

E-REFERENCES

- e1. Agency EM. Assessment report. Gilenya. International non-proprietary name: fingolimod. London, UK; 2014.
- e2. Coles AJ, Fox E, Vladic A, et al. Alemtuzumab versus interferon beta-1a in early relapsing-remitting multiple sclerosis: post-hoc and subset analyses of clinical efficacy outcomes. *Lancet Neurol* 2011;10:338–348.
- e3. Devonshire V, Havrdova E, Radue EW, et al.; FREEDOMS study group. Relapse and disability outcomes in patients with multiple sclerosis treated with fingolimod: subgroup analyses of the double-blind, randomised, placebo-controlled FREEDOMS study. *Lancet Neurol* 2012;11:420–428.
- e4. Hutchinson M. Predicting and preventing the future: actively managing multiple sclerosis. *Pract* 2009;9:133–143, discussion 144.
- e5. Coles A, Twyman CL, Arnold DL, et al.; the CARE-MS II Investigators. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised ; for the CARE-MS II investigator controlled phase 3 trial. *Lancet* 2012;380:1829–1839.
- e6. Cohen JA, Barkhof F, Comi G, et al.; on behalf of the TRANSFORMS Study Group. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med* 2010;362:402–415.
- e7. Cohen J, Coles AJ, Arnold DL, et al.; CARE-MS I Investigators. Alemtuzumab versus interferon beta 1a as first-line treatment for patients with relapsing-remitting multiple sclerosis: a randomised controlled phase 3 trial. *Lancet* 2012;380:1819–1828.
- e8. Rudick R, Stuart WH, Calabresi PA, et al.; for the SENTINEL Investigators. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911–923.
- e9. Browne P, Chandraratna D, Angood C, et al. Atlas of Multiple Sclerosis 2013: A growing global problem with widespread inequity. *Neurology* 2014;83:1022–1024.
- e10. Hawker K, O'Connor P, Freedman MS, et al. Rituximab in Patients with Primary Progressive Multiple Sclerosis Results of a Randomized Double-Blind Placebo-Controlled Multicenter Trial. *Ann Neurol* 2009;66:460–471.
- e11. Lublin F, Miller DH, Freedman MS, et al. Oral fingolimod in primary progressive multiple sclerosis (INFORMS): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet* 2016;387:1075–1084.
- e12. Wolinsky JS, Narayana PA, O'Connor P, et al. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. *Ann Neurol* 2007;61:14–24.
- e13. Montalban X, Sastre-Garriga J, Tintore M, et al. . A single-center, randomized, double-blind, placebo-controlled study of interferon beta-1b on primary progressive and transitional multiple sclerosis. *Mult Scler* 2009;15:1195–1205.
- e14. Fisniku LK, Brex PA, Altmann DR, et al. Disability and T2 MRI lesions: a 20-year follow-up of patients with relapse onset of multiple sclerosis. *Brain* 2008;131:808–817.
- e15. Rio J, Rovira A, Tintore M, et al. Relationship between MRI lesion activity and response to IFN-beta in relapsing-remitting multiple sclerosis patients. *Multiple Sclerosis* 2008;14:479–484.
- e16. Sormani MP, Rio J, Tintore M, et al. Scoring treatment response in patients with relapsing multiple sclerosis. *Mult Scler* 2013;19:605–612.
- e17. Prosperini L, Gallo V, Petsas N, Borriello G, Pozzilli C. One-year MRI scan predicts clinical response to interferon beta in multiple sclerosis. *Eur J Neurol* 2009;16:1202–1209.

- e18. Comi G, Filippi M, Wolinsky JS. European/Canadian multicenter, double-blind, randomized, placebo-controlled study of the effects of glatiramer acetate on magnetic resonance imaging-measured disease activity and burden in patients with relapsing multiple sclerosis. *Ann Neurol* 2001;49:290–297.
- e19. Confavreux C, O'Connor, P, Comi, G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol* 2014;13:247–256.
- e20. Johnson K, Brooks, BR, Cohen, JA, et al. Copolymer 1 reduces relapse rate and improves disability in relapsing-remitting multiple sclerosis. *Neurology* 1995;45:1268–1276.
- e21. PRISMS. Randomised double-blind placebo-controlled study of interferon -1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;352:1498–1504.
- e22. Traboulsee A, Simon JH, Stone L, et al. Revised Recommendations of the Consortium of MS Centers Task Force for a Standardized MRI Protocol and Clinical Guidelines for the Diagnosis and Follow-Up of Multiple Sclerosis. *Am J Neuroradiol* 2016;37:394–401.
- e23. Devonshire V, Lapierre Y, Macdonell R, et al. The Global Adherence Project (GAP): a multicenter observational study on adherence to disease-modifying therapies in patients with relapsing-remitting multiple sclerosis. *Eur J Neurol* 2011;18:69–77.
- e24. Clifford DB, De Luca A, Simpson DM, Arendt G, Giovannoni G, Nath A. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: lessons from 28 cases. *Lancet Neurol* 2010;9:438–446.
- e25. US Food and Drug Administration. FDA Drug Safety Communication: New risk factor for Progressive Multifocal Leukoencephalopathy (PML) associated with Tysabri (natalizumab). Available at: <https://www.fda.gov/drugs/drugsafety/ucm288186.htm>. Published January 20, 2012. Accessed June 1, 2016.
- e26. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about case of rare brain infection PML with MS drug Tecfidera (dimethyl fumarate). Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm424625.htm>. Published November 25, 2014. Accessed June 1, 2016.
- e27. Rosenkranz T, Novas M, Terborg C. PML in a patient with lymphocytopenia treated with dimethyl fumarate. *N Engl J Med* 2015;372:1476–1478.
- e28. Nieuwkamp DJ, Murk JL, van Oosten BW. PML in patients treated with dimethyl fumarate. *N Engl J Med* 2015;373:584.
- e29. US Food and Drug Administration. FDA Drug Safety Communication: FDA warns about cases of rare brain infection with MS drug Gilenya (fingolimod) in two patients with no prior exposure to immunosuppressant drugs. Available at: <https://www.fda.gov/Drugs/DrugSafety/ucm456919.htm>. Published August 4, 2015. Accessed June 1, 2016.
- e30. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* 2009;113:4834–4840.
- e31. Ocrevus [package insert]. In: Genentech, ed. South San Francisco, CA:2017.
- e32. Huang D. Disseminated cryptococcosis in a patient with multiple sclerosis treated with fingolimod. *Neurology* 2015;85:1001–1003.
- e33. Pelletier D, Hafler DA. Fingolimod for multiple sclerosis. *N Engl J Med* 2012;366:339–347.

- e34. Ratchford JN, Costello K, Reich DS, Calabresi PA. Varicella-zoster virus encephalitis and vasculopathy in a patient treated with fingolimod. *Neurology* 2012;79:2002–2004.
- e35. Fine AJ, Sorbello A, Kortepeter C, Scarazzini L. Central nervous system herpes simplex and varicella zoster virus infections in natalizumab-treated patients. *Clin Infect Dis* 2013;57:849–852.
- e36. Krumbholz M, Pellkofer H, Gold R, Hoffmann LA, Hohlfeld R, Kumpfel T. Delayed allergic reaction to natalizumab associated with early formation of neutralizing antibodies. *Arch Neurol* 2007;64:1331–1333.
- e37. Vennegoor A, Rispens T, Strijbis EM, et al. Clinical relevance of serum natalizumab concentration and anti-natalizumab antibodies in multiple sclerosis. *Mult Scler* 2013;19:593–600.
- e38. Prosperini L, Annovazzi P, Capobianco M, et al. Natalizumab discontinuation in patients with multiple sclerosis: Profiling risk and benefits at therapeutic crossroads. *Mult Scler* 2015;21:1713–1722.
- e39. Comi G, Gold R, Dahlke F, et al. Relapses in patients treated with fingolimod after previous exposure to natalizumab. *Mult Scler* 2015;21:786–790.
- e40. Iaffaldano P, Lucisano G, Pozzilli C, et al. Fingolimod versus interferon beta/glatiramer acetate after natalizumab suspension in multiple sclerosis. *Brain* 2015;138:3275–3286.
- e41. Alping P, Frisell T, Novakova L, et al. Rituximab versus fingolimod after natalizumab in multiple sclerosis patients. *Ann Neurol* 2016;79:950–958.
- e42. Finkelsztejn A, Brooks JBB, Paschoal Jr FM, Fragoso YD. What can we really tell women with multiple sclerosis regarding pregnancy? A systematic review and meta-analysis of the literature. *BJOG* 2011;118:790–797.
- e43. Lu E, Wang BW, Guimond C, Synnes A, Sadovnick D, Tremlett H. Disease-modifying drugs for multiple sclerosis in pregnancy: a systematic review. *Neurology* 2012;79:1130–1135.
- e44. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain* 1989;112 (Pt 1):133–146.
- e45. Paz Soldan MM, Novotna M, Abou Zeid N, et al. Relapses and disability accumulation in progressive multiple sclerosis. *Neurology* 2015;84:81–88.
- e46. Tremlett H, Zhao Y, Devonshire V. Natural history of secondary-progressive multiple sclerosis. *Mult Scler* 2008;14:314–324.
- e47. Polman CH R, SC, Banwell,B, et al. Diagnostic criteria for multiple sclerosis. *Ann Neurol* 2011;69:292–302.
- e48. Mowry EM, Pesic M, Grimes B et al. Clinical predictors of early second event in patients with clinically isolated syndrome. *J Neurol* 2009;256:1061–1066.
- e49. D’Alessandro, Roberto, et al. Risk of multiple sclerosis following clinically isolated syndrome: a 4-year prospective study. *J Neurol* 260.6:1583–1593.