Ocrelizumab

REJECTED

The Expert Committee, after evaluation, declines to list the medicine proposed in the application.
The Model List of Essential Medicines reports reasons that Committee Members have identified for denying listing.

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

EMLc | ATC codes: L04AG08

Indication	Relapsing-remitting multiple sclerosis ICD11 code: 8A40.0
INN	Ocrelizumab
Medicine type	Biological agent
List type	Complementary
Formulations	**Parenteral > General injections > IV:** 30 mg per mL in 10 mL vial
EML status history	Application rejected in 2019 (TRS 1021)
Sex	All
Age	Also recommended for children
Therapeutic alternatives	The recommendation is for this specific medicine
Patent information	Read more about patents.
Wikipedia	Ocrelizumab
DrugBank	Ocrelizumab

Expert Committee recommendation

The Expert Committee acknowledged the important public health burden of MS and the need for effective and affordable treatments and noted the large number of supporting letters that were received in relation to the application. The Committee appreciated the approach taken in the application to propose a limited number of essential medicines for MS, but noted that the superiority of the presented medicines over other therapeutic options in terms of benefits, harms and affordability did not clearly emerge. The Committee noted that some commonly used treatments were not included (e.g. azathioprine, natalizumab, dimethyl fumarate, cladribine) or were not given full consideration (rituximab) and the reasons for their exclusion were not clear. The Committee also noted ongoing development in international MS guidelines and would welcome a revised application for EML inclusion in the future that considers the relative roles of all available medicines for MS. In particular, the Committee noted the evidence presented in the application in relation to rituximab. The Committee agreed that rituximab could have a relevant clinical role in treatment of MS, and recommended that any future application should include evidence for rituximab versus active comparators, not just placebo. The Committee, therefore, did not recommend the addition of glatiramer acetate, fingolimod and ocrelizumab to the Model Lists at this time, and would welcome a revised application which comprehensively reviews the relative roles of relevant available medicines for MS.

Background

The application requested the addition of glatiramer acetate, fingolimod and ocrelizumab to the complementary

list of the EML and EMLc for use in the treatment of multiple sclerosis. In 2015, the Expert Committee reviewed an application requesting addition of azathioprine to the EML for the treatment of multiple sclerosis (MS). The Committee acknowledged the significant public health burden of MS but noted the availability of a number of well-established and more recent immunomodulating medicines for this condition. The Committee therefore recommended that a comprehensive review be undertaken of all medicines used for the management of relapsing–remitting and other forms of MS for future consideration (1). The Multiple Sclerosis International Federation (MSIF) is a non-state actor in official relations with WHO. They convened a taskforce of global experts in MS research and care to submit an application for disease-modifying therapies (DMTs) for the treatment of MS to be included on the EML. All approved DMTs used for the treatment of MS were summarized by comparative effectiveness in a variety of clinical settings based on the recently published ECTRIMS/ EAN (European Committee for Treatment and Research for Multiple Sclerosis/ European Association of Neurology) Guideline on the pharmacological treatment of people with MS (2). A comparison was also made with the American Academy of Neurology guidelines on DMTs in MS (3). Of the multiple therapies used for treating MS, the application prioritized three medications to be included on the EML. Prioritization was based on their efficacy/safety profiles, tolerability/liveability, monitoring needs, route of administration, licensed use in paediatric-onset and primary progressive MS, safety profile in pregnancy, and availability of generic and/or biosimilar substitutes.

Public health relevance

Multiple sclerosis is an immune-mediated disorder of the central nervous system (grey and white matter) characterized by inflammation, demyelination and degenerative changes including neuroaxonal loss and progressive brain and spinal cord atrophy. Approximately 85% of those with MS initially experience relapses and remissions of neurological symptoms, (relapsing–remitting MS, RRMS), with relapses often associated with new areas of central nervous system inflammation. Gradual worsening in this population, with or without additional inflammatory events, is known as secondary progressive MS. Progressive changes can occur at any time in the disease course, but usually become more prominent over time. Approximately 15% of people diagnosed with MS have a progressive course from disease onset (primary progressive MS). Some with primary progressive MS may have typical relapses later in their disease course, after a progressive course has been established (4, 5). In 2013, there were more than 2.3 million people with MS worldwide (6, 7). The incidence and prevalence of MS are rising, with studies showing significantly larger numbers than was previously estimated (8–15). Women are disproportionally affected, with prevalence in females two to three times that in males (7, 16). Although the cause is not fully understood, MS is considered to have complex causality blending genetic risk and environmental factors. People can be diagnosed throughout the age range, though MS is most often diagnosed between the ages of 20 and 50 years. Onset may also occur in childhood, and it is estimated that 3% to 10% of all individuals with MS experience their first attack prior to age 18 years (17). The incidence of paediatric-onset MS in North American and European studies has been reported to be between 0.13 to 0.6 cases per 100 000 children (18). Symptoms of MS negatively impact functional abilities and quality of life, and often include overwhelming fatigue, mood and cognitive changes, mobility impairment, sensory impairment, visual disturbances, sexual dysfunction, and impaired bowel and bladder control. People with MS report lower health-related quality of life compared to other populations – including those with other chronic illnesses. The prevalence of depression is estimated to be 70% in people with MS (19). The goal of treatment is to reduce the long-term burden of the disease, i.e. to delay disability progression and to prevent secondary progressive MS (20). Quality of life and the socioeconomic burden of MS are closely linked to disability, therefore, delaying and preventing disability worsening will have a major impact for individuals with the disease and for society (21).

Benefits

Glatiramer acetate Three trials (3217 patients) compared glatiramer acetate with placebo in patients with RRMS with follow up ranging from 52 to 104 weeks (22–24). Compared to placebo, glatiramer acetate lowered annualized relapse rates for follow ups of 52–96 weeks (mean difference (MD) −0.14, 95%CI −0.21 to −0.06, moderate quality evidence, n=2117, two studies) and resulted in more patients free from relapse at one to two years follow up (RR 1.17, 95%CI 1.10 to 1.24, moderate quality evidence, n=2360, three studies). Glatiramer

acetate was also shown to result in a lower number of cumulative gadolinium-enhancing (GAD) lesions (MD −0.73, 95%CI −1.15 to −0.31, high quality evidence, n=1325, one study) and new or newly enlarging T2 lesions at 6 and 12 months follow up (MD −1.94, 95%CI −3.03 to −0.85, high quality evidence, n=1325, one study)). Low quality evidence showed a non-statistically significant effect on disability at two years follow up (RR 0.86, 95%CI 0.66 to 1.11, n=964, two studies). Four trials compared glatiramer acetate to interferon in patients with RRMS (25–28). At two years' follow up, the number of participants free from relapse did not significantly differ (RR 0.98, 95%CI 0.90 to 1.06, moderate quality evidence, n=2175, 3 studies), nor did extent of disability worsening (RR 1.07, 95%CI 0.83 to 1.31, one study). One trial (970 patients) compared glatiramer acetate to placebo for patients with primary-progressive MS (29). There was a non-significant effect on the number of participants with disability worsening (RR 0.87, 95%CI 0.75 to 1.02) and longer time to disability worsening (HR 0.87, 95%CI 0.71 to 1.07) in the glatiramer acetate group. Fingolimod Two trials compared fingolimod with placebo in patients with RRMS, with two years follow up (30, 31). A larger proportion of patients were free from relapse at two years in the fingolimod arm (RR 1.44, 95%CI 1.28 to 1.63, moderate quality evidence, n=2355). The annualized relapse rate was also lower in the fingolimod arm (MD −0.21, 95%CI −0.25 to −0.16, moderate quality evidence). Fingolimod-treated patients had a lower risk of disability worsening compared to placebo (RR 0.71, 95%CI 0.56 to 0.90, moderate quality evidence, n=2355). Patients also had fewer new or newly enlarged T2 lesions (RR 2.16, 95%CI 1.77 to 2.63, moderate quality evidence, n=1192) and fewer GAD lesions (MD −0.87, 95%CI −1.10 to −0.64, moderate quality evidence, n=1216, two studies) at two years follow up. According to one study, fingolimod reduced percent change in brain volume at one to two years follow up (MD 0.3, 95%CI 0.16 to 0.44, moderate quality evidence, n=685). One trial compared fingolimod with interferon in patients with RRMS (32). Moderate quality evidence showed that participants in the fingolimod arm had lower annualized relapse rates (MD −0.17, 95%CI −0.26 to −0.08, n=860), and more participants were free from relapse at one year (RR 1.19, 95%CI 1.11 to 1.29, n=860) than the interferon group. Fingolimod was also associated with fewer new or newly enlarged T2 lesions (MD −0.90, 95%CI −1.62 to −0.18, n=733) and GAD lesions (MD −0.28, 95%CI −0.50 to −0.06, n=728). There was no significant difference in extent of disability progression between fingolimod and interferon in the trial. A Phase III trial investigated the safety and efficacy of fingolimod versus interferon beta-1a, in 215 children and adolescents (ages 10 to 17) with MS. Fingolimod significantly reduced annualized relapse rates by 82% (absolute difference, 0.55; 95%CI 0.36 to 0.74; relapses RR 0.18, 95%CI 0.11 to 0.30) over a period of up to two years compared to interferon beta-1a; reduced the number of new or newly enlarged T2 lesions up to 24 months by 53% (RR 0.47, 95%CI 0.36 to 0.62) and reduced the average number of gadolinium-enhancing T1 (Gd+) lesions per scan at 24 months by 66.0% (RR 0.34, 95%CI 0.22 to 0.54). Fingolimod was associated with a higher rate of serious adverse events (16.8% vs 6.5%) (33). One trial (970 participants) compared fingolimod with placebo in patients with primary-progressive MS (34). There was no difference in disability progression at 156 weeks follow up between fingolimod or placebo (RR 0.93, 95%CI 0.80 to 1.08, moderate quality evidence). The adjusted annualized relapse rate was 0.12 with fingolimod and 0.67 with interferon beta-1a (absolute difference, 0.55 relapses; relative difference, 82%; P<0.001). The key secondary end point of the annualized rate of new or newly enlarged lesions on T2-weighted magnetic resonance imaging (MRI) was 4.39 with fingolimod and 9.27 with interferon beta-1a (absolute difference, 4.88 lesions; relative difference, 53%; P<0.001). Adverse events, excluding relapses of multiple sclerosis, occurred in 88.8% of patients who received fingolimod and 95.3% of those who received interferon beta-1a. Serious adverse events occurred in 18 patients (16.8%) in the fingolimod group and included infection (in four patients) and leukopenia (in two patients). Six patients had convulsions. Serious adverse events occurred in seven patients (6.5%) in the interferon beta-1a group and included infection (in two patients) and supraventricular tachycardia (in one patient). Ocrelizumab A Phase II trial compared ocrelizumab (low and high dose) and placebo in patients with RRMS. At the end of the 24 weeks participants in both ocrelizumab groups had lower numbers of active brain lesions compared to the placebo group (89%, 95%CI 68 to 97, lower in low dose ocrelizumab group and 96%, 95%CI 89 to 99, lower in high dose ocrelizumab group). Annualized relapse rates over the 24 weeks were 0.13 (95%CI 0.03 to 0.29) in the low dose ocrelizumab group and 0.17 (95%CI 0.05 to 0.35) in the high dose ocrelizumab group compared to the 0.64 rate (95%CI 0.43 to 0.94) of the placebo group. Findings also showed that both doses of ocrelizumab were effective in reducing MRI and clinical disease activity (35). Two Phase III clinical trials, OPERA I and OPERA II, compared the effects of ocrelizumab (600 mg every 24 weeks) with interferon beta-1b (44 µg three times a week) for 96 weeks. Clinical

outcomes from 1656 participants show significantly reduced annualized relapse rates with ocrelizumab compared to interferon beta-1a at two years (MD −0.13, 95%CI −0.18 to −0.08) thus meeting its primary endpoint. Secondary outcomes showed ocrelizumab had lower rate of disability progression. For the total trial period of 96 weeks, the rate of disability progression at 24 weeks was 6.9% vs 10.5% in the ocrelizumab and interferon beta-1a groups, respectively (HR 0.60; 95%CI 0.43 to 0.84). Patients in the ocrelizumab group also had fewer GAD lesions (36). One trial compared ocrelizumab to placebo in patients with primary progressive MS. The ocrelizumab group had a greater time to disability progression at 120 weeks follow up when confirmed at both 12 weeks (HR 0.76, 95%CI 0.59 to 0.98, high quality evidence, n=732) and 24 weeks (HR 0.75, 95%CI 0.58 to 0.97, high quality evidence, n=732) (37). Rituximab A 2013 Cochrane systematic review found one trial comparing rituximab to placebo in 104 adult patients with RRMS (38). The mean number of total GAD lesions, the primary endpoint of this double-blind Phase II trial, was significantly decreased in patients receiving rituximab after 12, 16, 20 and 24 weeks (−5.0, 95%CI −9.99 to −0.01). The proportion of patients with relapses was significantly reduced in the rituximab group, both after 24 weeks (14.5% vs 34.3% in the placebo group; p=0.02) and 48 weeks (20.3% vs 40.0%, p=0.04) (39). A Phase II open-label study of 26 patients with RRMS receiving rituximab at baseline and six months found that mean annualised relapse rate reduced from 1.27 to 0.23, and mean number of GAD lesions reduced from 1.31 to 0.05 at week 48 and 0.0 at week 72. Mean number of new or newly enhancing T2 lesions also decreased from 0.92 at week 4 to 0.0 at week 72 (40). A randomized controlled trial (439 participants) compared rituximab versus placebo in patients with primary progressive MS (41). Patients were randomized (2:1) to receive two intravenous doses (two weeks apart) of rituximab (n=292) or placebo (n=147) infusions every 24 weeks, for 96 weeks. Results showed that fewer in the rituximab group (30.2%) experienced 12 weeks confirmed disease progression during 96 weeks compared to 38.5% in the placebo group, but the difference did not reach statistical significance (p=0.14). However, in a predefined sub-analysis, rituximab showed a significant effect in patients with active MRI lesions or aged less than 51 years. This effect was comparable with the effect seen in the ocrelizumab trial, which only included patients below the age of 55. Real-world data on treatment with rituximab in MS was available from a study that examined the disease course of 822 MS patients, 557 with RRMS, 198 with secondary progressive MS and 67 with primary progressive MS, who were followed for a mean duration of 22 months (42). RRMS patients treated with rituximab had a yearly relapse rate of 0.044 during the study period. In total, 5.2% of the patients stopped treatment because of side-effects or disease activity. The ratio of GAD lesions per MRI dropped significantly from approximately three months after treatment initiation, and was in total 0.054, present in 2.2% of MRIs. Moreover, the registry data suggest that the treatment efficacy of rituximab in RRMS could exceed the effect of fingolimod, dimethyl fumarate and beta-interferons. In addition, adherence was higher and side-effects were comparable to all other drugs (43, 44).

Harms

The application presented a summary description of adverse events associated with glatiramer acetate, fingolimod and ocrelizumab, and their associated frequencies, as reported in the respective approved prescribing information documents. Common and very common adverse events associated with glatiramer acetate include injection site reactions, lipoatrophy, vasodilation, rash, dyspnoea, chest pain and lymphadenopathy. Common and very common adverse events associated with fingolimod include headache, influenza, diarrhoea, back pain, elevated liver enzymes, cough, first-dose bradycardia, macular oedema, lymphopenia and bronchitis. Common and very common adverse events associated with ocrelizumab include infusion reactions and infections. Ocrelizumab has also been associated with a possible increased risk of malignancies.

Additional evidence

Glatiramer acetate A 2016 Cochrane systematic review of six trials (2904 participants) compared the safety and efficacy of glatiramer acetate and beta-interferons (45). Both medicines showed similar clinical efficacy at 24 months (three studies) for number of participants with relapse (RR 1.04, 95%CI 0.87 to 1.24) or confirmed progression (RR 1.11, 95%CI 0.91 to 1.35). At 36 months, results from a single study suggested that relapse rates were higher in the IFN group than in the GA group (RR 1.40, 95%CI 1.13 to 1.74). However, greater and faster reduction in MRI lesion load accrual was observed in IFN-treated compared with GA-treated participants with MS

(MD for T2 weighted lesion volume −0.58, 95%CI −0.99 to −0.18). Reviewers interpretation of overall evidence quality was cautious: the number of studies and participants was limited, the heterogeneity among studies was high and the clinical relevance of scales to measure disease progression was considered doubtful. The number of participants who withdrew from or dropped out of the study because of adverse events was available for four studies (2685 participants; 93%). No differences were found between the two treatment groups (RR 0.95, 95%CI 0.64 to 1.40). Results were similar for severe adverse events (RR 0.99, 95%CI 0.63 to 1.56). A 2018 network meta-analysis including direct and indirect evidence, including 24 trials published between 1987 and 2015, yielded a more precise estimate of effectiveness for both interferon beta-1a once a week versus placebo (HR 0.73, 95%CI 0.53 to 1.00) and glatiramer acetate (HR 0.76, 95%CI 0.60 to 0.97) at three months (46). There was little evidence of superiority of one drug over another but ranking of the medicines suggested that interferon beta-1a three times weekly had the highest cumulative probability of superiority. Interpretation of these findings should take into consideration the short length of follow up, the high risk of bias across studies, and the potential differences among trials that may act as effect modifiers and introduce bias in the network meta-analysis. This review also considered discontinuation due to adverse events, at different follow up times. Evidence that one medicine was more likely to lead to discontinuation than another was limited, as the confidence intervals were wide: more discontinuation were observed with interferon beta-1a three times weekly versus placebo (RR 2.49, 95%CI 0.89 to 6.95) and with glatiramer acetate (RR 2.36, 95%CI 0.74 to 7.53). Fingolimod A 2016 Cochrane systematic review of six trials (5512 participants) compared the safety and efficacy of fingolimod versus placebo or other disease modifying treatment for RRMS (47). Compared to placebo, fingolimod at 24 months increased the probability of being relapse-free (RR 1.44, 95%CI 1.28 to 1.63); moderate quality of evidence), little or no difference in preventing disability progression was observed (RR 1.07, 95%CI 1.02 to 1.11; primary clinical endpoints; low quality evidence). Benefit was observed for other measures of inflammatory disease activity including annualized relapse rate and GAD lesions. No significant increased risk of discontinuation due to adverse events was observed for fingolimod at recommended dose compared to placebo at six and 24 months. No significant increased risk of discontinuation due to serious adverse events was observed for fingolimod 0.5 mg compared to placebo at six and 24 months. A significant increased risk of discontinuation due to serious adverse events was found for fingolimod 5.0 mg (RR 2.77, 95%CI 1.04 to 7.38) compared to placebo at six months. Compared to intramuscular interferon beta-1a, there was moderate quality evidence fingolimod 0.5 mg at one year slightly increased the number of participants free from relapse (RR 1.18, 95%CI 1.09 to 1.27) or from GAD lesions (RR 1.12, 95%CI 1.05 to 1.19), and decreased the relapse rate (rate ratio 0.48, 95%CI 0.34 to 0.70). There was no observed advantage for preventing disability progression (RR 1.02, 95%CI 0.99 to 1.06; low quality evidence). There was a greater likelihood of participants discontinuing fingolimod, compared to other DMTs, due to adverse events at six months (RR 3.21, 95%CI 1.16 to 8.86), but there was no significant difference versus interferon beta-1a at 12 months (RR 1.51, 95%CI 0.81 to 2.80; moderate quality evidence). A higher incidence of adverse events was suggestive of the lower tolerability rate of fingolimod compared to interferon-beta 1a.

Cost / cost effectiveness

The cost-effectiveness of disease modifying treatments for MS have been assessed in multiple systematic reviews involving studies conducted in high-income countries in Europe and North America (48–51). The studies reported that DMTs (including glatiramer acetate, fingolimod, ocrelizumab and rituximab) were potentially cost-effective but several studies reported costs that were likely to be above particular countries' willingness to pay thresholds. Limitations of these studies noted in these reviews included the lack of head-to-head comparisons between different DMTs, variation in time-horizons, and variation in end-points. There were no cost-effectiveness studies identified from LMICs. Though there is significant variance globally, a North American study suggested that approximately 60% of people with MS are unemployed (52), accounting for about one third of the total economic burden of MS (53). In addition to a loss in productivity, people with MS will have additional care needs with advancing age and disease severity. The economic burden of MS per patient and year ranges from approximately US$ 24 666 to US$ 51 678 (54). These amounts represent direct costs, which include in and out patient care, medications, medical procedures and social services as well as indirect costs related to loss of employment, disability benefits, early pension plans, and loss of productivity for spouses or family members providing informal

care and death. Given the most frequent age of presentation (young adults), it is important to note that MS has both physical and cognitive impact, and also impacts the family development of the patients, as well as, determines a socioeconomic impact on society as a whole.

WHO guidelines

None available.

Availability

Glatiramer acetate has marketing approval in many countries. Generic versions of glatiramer acetate are available in some countries – for example, in India, the Russian Federation and the United States. Secondary patents concerning glatiramer acetate are active in some jurisdictions. Fingolimod also has marketing approval in many countries. Price and availability of fingolimod vary globally. Generic versions are available. The main product patent on fingolimod appears not to have been filed in the LMIC jurisdictions surveyed and expires between 2016 and 2018 in some European countries and 2019 in the United States. Ocrelizumab has marketing approval in 68 high- and middle-income countries. Ocrelizumab is protected by a product patent expiring in 2023 in many jurisdictions. It is likely that biosimilar ocrelizumab cannot enter the market where this patent has been granted before 2023. Rituximab has marketing approval for indications other than multiple sclerosis in high-, middle- and low-income countries. Biosimilar versions of rituximab have been approved in numerous countries, including Australia, Bolivia, Chile, India, Peru, the Republic of Korea, and the European Union.

Other considerations

Use in pregnancy A pregnancy registry maintained by the marketing company of branded glatiramer acetate captured over 7000 pregnancies exposed to glatiramer acetate. It did not find an increase in spontaneous abortions, premature births, neonatal complications or birth defects (55). No significant differences were observed in birth weight of babies born to mothers exposed to glatiramer during pregnancy compared with mothers not exposed to glatiramer acetate during pregnancy. Evidence supports the use of branded glatiramer acetate in pregnant women who are recommended to remain on treatment to manage disease activity. Fingolimod is a teratogen class C agent and should be considered an absolute contraindication in pregnancy and breastfeeding based on its known teratogenicity in animal studies and post-marketing data. Ocrelizumab is known to cross the placental barrier and is recommended to be avoided during pregnancy unless the potential benefit to the mother outweighs the potential risk to the fetus. There are no adequate data on the developmental risk associated with use of ocrelizumab in pregnant women. For rituximab, a large cohort study found that out of 153 pregnancies, 90 resulted in live births (56). Twenty-two infants were born prematurely; with one neonatal death at six weeks. Eleven neonates had haematologic abnormalities; none had corresponding infections. Two congenital malformations were identified. The European League Against Rheumatism (EULAR) considered use of rituximab before pregnancy and during pregnancy (57). Based on a systematic literature and consensus among experts, the recommendation considered that rituximab should be replaced by other medication before conception. It should be used during pregnancy only when no other pregnancy-compatible drug can effectively control maternal disease.

1. The selection and use of essential medicines. Report of the WHO Expert Committee, 2015 (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children) (WHO Technical Report Series, No. 994). Geneva: World Health Organization; 2015. Available from https://apps.who.int/iris/bitstream/handle/10665/189763/9789241209946_eng.pdf, accessed 30 October 2019.
2. Montalban X, Gold R, Thompson AJ, Otero-Romero S, Amato MP, Chandraratna D et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler. 2018;24(2):96–120.
3. Rae-Grant A, Day GS, Marrie RA, Rabinstein A, Cree BAC, Gronseth GS et al. Practice guideline recommendations summary: Disease-modifying therapies for adults with multiple sclerosis: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(17):777–88.
4. Lublin FD. New multiple sclerosis phenotypic classification. Eur Neurol. 2014;72 Suppl 1:1–5.

5. 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.
6. Browne P, Chandraratna D, Angood C, Tremlett H, Baker C, Taylor BV et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. Neurology. 2014;83(11):1022–4.
7. Atlas of MS 2013: mapping multiple sclerosis around the world. London: Multiple Sclerosis International Federation; 2013. Available from: http://www.msif.org/about-us/advocacy/reportsand-resources/, acces sed 29 September 2019.
8. Marrie RA, Yu N, Blanchard J, Leung S, Elliott L. The rising prevalence and changing age distribution of multiple sclerosis in Manitoba. Neurology. 2010;74(6):465–71.
9. Mackenzie IS, Morant SV, Bloomfield GA, MacDonald TM, O'Riordan J. Incidence and prevalence of multiple sclerosis in the UK 1990-2010: a descriptive study in the General Practice Research Database. J Neurol Neurosurg Psychiatry. 2014;85(1):76–84.
10. Benito-Leon J. Multiple sclerosis: is prevalence rising and if so why? Neuroepidemiology. 2011;37(3-4):236–7.
11. Amankwah N, Marrie RA, Bancej C, Garner R, Manuel DG, Wall R et al. Multiple sclerosis in Canada 2011 to 2031: results of a microsimulation modelling study of epidemiological and economic impacts. Health Promot Chronic Dis Prev Can. 2017;37(2):37–48.
12. Sahraian MA, Sahebkar M, Dehghani R, Derakhshan-Jazari M, Kazami-Moghaddam V, Kouchaki E. Multiple sclerosis-A disease on a dramatically rising trend in Iran: Review of possible reasons. Iran J Neurol. 2017;16(1):34–40.
13. Chinea A, Rios-Bedoya CF, Vicente I, Rubi C, Garcia G, Rivera A et al. Increasing Incidence and Prevalence of Multiple Sclerosis in Puerto Rico (2013-2016). Neuroepidemiology. 2017;49(3-4):106–12.
14. Brola W, Sobolewski P, Flaga S, Fudala M, Jantarski K. Increasing prevalence and incidence of multiple sclerosis in Poland. Neurol Neurochir Pol. 2017;51(1):82–5.
15. Bezzini D, Policardo L, Profili F, Meucci G, Ulivelli M, Bartalini S et al. Multiple sclerosis incidence in Tuscany from administrative data. Neurol Sci. 2018;39(11):1881–5.
16. Ascherio A, Munger KL. Epidemiology of Multiple Sclerosis: From Risk Factors to Prevention-An Update. Semin Neurol. 2016;36(2):103–14.
17. Chitnis T. Disease-modifying therapy of pediatric multiple sclerosis. Neurotherapeutics. 2013; 10(1):89–96.
18. Waldman A, Ghezzi A, Bar-Or A, Mikaeloff Y, Tardieu M, Banwell B. Multiple sclerosis in children: an update on clinical diagnosis, therapeutic strategies, and research. Lancet Neurol. 2014;13(9):936–48.
19. Marrie RA, Fisk JD, Tremlett H, Wolfson C, Warren S, Tennakoon A et al. Differences in the burden of psychiatric comorbidity in MS vs the general population. Neurology. 2015;85(22):1972–9.
20. Giovannoni G, Butzkueven H, Dhib-Jalbut S, Hobart J, Kobelt G, Pepper G et al. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord. 2016;9 Suppl 1:S5–s48.
21. Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. Mult Scler. 2017;23(8):1123–36.
22. 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.
23. Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012;367(12):1087–97.
24. Khan O, Rieckmann P, Boyko A, Selmaj K, Zivadinov R. Three times weekly glatiramer acetate in relapsing-remitting multiple sclerosis. Ann Neurol. 2013;73(6):705–13.
25. Mikol DD, Barkhof F, Chang P, Coyle PK, Jeffery DR, Schwid SR et al. Comparison of subcutaneous interferon beta-1a with glatiramer acetate in patients with relapsing multiple sclerosis (the REbif vs Glatiramer Acetate in Relapsing MS Disease [REGARD] study): a multicentre, randomised, parallel, open-label trial. Lancet Neurol. 2008;7(10):903–14.
26. Cadavid D, Wolansky LJ, Skurnick J, Lincoln J, Cheriyan J, Szczepanowski K et al. Efficacy of treatment of MS with IFNbeta-1b or glatiramer acetate by monthly brain MRI in the BECOME study. Neurology. 2009;72(23):1976–83.
27. Calabrese M, Bernardi V, Atzori M, Mattisi I, Favaretto A, Rinaldi F et al. Effect of disease-modifying drugs on cortical lesions and atrophy in relapsing-remitting multiple sclerosis. Mult Scler. 2012;18(4):418–24.
28. O'Connor P, Filippi M, Arnason B, Comi G, Cook S, Goodin D et al. 250 microg or 500 microg interferon beta-1b versus 20 mg glatiramer acetate in relapsing-remitting multiple sclerosis: a prospective, randomised, multicentre study. Lancet Neurol. 2009;8(10):889–97.
29. 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.
30. Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010;362(5):387–401.
31. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014;13(6):545–56.
32. Cohen JA, Barkhof F, Comi G, Hartung HP, Khatri BO, Montalban X et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. N Engl J Med. 2010;362(5):402–15.
33. Chitnis T, Arnold DL, Banwell B, Bruck W, Ghezzi A, Giovannoni G et al. Trial of Fingolimod versus

Interferon Beta-1a in Pediatric Multiple Sclerosis. N Engl J Med. 2018;379(11):1017–27.
34. Lublin F, Miller DH, Freedman MS, Cree BAC, Wolinsky JS, Weiner H et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebocontrolled trial. Lancet. 2016;387(10023):1075–84.
35. Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F et al. Ocrelizumab in relapsingremitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet. 2011;378(9805):1779–87.
36. Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B et al. Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis. N Engl J Med. 2017;376(3):221–34.
37. Montalban X, Hauser SL, Kappos L, Arnold DL, Bar-Or A, Comi G et al. Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis. N Engl J Med. 2017;376(3):209–20.
38. He D, Guo R, Zhang F, Zhang C, Dong S, Zhou H. Rituximab for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2013(12):CD009130.
39. 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.
40. Bar-Or A, Calabresi PA, Arnold D, Markowitz C, Shafer S, Kasper LH et al. Rituximab in relapsingremitting multiple sclerosis: a 72-week, open-label, phase I trial. Ann Neurol. 2008;63(3):395–400.
41. 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.
42. Salzer J, Svenningsson R, Alping P, Novakova L, Bjorck A, Fink K et al. Rituximab in multiple sclerosis: A retrospective observational study on safety and efficacy. Neurology. 2016;87(20):2074–81.
43. 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.
44. Alping P, Frisell T, Novakova L, Islam-Jakobsson P, Salzer J, Bjorck A et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. Ann Neurol. 2016;79(6):950–8.
45. La Mantia L, Di Pietrantonj C, Rovaris M, Rigon G, Frau S, Berardo F et al. Interferons-beta versus glatiramer acetate for relapsing-remitting multiple sclerosis. Cochrane Database Syst Rev. 2016;11:CD009333.
46. Melendez-Torres GJ, Armoiry X, Court R, Patterson J, Kan A, Auguste P et al. Comparative effectiveness of beta-interferons and glatiramer acetate for relapsing-remitting multiple sclerosis: systematic review and network meta-analysis of trials including recommended dosages. BMC Neurol. 2018;18(1):162.
47. La Mantia L, Tramacere I, Firwana B, Pacchetti I, Palumbo R, Filippini G. Fingolimod for relapsingremitting multiple sclerosis. Cochrane Database Syst Rev. 2016;4:CD009371.
48. Sharac J, McCrone P, Sabes-Figuera R. Pharmacoeconomic considerations in the treatment of multiple sclerosis. Drugs. 2010;70(13):1677–91.
49. Hawton A, Shearer J, Goodwin E, Green C. Squinting through layers of fog: assessing the cost effectiveness of treatments for multiple sclerosis. Appl Health Econ Health Policy. 2013; 11(4):331–41.
50. Thompson JP, Abdolahi A, Noyes K. Modelling the cost effectiveness of disease-modifying treatments for multiple sclerosis: issues to consider. Pharmacoeconomics. 2013;31(6):455–69.
51. Hernandez L, O'Donnell M, Postma M. Modeling Approaches in Cost-Effectiveness Analysis of Disease-Modifying Therapies for Relapsing-Remitting Multiple Sclerosis: An Updated Systematic Review and Recommendations for Future Economic Evaluations. Pharmacoeconomics. 2018; 36(10):1223–52.
52. Dobrescu A, Dinh T, Stonebridge C. Multiple Sclerosis in the Workplace: Making the Case for Enhancing Employment and Income Supports. Ottawa: The Conference Board of Canada; 2018. Available from https://www.conferenceboard.ca/e-library/abstract.aspx?did=9611, accessed 29 September 2019.
53. Dinh T, Astles P, Turpin K. Multiple Sclerosis in the Workplace: Supporting Successful Employment Experiences. Ottawa: The Conference Board of Canada, 2016. Available from: https://www.conferenceboard.ca/e-library/abstract.aspx?did=7921, accessed 29 September 2019.
54. Ernstsson O, Gyllensten H, Alexanderson K, Tinghog P, Friberg E, Norlund A. Cost of Illness of Multiple Sclerosis - A Systematic Review. PLoS One. 2016;11(7):e0159129.
55. Sandberg-Wollheim M, Neudorfer O, Grinspan A, Weinstock-Guttman B, Haas J, Izquierdo G et al. Pregnancy Outcomes from the Branded Glatiramer Acetate Pregnancy Database. Int J MS Care. 2018;20(1):9–14.
56. Chakravarty EF, Murray ER, Kelman A, Farmer P. Pregnancy outcomes after maternal exposure to rituximab. Blood. 2011;117(5):1499–506.
57. Gotestam Skorpen C, Hoeltzenbein M, Tincani A, Fischer-Betz R, Elefant E, Chambers C et al. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. Ann Rheum Dis. 2016;75(5):795–810.

