizumab potentially more acceptable and/or feasible in these settings. Rituximab is already listed on the WHO EML for other indications, is off-patent with many authorized biosimilar products, and is part of the WHO prequalification programme. For these reasons, rituximab was proposed as the representative of the square box grouping. Rituximab A randomized controlled trial compared rituximab with placebo in patients with relapsing-remitting MS switching from a previous disease-modifying therapy (27). There was low-certainty evidence of an appreciable benefit in the number of patients presenting with relapses at 48 weeks: absolute difference 198 fewer per 1000 (95% confidence interval (CI) 304 fewer to 17 fewer), and very low-certainty evidence of benefit in terms of the number of patients with new gadolinium-enhancing positive T1 lesions seen on magnetic resonance imaging (MRI): absolute difference 307 fewer per 1000 (95% CI 394 to 141 fewer). A non-randomized study compared rituximab with other disease modifying therapies (interferon beta or glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab) as initial treatment in patients with relapsing-remitting MS, assessing relapse and new gadolinium-enhancing positive T1 lesions seen on MRI as desirable effects (28). There was low-certainty evidence of a large effect in relapse risk over 24 months for rituximab compared with interferon beta or glatiramer acetate: absolute difference 227 fewer per 1000 (95% CI 254 to 154 fewer). There was low-certainty evidence that rituximab may result in an appreciable reduction in relapses when compared with natalizumab (absolute difference 148 fewer per 1000, 95% CI 187 to 0 fewer) and dimethyl fumarate (absolute difference 84 fewer per 1000, 95% CI 110 to 0 fewer). Efficacy data on rituximab versus other disease-modifying therapies in patients with relapsing-remitting MS switching from a previous disease-modifying therapy were evaluated in three Swedish cohort register-based studies (29-31). There was moderate-certainty evidence that rituximab showed the highest appreciable benefit in terms of risk of relapse versus interferon beta or glatiramer acetate (absolute risk difference 215 fewer patients with relapse per 1000, 95% CI 248 to 127 fewer) over a median follow-up of 24 and 18 months. There was also very low-certainty evidence of benefit for rituximab in terms of new or enlarging T2 weighted lesions seen on MRI versus fingolimod (absolute risk difference 286 fewer per 1000, 95% CI 290 to 266 fewer), over median follow up of 24 and 18 months, respectively. Other desirable effects for which rituximab showed appreciable benefit versus fingolimod were: fewer new gadolinium-enhancing positive T1 weighted lesions seen on MRI (172 fewer per 1000, 95% CI 186 to 126 fewer, very low-certainty evidence); fewer relapses (161 fewer per 1000, 95% CI 172 to 116 fewer; moderate-certainty evidence) with median follow up of 18 months; and disability versus interferon or glatiramer acetate (12 fewer per 1000, 95% CI 42 fewer to 35 more; very low-certainty evidence), with median follow up of 24 months. A randomized controlled trial conducted in the United States and Canada assessed the efficacy and safety of rituximab versus placebo as

initial treatment in patients with primary progressive MS over 24 months' follow-up (32). Both disability and frequency of relapse were reduced in patients treated with rituximab (absolute risk reduction: 75 fewer per 1000 (95% CI 158 fewer to 24 more; moderate-certainty evidence) and 13 fewer per 1000 (95% CI 28 fewer to 31 more; low-certainty evidence), respectively. Rituximab in patients with secondary progressive MS switching from a previous disease modifying therapy was assessed in two small randomized controlled trials in the Islamic Republic of Iran (33, 34), and one small case–control study in Switzerland and the Kingdom of the the Netherlands (35). One of the trials comparing rituximab with cyclophosphamide did not report any prioritized benefit outcome (34). The other trial compared rituximab with glatiramer acetate and showed a benefit on new gadolinium-enhancing positive T1 weighted MRI lesions in favour of rituximab (absolute risk difference: 28 fewer lesions per 1000, 95% CI 82 fewer to 166 more; very low-certainty evidence) over a median follow-up of 12 months (33). The non-randomized study showed a benefit on disability in patients treated with rituximab versus those treated with other disease modifying therapies (absolute risk difference 164 fewer per 1000, 95% CI 250 to 20 fewer; very low-certainty evidence) (35). Ocrelizumab No direct evidence of ocrelizumab versus placebo in patients with relapsing forms of MS was available. Two pivotal randomized controlled trials (OPERA I and OPERA II) assessed the efficacy and safety of ocrelizumab versus interferon beta 1a in this patient population (36). The OPERA studies used the calculated annualized relapse rate as the outcome measure of relapse reduction. These results were not included in the network meta-analysis performed by the applicants, which instead used as the outcome measure, the proportion of people who had or did not have a relapse within defined time periods. Refer to the ocrelizumab summary for details of the evidence from the OPERA I and OPERA II studies. One randomized controlled trial (ORATORIO) assessed the efficacy and safety of ocrelizumab versus placebo in patients with primary progressive MS (37). Ocrelizumab was associated with a benefit on disability (absolute risk difference 61 fewer per 1000, 95% CI 160 fewer to 89 more; very low-certainty evidence) and on quality of life measured using the SF-36 (physical) scale (standardized mean difference 0.04 higher; 95% CI 0.12 lower to 0.19 higher; moderate-certainty evidence) at 36 months' follow-up. Cladribine Cladribine, fingolimod and dimethyl fumarate were all considered to be feasible and acceptable options in resource-constrained settings due to the balance of effects, mode of administration (oral) and easy storage. Fingolimod requires more maintenance for screening and monitoring and has a risk of rebound of MS disease activity if access to treatment is discontinued suddenly, for example, due to unreliable supply of medicine, and it can diminish response to vaccines. Dimethyl fumarate has low requirements for screening and monitoring but has a higher discontinuation rate compared with other oral treatments. Cladribine has a short treatment period of four short courses over 2 years (although subsequent treatment may be required in some people), which is an advantage for settings where drug supply irregularities are common. Further advantages of cladribine include its allowance of family planning (because of its treatment period of four short courses over 2 years), a low risk of rebound, low requirements for screening and monitoring, a low discontinuation rate, and potentially favourable cost–effectiveness. Cladribine, while contraindicated in pregnancy, may be used in women of childbearing age with careful timing of treatment. A randomized controlled trial (CLARITY) assessed the efficacy and safety of cladribine versus placebo in patients with relapsing-remitting MS (38). Cladribine produced appreciable benefit on disability (absolute risk difference 53 fewer people developing disability per 1000, 95% CI 83 to 17 fewer; low-certainty evidence), on relapse (240 fewer per 1000, 95% CI 285 to 183 fewer; high-certainty evidence), quality of life assessed using the EQ-5D VAS (standardized mean difference (SMD) 0.19 higher, 95% CI 0.06 to 0.32 higher; moderate-certainty evidence) and the EQ-5D index (SMD 0.24 higher, 95% CI 0.11 to 0.37 higher; moderate-certainty evidence) at 24 months' follow-up. No evidence from randomized controlled trials was identified for cladribine in progressive MS. Glatiramer acetate Glatiramer acetate was considered an important treatment option mainly for special populations, as it is safe for use in pregnancy and during breastfeeding, and is used in paediatric MS. The most appropriate medicines during pregnancy are glatiramer acetate and interferon, both of which are also safe to use during breastfeeding. Glatiramer acetate was judged to have a better safety profile than interferon, and is generally more tolerated than interferons, which may cause flu-like adverse effects. Both medicines have the disadvantage of the need for frequent injections as their mode of administration and require refrigeration. While both have few screening and monitoring requirements, glatiramer acetate has the fewest requirements. Glatiramer acetate also has the advantage of no known drug interactions. Generic forms are available. Three randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in

patients with relapsing-remitting MS (39-41). Treatment with glatiramer acetate reduced: disability at 24 months (absolute risk difference 49 fewer per 1000, 95% CI 73 to 21 fewer; very low-certainty evidence); relapse at 24 months (82 fewer per 1000, 95% CI 122 to 36 fewer; very low-certainty evidence); and new MRI gadolinium-enhancing positive T1 lesions at 24 months (135 fewer per 1000, 95% CI 191 to 53 fewer; very low-certainty evidence). Two randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in patients with primary progressive MS (42, 43). Treatment with glatiramer acetate reduced disability at 24 months (absolute risk difference 68 fewer per 1000, 95% CI 174 fewer to 85 more; very low-certainty evidence).

Harms

Rituximab Two randomized controlled trials assessed the safety of rituximab in patients switching from a previous disease modifying therapy in relapsing-remitting MS (27) and primary progressive MS (32) and showed a higher frequency of serious adverse events versus placebo (pooled absolute risk difference 21 more adverse events per 1000, 95% CI 36 fewer to 100 more), including common infections (19 more per 1000, 95% CI 67 fewer to 96 more) and infusion reactions within 24 hours of the first infusion (435 more per 1000, 95 % CI 344 more to 513 more). Conversely, death, cancer and infusion reaction after the second infusion were less frequent in patients treated with rituximab – absolute differences: six fewer deaths per 1000, 95% CI 10 fewer to 24 more); three fewer cancers per 1000, 95% CI 10 fewer to 28 more); and 28 fewer infusion reactions per 1000, 95% CI 151 fewer to 266 more). A Swedish non-randomized study compared rituximab with other disease modifying therapies (interferon or glatiramer acetate, dimethyl fumarate, fingolimod, natalizumab) in treatment-naive patients with relapsing-remitting MS (28). Rituximab versus interferon or glatiramer acetate produced fewer serious adverse effects (grade 3 or 4): four fewer serious adverse effects per 1000, 95% CI 27 fewer to 68 more; very low-certainty evidence. It also produced fewer serious adverse effects than natalizumab (46 fewer per 1000, 95% CI 71 fewer to 45 more; very low-certainty evidence). In comparison with dimethyl fumarate, more patients treated with rituximab experienced serious adverse effects (22 more per 1000, 95% CI 8 fewer to 227 more). No absolute difference in estimates on serious adverse effects could be drawn with fingolimod, given the extremely wide 95% CI of the odds ratio (0.07 to 26.21). For opportunistic infections, the point estimate versus natalizumab favoured rituximab (17 fewer infections per 1000, 95% CI 20 fewer to 45 more; very low-certainty evidence). Six retrospective non-randomized studies reported undesirable effects of rituximab versus other disease-modifying therapies in patients with relapsing-remitting MS switching treatment (29-31, 44-46). Rituximab a lower frequency of serious adverse effects when compared with fingolimod and natalizumab (17 fewer per 1000; 95% CI 24 fewer to 27 more, and 29 fewer per 1000; 95% CI 38 fewer to 111 more, respectively, very low certainty evidence). Similarly, the frequency of common infections was lower among patients treated with rituximab compared to those on ocrelizumab (61 fewer per 1000; 95% CI 62 fewer to 36 fewer; very low-certainty evidence) and higher than interferon or glatiramer acetate, fingolimod or natalizumab: 24 more per 1000, 95% CI 4 to 53 more; 14 more per 1000, 95% CI 5 fewer to 39 more; and 27 more per 1000, 95% CI 4 to 59 more, respectively; very low-certainty evidence in all comparisons. Cancer was less frequent in patients treated with rituximab compared with patients treated with fingolimod and natalizumab: 7 fewer per 1000, 95% CI 11 fewer to 1 more; and 3 fewer per 1000, 95% CI 6 fewer to 3 more, respectively; very low-certainty evidence in both comparisons. Infusion reactions within 24 hours of the first infusion were less common with rituximab than ocrelizumab (6 fewer per 1000, 95% CI 12 fewer to 35 more; very low-certainty evidence). Relative estimates on mortality were too imprecise (few events, very wide CIs) to allow reporting absolute differences. Two small randomized controlled trials assessed safety of rituximab compared with glatiramer acetate (33) and cyclophosphamide (34) in patients with progressive MS switching from a previous disease-modifying therapy. Their results were not pooled with those of the non-randomized studies. Common infections were more frequent in patients treated with rituximab than those on glatiramer acetate (45 more per 1000, 95% CI 17 fewer to 405 more; very low-certainty evidence) and less frequent than in patients on cyclophosphamide (204 fewer per 1000, 95% CI 337 fewer to 26 more; very low-certainty evidence). Ocrelizumab No direct evidence of safety of ocrelizumab versus placebo in patients with relapsing MS was available. Safety data of ocrelizumab versus placebo in patients with primary progressive MS from the ORATORIO trial (37) showed that serious adverse events were more common in patients treated with ocrelizumab (18 more per 1000, 95% CI 99 fewer to 97 more; very low-certainty evidence), as was treatment

discontinuation due to adverse events (8 more discontinuations per 1000, 95% CI 15 fewer to 57 more; moderate-certainty evidence) and death (4 more per 1000, 95% CI 3 fewer to 65 more; very low-certainty evidence). Cladribine From the CLARITY trial of cladribine versus placebo in patients with relapsing-remitting MS (38), mortality was not higher (0 fewer per 1000, 95% CI 2 fewer to 12 more; moderate-certainty evidence), while serious adverse events were more common with cladribine (27 more per 1000, 95% CI 15 fewer to 92 more; very low-certainty evidence). Treatment discontinuation due to adverse events was also higher with cladribine (18 more per 1000, 95% CI 26 fewer to 128 more; low-certainty evidence). No evidence from randomized controlled trials was identified for cladribine in progressive MS. Glatiramer acetate Three randomized controlled trials provided direct evidence of glatiramer acetate versus placebo in patients with relapsing-remitting MS (39-41), showing similar mortality (1 fewer per 1000, 95% CI 2 fewer to 4 more; low-certainty evidence) and serious adverse events (4 fewer per 1000, 95% CI 24 fewer to 20 more; low-certainty evidence). More patients on glatiramer acetate discontinued treatment due to adverse events (22 more per 1000, 95% CI 1 to 51 more; moderate-certainty evidence). One randomized controlled trial compared glatiramer acetate with placebo in patients with progressive MS (43). Compared with placebo, serious adverse events were more frequent with glatiramer acetate (9 more per 1000, 95% CI 9 fewer to 55 more; low-certainty evidence), as was treatment discontinuation due to adverse events (36 more per 1000, 95% CI 6 to 108 more; moderate-certainty evidence). Mortality was lower in the glatiramer acetate group (16 fewer per 1000, 95% CI 20 to 0 fewer; moderate-certainty evidence).

Cost / cost effectiveness

Median prices (cost per patient per year in US$), and price ranges for the proposed medicines based on 18 countries across different income settings were identified in the application (Table 8, refer TRS 1049). Ex-factory price was retrieved whenever available. The dynamic nature and wide variations observed among countries may depend on context-dependent price components such as the local health system, supply chain, regulatory measures, ability and willingness to negotiate, and non-context-specific factors, such as market fluctuations, availability of alternatives, and available follow-on products (47). The information is also unreliable as national drug agency price databases are often unavailable, or their access may be restricted due to pharmaceutical companies requesting non-disclosure agreements. Negotiations between the local ministry of health and drug companies may end in substantial discounts, up to > 70%, and are usually confidential. Evidence on cost–effectiveness of disease modifying therapies included in the application was retrieved through a systematic search of economic analysis studies on all available disease-modifying therapies, but these data have several limitations when used to inform clinical practice recommendations. Most economic analyses are available on recently marketed drugs and most studies are performed in high-income settings. Therefore, their results may not be transferable to countries with a different income level and willingness-to-pay threshold. Most studies are funded by the company producing the medicine being assessed, thus their results should be interpreted with caution. Moreover, the results of economic analysis studies cannot be quantitatively pooled in a meta-analysis, and their methodological quality is hard to assess due to the lack of established evaluation criteria. In some cases, parameters used by the analysis authors to assess clinical effectiveness and cost vary, producing inconsistent and sometimes conflicting results. Most of the studies identified focused on specific direct costs (e.g. medicine price) while other direct costs (e.g. for administration, monitoring of MS course and activity, relapse treatment, and adverse event management), as well as indirect costs (e.g. loss of productivity, absenteeism, early retirement, and travel costs to reach health care facilities) are often not considered in economic modelling. Among the studies identified in the application, several suggested a superiority of cladribine over other disease-modifying therapies for cost–effectiveness, but they were all funded by the company producing the medicine, so their results should be interpreted with caution. Similar considerations can be made for studies of glatiramer acetate and ocrelizumab. An independent cost–effectiveness analysis from the Islamic Republic of Iran found rituximab to be cost-effective when compared with natalizumab in the treatment of relapsing-remitting MS (48).

WHO guidelines

WHO guidelines for the treatment of MS are not currently available.

Availability

Cladribine, glatiramer acetate and ocrelizumab are approved by stringent regulatory authorities including in Australia, Canada, European Union, Switzerland, the United Kingdom and the United States for the treatment of relapsing-remitting MS. Only ocrelizumab has regulatory approval for treatment of progressive forms of MS. Rituximab is used off-label for MS but has regulatory approval for other indications. The availability of the medicines proposed in this application varies between regions and country-income classifications. Survey data on global use of the proposed medicines from the Multiple Sclerosis International Federation Atlas are shown in Table 9 (refer TRS 1049) (49). An evaluation of 137 national essential medicines lists (50) found the following information. • Rituximab is included in 41 of the national EMLs assessed, however it was not possible to determine if the listing is for the indication of MS. • Ocrelizumab is not included in any of the national EMLs assessed. • Cladribine is included in national EMLs of 16/137 countries, however it was not possible to determine whether this is the oral or intravenous formulation, nor if the listing is for the indication of MS. • Glatiramer acetate is included in 19 of the national EMLs assessed. Rituximab 500 mg/50 mL injection was produced by three manufacturers (Celltrion Inc., Sandoz GmbH and Roche Products Limited) at the time for the application and has been prequalified by WHO under the pilot programme for prequalification of biotherapeutics. In line with prequalification processes, these products were prequalified for the indications for which rituximab is included on the EML, namely oncology indications.

Other considerations

The product patents on rituximab and glatiramer acetate have expired, and several biosimilar and generic products have been approved and are used in several countries. Secondary patents have been granted in some jurisdictions, but they may not prevent entry of follow-on products. Cladribine compound patents expired in 2005. Secondary patent applications on the treatment regimen for MS, expected expiry in 2025, were filed in several countries and granted (e.g. in Brazil, China, Russia, South Africa, Ukraine, United States and Europe). In India the equivalent application was abandoned. A secondary patent for oral formulation of cladribine has been granted in several countries including Brazil, China, India, South Africa, United States, and also in Europe. Patents originally expiring in 2024 have been extended by way of Supplementary Protection Certificates in Europe until 2029. A United States patent owned by Merck for treating progressive forms of MS was recently granted with equivalents pending in several countries; the expected expiry is 2041. Ocrelizumab is protected by a product patent expiring in 2023, sometimes extended by patent term extensions or supplementary protection certificates until 2028 or 2029. It is unlikely follow-on products can enter the market before expiry. Secondary patents have been filed and granted, which are expiring in 2029 or possibly as late as 2036. The Department of Mental Health and Substance Use provided comments on two applications submitted for Expert Committee consideration for disease-modifying therapies for MS – this application and an application for ocrelizumab submitted by the patent holder, Roche. The technical department supported the inclusion of disease-modifying therapies for MS on the EML, highlighting that the proposals were well aligned with the mandate of the intersectoral global action plan on epilepsy and other neurological disorders (1), which includes a strategic objective to “provide effective, timely and responsive diagnosis, treatment, and care” for people with neurological disorders such as MS.

1. Intersectoral global action plan on epilepsy and other neurological disorders 2022–2031. Geneva: World Health O rganization; 2021 (https://apps.who.int/iris/handle/10665/371495, accessed 6 October 2023).
2. The selection and use of essential medicines. Report of the WHO Expert Committee, 2019 (including the 21st WH O Model List of Essential Medicines and the 7th WHO Model List of Essential Medicines for Children). Geneva: World Health Organization; 2019 (WHO Technical Report Series, No. 1021; https://apps.who.int/iris/handle/10665/330668, accessed 6 October 2023).
3. Compston A, Coles A. Multiple sclerosis. Lancet. 2008;372(9648):1502–17.
4. Nylander A, Hafler DA. Multiple sclerosis. J Clin Invest. 2012;122(4):1180–8.
5. Global Burden of Disease database [internet]. Seattle, WA: Institute for Health Metrics and Evaluation; 2019 (http s://vizhub.healthdata.org/gbd-results/, accessed 6 October 2023).
6. Atlas of MS, 3rd edition. Part 1. Mapping multiple sclerosis around the world: key epidemiology findings. London: Multiple Sclerosis International Federation; 2020 (https://www.msif.org/wp-content/uploads/2020/10/Atlas-3rd-Editio n-Epidemiology-report-EN-updated-30-9-20.pdf, accessed 6 October 2023).
7. Walton C, King R, Rechtman L, Kaye W, Leray E, Marrie RA, et al. Rising prevalence of multiple sclerosis worldwid

e: insights from the Atlas of MS, third edition. Mult Scler. 2020;26(14):1816–21.
8. Ascherio A, Munger KL. Epidemiology of multiple sclerosis: from risk factors to prevention-an update. Semin Neurol. 2016;36(2):103–14.
9. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology. 2014;83(3):278–86.
10. Frischer JM, Bramow S, Dal-Bianco A, Lucchinetti CF, Rauschka H, Schmidbauer M, et al. The relation between inflammation and neurodegeneration in multiple sclerosis brains. Brain. 2009;132(Pt 5):1175–89.
11. Kingwell E, van der Kop M, Zhao Y, Shirani A, Zhu F, Oger J, et al. Relative mortality and survival in multiple sclerosis: findings from British Columbia, Canada. J Neurol Neurosurg Psychiatry. 2012;83(1):61–6.
12. Brønnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with multiple sclerosis. Brain. 2004;127(Pt 4):844–50.
13. Ng HS, Zhu F, Kingwell E, Yao S, Ekuma O, Evans C, et al. Disease-modifying drugs for multiple sclerosis and association with survival. Neurol Neuroimmunol Neuroinflamm. 2022;9(5):e200005.
14. Nortvedt MW, Riise T, Myhr KM, Nyland HI. Quality of life in multiple sclerosis: measuring the disease effects more broadly. Neurology. 1999;53(5):1098–103.
15. Orme M, Kerrigan J, Tyas D, Russell N, Nixon R. The effect of disease, functional status, and relapses on the utility of people with multiple sclerosis in the UK. Value Health. 2007;10(1):54–60.
16. Zwibel HL, Smrtka J. Improving quality of life in multiple sclerosis: an unmet need. Am J Manag Care. 2011;17(Suppl 5 Improving):S139–45.
17. Kobelt G, Kasteng F. Access to innovative treatments in multiple sclerosis in Europe. A report prepared for the European Federation of Pharmaceutical Industry Associations (EFPIA). Brussels: European Federation of Pharmaceutical Industry Associations; 2009.
18. Bishop M, Rumrill PD. Multiple sclerosis: etiology, symptoms, incidence and prevalence, and implications for community living and employment. Work. 2015;52(4):725–34.
19. Doogan C, Playford ED. Supporting work for people with multiple sclerosis. Mult Scler. 2014;20(6):646–50.
20. Schiavolin S, Leonardi M, Giovannetti AM, Antozzi C, Brambilla L, Confalonieri P, et al. Factors related to difficulties with employment in patients with multiple sclerosis: a review of 2002–2011 literature. Int J Rehabil Res. 2013;36(2):105–11.
21. Maguire R, Maguire P. Caregiver burden in multiple sclerosis: recent trends and future directions. Curr Neurol Neurosci Rep. 2020;20(7):18.
22. Hategeka C, Traboulsee AL, McMullen K, Lynd LD. Association of unemployment and informal care with stigma in multiple sclerosis: evidence from the survey on living with neurological conditions in Canada. Int J MS Care. 2019;21(5):214–25.
23. McKenzie T, Quig ME, Tyry T, Marrie RA, Cutter G, Shearin E, et al. Care partners and multiple sclerosis: differential effect on men and women. Int J MS Care. 2015;17(6):253–60.
24. Figved N, Myhr K-M, Larsen J-P, Aarsland D. Caregiver burden in multiple sclerosis: the impact of neuropsychiatric symptoms. J Neurol Neurosurg Psychiatry. 2007;78(10):1097–102.
25. Ridley B, Minozzi S, Gonzalez-Lorenzo M, Del Giovane C, Filippini G, Peryer G, et al. Immunomodulators and immunosuppressants for progressive multiple sclerosis: a network meta-analysis (protocol). Cochrane Database Syst Rev. 2022(11):CD015443.
26. Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015(9):CD011381.
27. Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676–88.
28. Granqvist M, Boremalm M, Poorghobad A, Svenningsson A, Salzer J, Frisell T, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. JAMA Neurol. 2018;75(3):320–7.
29. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Björck A, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol. 2016;79(6):950–8.
30. Boremalm M, Juto A, Axelsson M, Novakova L, Frisell T, Svenningsson A, et al. Natalizumab, rituximab and fingolimod as escalation therapy in multiple sclerosis. Eur J Neurol. 2019;26(8):1060–7.
31. Spelman T, Frisell T, Piehl F, Hillert J. Comparative effectiveness of rituximab relative to IFN-β or glatiramer acetate in relapsing-remitting MS from the Swedish MS registry. Mult Scler. 2018;24(8):1087–95.
32. Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009;66(4):460–71.
33. Cheshmavar M, Mirmosayyeb O, Badihian N, Badihian S, Shaygannejad V. Rituximab and glatiramer acetate in secondary progressive multiple sclerosis: a randomized clinical trial. Acta Neurol Scand. 2021;143(2):178–87.
34. Etemadifar M, Ghourchian S, Mahinparvar N, Salari M, Etemadifar F, Nikanpour Y, et al. Cyclophosphamide versus rituximab in progressive forms of multiple sclerosis. Acta Med Iran. 2019;57(8):484–91.
35. Naegelin Y, Naegelin P, Felten S, Lorscheider J, Sonder J, Uitdehaag BMJ, et al. Association of rituximab treatment with disability progression among patients with secondary progressive multiple sclerosis. JAMA Neurol. 2019;76(3):274–81.
36. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung H-P, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med. 2017;376(3):221–34.
37. Wolinsky JS, Montalban X, Hauser SL, Giovannoni G, Vermersch P, Bernasconi C, et al. Evaluation of no evidence of progression or active disease (NEPAD) in patients with primary progressive multiple sclerosis in the ORATORIO trial. Ann Neurol. 2018;84(4):527–36.
38. Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sorensen P, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):416–26.
39. Bornstein MB, Miller A, Slagle S, Weitzman M, Crystal H, Drexler E, et al. A pilot trial of Cop 1 in exacerbating-remitting multiple sclerosis. N Engl J Med. 1987;317(7):408–14.
40. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R, Group GS. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013;73(6):705–13.

41. Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis: results of a phase III multicenter, double-blind placebo-controlled trial. The Copolymer 1 Multiple Sclerosis Study Group. Neurology. 1995;45(7):1268–76.
42. Bornstein MB, Miller A, Slagle S, Weitzman M, Drexler E, Keilson M, et al. A placebo-controlled, double-blind, randomized, two-center, pilot trial of Cop 1 in chronic progressive multiple sclerosis. Neurology. 1991;41(4):533–9.
43. Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007;61(1):14–24.
44. Evertsson B, Hoyt T, Christensen A, Nimer FA, Foley J, Piehl F. A comparative study of tolerability and effects on immunoglobulin levels and CD19 cell counts with ocrelizumab vs low dose of rituximab in multiple sclerosis. Mult Scler J Exp Transl Clin. 2020;6(4):2055217320964505.
45. Luna G, Alping P, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol. 2020;77(2):184–91.
46. Alping P, Askling J, Burman J, Fink K, Fogdell-Hahn A, Gunnarsson M, et al. Cancer risk for fingolimod, natalizumab, and rituximab in multiple sclerosis patients. Ann Neurol. 2020;87(5):688–99.
47. Moon S, Mariat S, Kamae I, Pedersen HB. Defining the concept of fair pricing for medicines. BMJ. 2020;368:l4726.
48. Rezaee M, Morowvat MH, Poursadeghfard M, Radgoudarzi A, Keshavarz K. Cost-effectiveness analysis of rituximab versus natalizumab in patients with relapsing remitting multiple sclerosis. BMC Health Serv Res. 2022;22(1):118.
49. Atlas of MS, 3rd edition. Part 2: Clinical management of multiple sclerosis around the world: key findings about the diagnosis and clinical management of MS. London: Multiple Sclerosis International Federation; 2020 (https://www.msif.org/wp-content/uploads/2021/05/Atlas-3rd-Edition-clinical-management-report-EN-5-5-21.pdf, accessed 6 October 2023).
50. Global essential medicines [internet]. Geneva: World Health Organization; 2019 (https://global.essentialmeds.org/dashboard/countries, accessed 6 October 2023).

