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REVIEW
Bilingual edition English/Spanish

Disease modifying therapies in multiple sclerosis: cost-effectiveness systematic review

Terapias modificadoras de la enfermedad en esclerosis múltiple: revisión sistemática de costo-efectividad

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ADDITIONAL MATERIAL-APPENDICES

Appendix A. MEDLINE search strategy

Number	Term
1	(Multiple Sclerosis).tw
2	Multiple Sclerosis/exp
3	(Multiple adj2 Sclerosis).tw
4	Relapsing-Remitting/exp
5	Relapsing-Remitting.tw
6	1 OR 2 OR 3
7	4 OR 5
8	6 AND 7
9	Interferon ß/exp
10	Interferon beta/exp
11	Interferon beta-1a/exp
12	Interferon ß-1a/exp
13	Interferon beta-1b/exp
14	Interferon ß-1b/exp
15	Glatiramer acetate/exp
16	Teriflunomide/exp
17	Fingolimod/exp
18	Fingolimod Hydrochloride/exp
19	Dimethyl Fumarate/exp

Appendix A ***(cont.).*** MEDLINE search strategy

Number	Term
20	Natalizumab/exp
21	Alemtuzumab/exp
22	Rituximab/exp
23	Interferon ß.tw
24	Interferon beta.tw
25	Interferon beta-1a.tw
26	Interferon ß-1a.tw
27	Interferon beta-1b.tw
28	Interferon ß-1b.tw
29	Glatiramer acetate.tw
30	Teriflunomide.tw
31	Fingolimod.tw
32	Fingolimod Hydrochloride.tw
33	Dimethyl Fumarate.tw
34	Natalizumab.tw
35	Alemtuzumab.tw
36	Rituximab.tw
37	(Interferon adj2 ß).tw
38	(Interferon ad2 beta).tw
39	(Interferon adj2 beta-1a).tw
40	(Interferon adj2 ß-1a).tw
41	(Interferon adj2 beta-1b).tw
42	(Interferon adj2 ß-1b).tw
43	(Glatiramer adj2 acetate).tw
44	(Fingolimod qdj2 Hydrochloride).tw
45	(Dimethyl adj2 Fumarate).tw
46	OR/9-45
47	(every-other-day interferon).tw
48	(once-weekly interferon).tw
49	(interferon three-times weekly).tw
50	(glatiramer acetate daily).tw
51	(glatiramer acetate three-time weekly).tw
52	(every-other-day glatiramer acetate).tw
53	(every-other-day adj3 interferon).tw
54	(once-weekly adj3 interferon).tw
55	(interferon adj2 three-times adj2 weekly).tw
56	(glatiramer adj2 acet* adj2 daily).tw
57	(glatiramer adj2 aceta* adj2 three-time weekly).tw
58	(every-other-day adj2 glatiramer adj2 aceta*).tw
59	OR/47-58
60	Cost Effectiveness Analysis/exp
61	Cost Effectiveness Study/exp
62	Cost Utility Analysis/exp
63	Cost Utility Study/exp
64	Quality Adjusted Life-Years/exp
65	Incremental Cost-Effectiveness Ratio/exp
66	(Cost Effectiveness Analysis).tw
67	(Cost Effectiveness Study).tw
68	(Cost Utility Analysis).tw
69	(Cost Utility Study).tw
70	(Quality Adjusted Life-Years).tw
71	(Incremental Cost-Effectiveness Ratio).tw
72	(Cost Effectiveness adj2 Analysis).tw
73	(Cost Effectiveness adj2 Study).tw
74	(Cost Utility adj2 Analysis).tw
75	(Cost Utility adj2 Study).tw
76	(Incremental Cost-Effectiveness adj2 Ratio).tw
77	OR/60-76
78	8 AND 46 AND 59 AND 77

Search executed on January 1, 2018.

Records identified: 108.
Records evaluated based on title and abstract: 108.
Full text records evaluated: 3.
Records included in the qualitative summary: 2.

Appendix B. Embase search strategy

Number	Term
1	(Multiple Sclerosis):ab,ti
2	Multiple Sclerosis/exp
3	(Multiple NEAR/2 Sclerosis):ab,ti
4	Relapsing-Remitting/exp
5	Relapsing-Remitting:ab,ti
6	1 OR 2 OR 3
7	4 OR 5
8	6 AND 7
9	Interferon ß/exp
10	Interferon beta/exp
11	Interferon beta-1a/exp
12	Interferon ß-1a/exp
13	Interferon beta-1b/exp
14	Interferon ß-1b/exp
15	Glatiramer acetate/exp
16	Teriflunomide/exp
17	Fingolimod/exp
18	Fingolimod Hydrochloride/exp
19	Dimethyl Fumarate/exp
20	Natalizumab/exp
21	Alemtuzumab/exp
22	Rituximab/exp
23	Interferon ß:ab,ti
24	Interferon beta:ab,ti
25	Interferon beta-1a:ab,ti
26	Interferon ß-1a:ab,ti
27	Interferon beta-1b:ab,ti
28	Interferon ß-1b:ab,ti
29	Glatiramer acetate:ab,ti
30	Teriflunomide:ab,ti
31	Fingolimod:ab,ti
32	Fingolimod Hydrochloride:ab,ti
33	Dimethyl Fumarate:ab,ti
34	Natalizumab:ab,ti
35	Alemtuzumab:ab,ti
36	Rituximab:ab,ti
37	(Interferon NEAR/2 ß):ab,ti
38	(Interferon NEAR/2 beta):ab,ti
39	(Interferon NEAR/2 beta-1a):ab,ti
40	(Interferon NEAR/2 ß-1a):ab,ti
41	(Interferon NEAR/2 beta-1b):ab,ti
42	(Interferon NEAR/2 ß-1b):ab,ti
43	(Glatiramer NEAR/2 acetate):ab,ti
44	(Fingolimod NEAR/2 Hydrochloride):ab,ti
45	(Dimethyl NEAR/2 Fumarate):ab,ti
46	OR/9-45
47	(every-other-day interferon):ab,ti
48	(once-weekly interferon):ab,ti
49	(interferon three-times weekly):ab,ti
50	(glatiramer acetate daily):ab,ti
51	(glatiramer acetate three-time weekly):ab,ti
52	(every-other-day glatiramer acetate):ab,ti
53	(every-other-day NEAR/3 interferon):ab,ti
54	(once-weekly NEAR/3 interferon):ab,ti
55	(interferon NEAR/2 three-times NEAR/2 weekly):ab,ti
56	(glatiramer NEAR/2 acet* NEAR/2 daily):ab,ti
57	(glatiramer NEAR/2 aceta* NEAR/2 three-time weekly):ab,ti
58	(every-other-day NEAR/2 glatiramer NEAR/2 aceta*):ab,ti
59	OR/47-58
60	Cost Effectiveness Analysis/exp
61	Cost Effectiveness Study/exp
62	Cost Utility Analysis/exp
63	Cost Utility Study/exp
64	Quality Adjusted Life-Years/exp
65	Incremental Cost-Effectiveness Ratio/exp
66	(Cost Effectiveness Analysis):ab,ti
67	(Cost Effectiveness Study):ab,ti
68	(Cost Utility Analysis):ab,ti
69	(Cost Utility Study):ab,ti
70	(Quality Adjusted Life-Years):ab,ti
71	(Incremental Cost-Effectiveness Ratio):ab,ti
72	(Cost Effectiveness NEAR/2 Analysis):ab,ti
73	(Cost Effectiveness NEAR/2 Study):ab,ti
74	(Cost Utility NEAR/2 Analysis):ab,ti
75	(Cost Utility NEAR/2 Study):ab,ti
76	(Incremental Cost-Effectiveness NEAR/2 Ratio):ab,ti
77	OR/60-76
78	8 AND 46 AND 59 AND 77

Search executed on January 1, 2018.

Records identified: 161.
Records evaluated based on title and abstract: 161.
Full text records evaluated: 3.
Records included in the qualitative summary: 1.

Appendix C. Cochrane Library search strategy

Number	Term
1	(Multiple Sclerosis).tw
2	Multiple Sclerosis/exp
3	(Multiple adj2 Sclerosis).tw
4	Relapsing-Remitting/exp
5	Relapsing-Remitting.tw
6	1 OR 2 OR 3
7	4 OR 5
8	6 AND 7
9	Interferon ß/exp
10	Interferon beta/exp
11	Interferon beta-1a/exp
12	Interferon ß-1a/exp
13	Interferon beta-1b/exp
14	Interferon ß-1b/exp
15	Glatiramer acetate/exp
16	Teriflunomide/exp
17	Fingolimod/exp
18	Fingolimod Hydrochloride/exp
19	Dimethyl Fumarate/exp
20	Natalizumab/exp
21	Alemtuzumab/exp
22	Rituximab/exp
23	Interferon ß.tw
24	Interferon beta.tw
25	Interferon beta-1a.tw
26	Interferon ß-1a.tw
27	Interferon beta-1b.tw
28	Interferon ß-1b.tw
29	Glatiramer acetate.tw
30	Teriflunomide.tw
31	Fingolimod.tw
32	Fingolimod Hydrochloride.tw
33	Dimethyl Fumarate.tw
34	Natalizumab.tw
35	Alemtuzumab.tw
36	Rituximab.tw
37	(Interferon adj2 ß).tw
38	(Interferon ad2 beta).tw
39	(Interferon adj2 beta-1a).tw
40	(Interferon adj2 ß-1a).tw
41	(Interferon adj2 beta-1b).tw
42	(Interferon adj2 ß-1b).tw
43	(Glatiramer adj2 acetate).tw
44	(Fingolimod qdj2 Hydrochloride).tw
45	(Dimethyl adj2 Fumarate).tw
46	OR/9-45
47	(every-other-day interferon).tw
48	(once-weekly interferon).tw
49	(interferon three-times weekly).tw
50	(glatiramer acetate daily).tw
51	(glatiramer acetate three-time weekly).tw
52	(every-other-day glatiramer acetate).tw
53	(every-other-day adj3 interferon).tw
54	(once-weekly adj3 interferon).tw
55	(interferon adj2 three-times adj2 weekly).tw
56	(glatiramer adj2 acet* adj2 daily).tw
57	(glatiramer adj2 aceta* adj2 three-time weekly).tw
58	(every-other-day adj2 glatiramer adj2 aceta*).tw
59	OR/47-58
60	Cost Effectiveness Analysis/exp
61	Cost Effectiveness Study/exp
62	Cost Utility Analysis/exp
63	Cost Utility Study/exp
64	Quality Adjusted Life-Years/exp
65	Incremental Cost-Effectiveness Ratio/exp
66	(Cost Effectiveness Analysis).tw
67	(Cost Effectiveness Study).tw
68	(Cost Utility Analysis).tw
69	(Cost Utility Study).tw
70	(Quality Adjusted Life-Years).tw
71	(Incremental Cost-Effectiveness Ratio).tw
72	(Cost Effectiveness adj2 Analysis).tw
73	(Cost Effectiveness adj2 Study).tw
74	(Cost Utility adj2 Analysis).tw
75	(Cost Utility adj2 Study).tw
76	(Incremental Cost-Effectiveness adj2 Ratio).tw
77	OR/60-76
78	8 AND 46 AND 59 AND 77

Search executed on January 1, 2018.

Records identified: 55.
Records evaluated based on title and abstract: 55.
Full text records evaluated: 0.
Records included in the qualitative summary: 0.

Appendix D. LILACS search strategy

(Multiple Sclerosis AND Relapsing-Remitting) AND (Interferon ß OR Interferon beta OR Interferon beta-1a OR Interferon ß-1a OR Interferon beta-1b OR Interferon ß-1b OR Glatiramer acetate OR Teriflunomide OR Fingolimod OR Fingolimod Hydrochloride OR Dimethyl Fumarate OR Natalizumab OR Alemtuzumab OR Rituximab) AND (every-other-day interferon OR once-weekly interferon OR Interferon three-times weekly OR glatiramer acetate daily OR glatiramer acetate three-time weekly OR every-other-day glatiramer acetate) AND (Cost Effectiveness Analysis OR Cost Effectiveness Study OR Cost Utility Analysis OR Cost Utility Study OR Quality Adjusted Life-Years OR Incremental Cost-Effectiveness Ratio)

Search executed on January 1, 2018.

Records identified: 0.
Records evaluated based on title and abstract: 0.
Full text records evaluated: 0.
Records included in the qualitative summary: 0.

Appendix E. Search strategy for the Tufts Medical Center Cost-Effectiveness Analysis Registry

(Multiple Sclerosis AND Relapsing-Remitting) AND (Interferon ß OR Interferon beta OR Interferon beta-1a OR Interferon ß-1a OR Interferon beta-1b OR Interferon ß-1b OR Glatiramer acetate OR Teriflunomide OR Fingolimod OR Fingolimod Hydrochloride OR Dimethyl Fumarate OR Natalizumab OR Alemtuzumab OR Rituximab) AND (every-other-day interferon OR once-weekly interferon OR Interferon three-times weekly OR glatiramer acetate daily OR glatiramer acetate three-time weekly OR every-other-day glatiramer acetate) AND (Cost Effectiveness Analysis OR Cost Effectiveness Study OR Cost Utility Analysis OR Cost Utility Study OR Quality Adjusted Life-Years OR Incremental Cost-Effectiveness Ratio)

Search executed on January 1, 2018.

Records identified: 26.
Records evaluated based on title and abstract: 26.
Full text records evaluated: 16.
Records included in the qualitative summary: 6.

Appendix F. Search strategy for the National Health Service Economic Evaluation Database

(Multiple Sclerosis AND Relapsing-Remitting) AND (Interferon ß OR Interferon beta OR Interferon beta-1a OR Interferon ß-1a OR Interferon beta-1b OR Interferon ß-1b OR Glatiramer acetate OR Teriflunomide OR Fingolimod OR Fingolimod Hydrochloride OR Dimethyl Fumarate OR Natalizumab OR Alemtuzumab OR Rituximab) AND (every-other-day interferon OR once-weekly interferon OR Interferon three-times weekly OR glatiramer acetate daily OR glatiramer acetate three-time weekly OR every-other-day glatiramer acetate) AND (Cost Effectiveness Analysis OR Cost Effectiveness Study OR Cost Utility Analysis OR Cost Utility Study OR Quality Adjusted Life-Years OR Incremental Cost-Effectiveness Ratio)

Search executed on January 1, 2018.

Records identified: 50.
Records evaluated based on title and abstract: 16.
Full text records evaluated: 0.
Records included in the qualitative summary: 0.

Appendix G. Open Grey search strategy

(Multiple Sclerosis AND Relapsing-Remitting) AND (Interferon ß OR Interferon beta OR Interferon beta-1a OR Interferon ß-1a OR Interferon beta-1b OR Interferon ß-1b OR Glatiramer acetate OR Teriflunomide OR Fingolimod OR Fingolimod Hydrochloride OR Dimethyl Fumarate OR Natalizumab OR Alemtuzumab OR Rituximab) AND (every-other-day interferon OR once-weekly interferon OR Interferon three-times weekly OR glatiramer acetate daily OR glatiramer acetate three-time weekly OR every-other-day glatiramer acetate) AND (Cost Effectiveness Analysis OR Cost Effectiveness Study OR Cost Utility Analysis OR Cost Utility Study OR Quality Adjusted Life-Years OR Incremental Cost-Effectiveness Ratio)

Search executed on January 1, 2018.

Records identified: 1.
Records evaluated based on title and abstract: 1.
Full text records evaluated: 0.
Records included in the qualitative summary: 0.

Appendix H. Contraindications to the use of disease-modifying therapies

Source: *European Medicines Agency* (EMA) 2017.

Interferon beta-1a: Hypersensitivity to human albumin, severe depression.
Interferon beta-1b: Hypersensitivity to human albumin, severe depression, decompensated alcohol liver disease.
Glatiramer acetate: Hypersensitivity to mannitol.
Teriflunomide: Severe liver failure (Child-Pugh C), immunosuppression, bone marrow dysfunction, severe active infection, chronic kidney disease (dialysis), severe hypoproteinemia.
Fingolimod: Immunosuppression, use of other immunosuppressive drugs, severe active infection, chronic infection (hepatitis and tuberculosis), active malignant neoplasms, severe liver failure (Child-Pugh C).
Dimethyl fumarate: No additional contraindications.
Natalizumab: Progressive multifocal leukoencephalopathy, use of other immunosuppressive drugs, use of other disease-modifying therapies, active malignant neoplasms.
Alemtuzumab: Human Immunodeficiency Virus infection.
Rituximab: Severe active infection, immunosuppression, severe heart failure.

Appendix I. Studies included

Imani A, Golestani M. Cost-utility analysis of disease-modifying drugs in relapsing-remitting multiple sclerosis in Iran. Iran J Neurol. 2012;11(3):87-90.
Montgomery SM, Maruszczak MJ, Slater D, Kusel J, Nicholas R, Adlard N. A discrete event simulation to model the cost-utility of fingolimod and natalizumab in rapidly evolving severe relapsing-remitting multiple sclerosis in the UK. J Med Econ. 2017;20(5):474-82.
Maruszczak MJ, Montgomery SM, Griffiths MJS, Bergvall N, Adlard N. Cost-utility of fingolimod compared with dimethyl fumarate in highly active relapsing-remitting multiple sclerosis (RRMS) in England. J Med Econ. 2015;18(11):874-85.
Montgomery SM, Kusel J, Nicholas R, Adlard N. Costs and effectiveness of fingolimod versus alemtuzumab in the treatment of highly active relapsing-remitting multiple sclerosis in the UK: re-treatment, discount, and disutility. J Med Econ. 2017;20(9):962-73.
Su W, Kansal A, Vicente C, Deniz B, Sarda S. The cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing-remitting multiple sclerosis in Canada. J Med Econ. 2016;6998:1-10.
Mauskopf J, Fay M, Iyer R, Sarda S, Livingston T. Cost-effectiveness of delayed-release dimethyl fumarate for the treatment of relapsing forms of multiple sclerosis in the United States. J Med Econ. 2016;19(4):432-42.
Bin Sawad A, Seoane-Vasquez E, Rodríguez-Monguio R, Turkistani F. Cost-effectiveness of different strategies for treatment relapsing-remitting multiple sclerosis. J Comp Eff Res. 2017;6(2):97-108.
Noyes K, Bajorska A, Chappel A, Schwid SR, Mehta LR, Weinstock-Guttman B, *et al.* Cost-effectiveness of disease-modifying therapy for multiple sclerosis: A population-based study. Neurology. 2011;*77*(4):355-63.
Soini E, Joutseno J, Sumelahti ML. Cost-utility of first-line disease-modifying treatments for relapsing-remitting multiple sclerosis. Clin Ther. 2017;39(3):537-557.e10.

Appendix J. Studies excluded

Sánchez-de la Rosa R, Sabater E, Casado MA, Arroyo R. Cost-effectiveness analysis of disease modifiying drugs (interferons and glatiramer acetate) as first line treatments in remitting-relapsing multiple sclerosis patients. J Med Econ. 2012;15(3):424-33.
Nikfar S, Kebriaeezadeh A, Dinarvand R, Abdollahi M, Sahraian MA, Henry D, *et al.* Cost-effectiveness of different interferon beta products for relapsing-remitting and secondary progressive multiple sclerosis: Decision analysis based on long-term clinical data and switchable treatments. Daru. 2013;21(1):50.
Darbà J, Kaskens L, Sánchez-de la Rosa R. Cost-effectiveness of glatiramer acetate and interferon beta-1a for relapsing-remitting multiple sclerosis, based on the CombiRx study. J Med Econ. 2014;17(3):215-22.
Dembek C, White LA, Quach J, Szkurhan A, Rashid N, Blasco MR. Cost-effectiveness of injectable disease-modifying therapies for the treatment of relapsing forms of multiple sclerosis in Spain. Eur J Heal Econ. 2014;15(4):353-62.
Pan F, Goh JW, Cutter G, Su W, Pleimes D, Wang C. Long-term cost-effectiveness model of interferon beta-1b in the early treatment of multiple sclerosis in the United States. Clin Ther. 2012;34(9):1966-76.
Zhang X, Hay JW, Niu X. Cost effectiveness of fingolimod, teriflunomide, dimethyl fumarate and intramuscular interferon-β1a in relapsing-remitting multiple sclerosis. CNS Drugs. 2015;29(1):71-81.
Lee S, Baxter DC, Limone B, Roberts MS, Coleman CI. Cost-effectiveness of fingolimod versus interferon beta-1ª for relapsing remitting multiple sclerosis in the United States. J Med Econ. 2012;15(6):1088-96.
Chevalier J, Chamoux C, Hammès F, Chicoye A. Cost-effectiveness of treatments for relapsing remitting multiple sclerosis: A French societal perspective. PLoS One. 2016;11(3):e0150703.
O'Day K, Meyer K, Stafkey-Mailey D, Watson C. Cost-effectiveness of natalizumab vs fingolimod for the treatment of relapsing-remitting multiple sclerosis: analyses in Sweden. J Med Econ. 2015;18(4):295-302.
Nuijten M, Mittendorf T. A health-economic evaluation of disease-modifying drugs for the treatment of relapsing-remitting multiple sclerosis from the German societal perspective. Clin Ther. 2010;32(4):717-28.
Agashivala NV, Dastani HB, Carlton R, Sarnes E. Cost-effectiveness of fingolimod in treating patients with relapsing-remitting multiple sclerosis. Am J Pharm Benefits. 2011;3(6):320-8.
Palace J, Duddy M, Bregenzer T, Lawton M, Zhu F, Boggild M, *et al.* Effectiveness and cost-effectiveness of interferon beta and glatiramer acetate in the UK Multiple Sclerosis Risk Sharing Scheme at 6 years: A clinical cohort study with natural history comparator. Lancet Neurol. 2015;14(5):497-505.
Bozkaya D, Livingston T, Migliaccio-Walle K, Odom T. The cost-effectiveness of disease-modifying therapies for the treatment of relapsing-remitting multiple sclerosis. J Med Econ. 2017;20(3):297-302.

Appendix K. Characteristics of the studies included

Table K.1. Characteristics of the study by Imani *et al.*

Country, year	Iran, 2012
Model	Markov's model
Cycles and health status	Monthly cycles EDSS 0.0-2.5 EDSS 3.0-5.5 EDSS 6.0-7.5 EDSS 8.0-9.5 Relapse EDSS 0.0-2.5 Relapse EDSS 3.0-5.5 Death
Origen de los datos	Similar cost-effectiveness studies
Currency	US dollar, 2011
Time horizon	Lifespan (unspecified)
Discount rate	Costs: 7.2% Effects: 7.2%
Population	Unspecified characteristics
Interventions	Four arms IM interferon beta 1a SC interferon beta 1a Interferon beta 1b Symptomatic treatment-placebo (control)
Outcomes	ICER/QALY Lost productivity cost
Sponsor	None

Table K.2. Characteristics of the study by Montgomery *et al.*

Country, year	United Kingdom, 2016
Model	Discrete event simulation
Cycles and health status	The events listed are not status EDSS change Progression to secondary MS EDSS change in secondary MS Relapse Drug withdrawal Adverse event Death
Data source	Theoretical cohort based on the FREEDOMS and TRANSFORMS trials. The London, Ontario Registry was used for EDSS > 8
Currency	Pound sterling, 2015
Time horizon	Lifespan (maximum 100 years)
Discount rate	Costs: 3.5% Effects: 3.5%
Population	Patients in the phase III fingolimod studies (severe rapidly progressive MS).
Interventions	Two arms Fingolimod (control) Natalizumab
Outcomes	Net monetary benefit QALY Cost of administering DMT Cost of disease Cost per relapse Treatment cost Adverse effect cost
Sponsor	Novartis pharmaceuticals (fingolimod)

Table K.3. Characteristics of the study by Maruszczak *et al.*

Country, year	United Kingdom, 2014
Model	Markov's model
Cycles and health status	Annual cycles EDSS RRMS 0 EDSS RRMS 1 EDSS RRMS 2 EDSS RRMS 3 EDSS RRMS 4 EDSS RRMS 5 EDSS RRMS 6 EDSS RRMS 7 EDSS RRMS 8 EDSS RRMS 9 EDSS SPMS 0 EDSS SPMS 1 EDSS SPMS 2 EDSS SPMS 3 EDSS SPMS 4 EDSS SPMS 5 EDSS SPMS 6 EDSS SPMS 7 EDSS SPMS 8 EDSS SPMS 9 Death
Data source	Two comparative theoretical cohorts of patients with highly active multiple sclerosis, based on the FREEDOMS, FREEDOMS II and TRANSFORMS trials.
Currency	Pound sterling, 2013-2014
Time horizon	50 years
Discount rate	Costs: 3.5% Effects: 75% at 2 years, 50% at 5 years
Population	Characteristics left unspecified
Interventions	Two arms Fingolimod Dimethyl fumarate (control)
Outcomes	QALY Costs
Sponsor	Novartis pharmaceuticals (fingolimod)

Table K.4. Characteristics of the study by Montgomery *et al.*

Country, year	United Kingdom, 2017
Model	Discrete event simulation
Cycles and health status	The events listed are not status EDSS change Progression to secondary MS EDSS change in secondary MS Relapse Withdrawal of the drug Adverse event Death
Data source	Aggregate cohort of patients with highly active multiple sclerosis, based on the FREEDOMS, FREEDOMS II and TRANSFORMS trials.

Appendix K *(cont.)*. Characteristics of the studies included

Table K.4 *(cont.)*. Characteristics of the study by Montgomery *et al.*

Currency	Pound sterling, 2015
Time horizon	100 years
Discount rate	Costs: 3.5% Effects: 3.5%
Population	1,381 patients, mean age 38.2 years, 2.8 times more women than men, 6.42 years from diagnosis
Interventions	Two arms Fingolimod (control) Alentuzumab
Outcomes	Total cost QALY ICER Net monetary benefit
Sponsor	Novartis pharmaceuticals (fingolimod)

Table K.5. Characteristics of the study by Mauskopf *et al.*

Country, year	USA, 2015
Model	Markov's model
Cycles and health status	Annual cycles EDSS 0 EDSS 1.0-1.5 EDSS 2.0-2.5 EDSS 3.0-3.5 EDSS 4.0-4.5 EDSS 5.0-5.5 EDSS 6.0-6.5 EDSS 7.0-7.5 EDSS 8.0-8.5 EDSS 9.0-9.5 Death
Data source	Theoretical cohort based on the DEFINE and CONFIRM trials, up to EDSS = 6 The London, Ontario Registry was used for EDSS > 7
Currency	US dollar, 2015
Time horizon	20 years
Discount rate	Costs: 3% Effects: 3%
Population	Mean age: 38 years, EDSS 0-6
Interventions	Three arms Dimethyl fumarate 240 mg (control) Glatiramer acetate 20 mg Fingolimod 0,5 mg
Outcomes	Total cost QALY ICER Life years gained
Sponsor	Biogen Idec (dimethyl fumarate)

Table K.6. Characteristics of the study by Su *et al.*

Country, year	Canada, 2016
Model	Markov's model
Cycles and health status	Annual cycles EDSS RRMS 0 EDSS RRMS 1 EDSS RRMS 2 EDSS RRMS 3 EDSS RRMS 4 EDSS RRMS 5 EDSS RRMS 6 EDSS RRMS 7 EDSS RRMS 8 EDSS RRMS 9 EDSS SPMS 0 EDSS SPMS 1 EDSS SPMS 2 EDSS SPMS 3 EDSS SPMS 4 EDSS SPMS 5 EDSS SPMS 6 EDSS SPMS 7 EDSS SPMS 8 EDSS SPMS 9 Death
Data source	Theoretical cohort based on the DEFINE and CONFIRM trials, up to EDSS = 6 The London, Ontario Registry was used for EDSS > 7
Currency	Canadian dollar, 2013
Time horizon	20 years
Discount rate	Costs: 5% Effects: 5%
Population	Cohort: mean age 37.8 years, 2.5 times more women than men, EDSS 0-6
Interventions	Three arms Dimethyl fumarate (control) Interferon beta 1a 44 µg SC Glatiramer acetate
Outcomes	Progression to disability cost Mean cost per relapse Treatment cost (administration, acquisition) Cost per adverse event Cost according to EDSS Total costs QALY ICER
Sponsor	Biogen Idec (dimethyl fumarate)

Appendix K *(cont.)*. Characteristics of the studies included

Table K.7. Characteristics of the study by Bin Sawad *et al.*

Country, year	USA, 2017
Model	Markov's model
Cycles and health status	Annual cycles EDSS 0.0-2.5 EDSS 3.0-5.5 EDSS 6.0-7.5 EDSS 8.0-9.5 Relapse EDSS 0.0-2.5 Relapse EDSS 3.0-5.5 Death
Data source	Unspecified
Currency	US dollar, 2014
Time horizon	20 years
Discount rate	Costs: 3% Effects: 3%
Population	Characteristics left unspecified
Interventions	Four arms Symptomatic management I interferon beta 1a as first line Natalizumab as second line Alemtuzumab as third line
Outcomes	ICER QALY
Sponsor	None

Table K.8. Characteristics of the study by Noyes *et al.*

Country, year	USA, 2011
Model	Markov's model
Cycles and health status	Annual cycles Status are left unspecified
Data source	Sonya Slifka trial
Currency	US dollar, 2005
Time horizon	10 years
Discount rate	Costs: 3% Effects: unspecified
Population	1,121 participants, who participated in the survey
Interventions	Five arms IM interferon beta 1a SC interferon beta 1a Interferon beta 1b Glatiramer acetate Basic support treatment (control)
Outcomes	QALY of each drug over 10 years ICER/QALY
Sponsor	Biogen Idec (Avonex), NIH/NMSS and others

Table K.9. Characteristics of the study by Soini *et al.*

Country, year	Finland, 2017
Model	Markov's model
Cycles and health status	Annual cycles EDSS RRMS 0 EDSS RRMS 1 EDSS RRMS 2 EDSS RRMS 3 EDSS RRMS 4 EDSS RRMS 5 EDSS RRMS 6 EDSS RRMS 7 EDSS RRMS 8 EDSS RRMS 9 EDSS SPMS 0 EDSS SPMS 1 EDSS SPMS 2 EDSS SPMS 3 EDSS SPMS 4 EDSS SPMS 5 EDSS SPMS 6 EDSS SPMS 7 EDSS SPMS 8 EDSS SPMS 9 Death
Data source	Finnish registry 1991-2010 London, Ontario Registry for progressive MS Cost of the DEFENSE survey
Currency	Euro, 2013-2014
Time horizon	15 years
Discount rate	Costs: 3% Effects: 3%
Population	Cohort: 713 patients, mean age 35.6 years, 2.57 times more women than men, EDSS 0-6.5
Interventions	Seven arms IM interferon beta 1a 30 µg SC interferon beta 1a 44 µg Interferon beta 1b 250 µg Glatiramer acetate 20 mg Teriflunomide 14 mg Dimethyl fumarate 240 mg Placebo (control)
Outcomes	ICER/QALY
Sponsor	Sanofi Genzyme (teriflunomide)

DMT: Disease-Modifying Therapy; EDSS: Expanded Disability Status Scale; ICER: Incremental Cost-Effectiveness Ratio; IM: Intramuscular; QALY: Quality-Adjusted Life-Year; RRMS: Relapsing-Remitting Multiple Sclerosis; SC: Subcutaneous; SPMS: Secondary Progressive Multiple Sclerosis.

Appendix L. Bias assessment as proposed by Evers S, Hiligsmann M, Adarkwah CC. Risk of bias in trial-based economic evaluations: Identification of sources and bias-reducing strategies. Psychol Health. 2015;30(1):52-71.

Biases appeared at three different stages in the pharmaco-economic analysis: at the pre-trial phase (planning and design), at the trial phase proper (data collection and analysis) and at the post-trial phase (publication). The biases identified at each phase are as follows:

- Pre-trial phase:
  - Narrow perspective bias: selecting a perspective that does not encompass all the different outcomes, leaving out key costs and results.
  - Inefficient comparator bias: the most cost-effective therapy is not made available; new treatments are compared with the "best standard of care", resulting in an overestimation of costs and outcomes.
  - Unmeasured costs bias: expenses that could negatively affect the cost-effectiveness of the new therapy are not taken into consideration, which leads to an overestimation of incremental costs.
  - Intermittent data collection bias: no information is provided regarding the periods of time during which information must be collected. Given the variability of costs, this may lead to costs being over- or underestimated.
- Trial phase:
  - Invalid valuation bias: the monetary value given to some measurements may be incorrect, which leads to costs being over- or underestimated.
  - Ordinal incremental cost-effectiveness ratio bias: it occurs when the ICER value is calculated on an ordinal scale (i.e. low, intermediate, high) rather than an interval one (i.e. from 0 to 100). As a result, the value obtained cannot be used for mathematical calculations, which makes the ratio uninformative and/or uninterpretable.
  - Double counting bias: the value of some cost or benefit associated with the treatment was considered more than once when calculating the results, which leads to costs being over- or underestimated.
  - Inappropriate discount bias: the ICER value may indicate that a treatment is cost-effective or not depending on the discount applied within the time horizon, and on the cycles proposed.
  - Limited sensitivity analysis bias: such an analysis makes it possible to test the ICER in other contexts, where significant variables are modified within an established range. If the analysis cannot be conducted properly, the level of certainly associated to the ICER may be erroneously considered to be too low.
- Post-trial phase:
  - Sponsorship bias: sponsor-led pharmacoeconomic studies tend to result in favorable ICERs given their low methodological quality or interferences in the outcome analysis process.
  - Dissemination and reporting bias: this indicates a tendency not to report non-significant findings in indexed journals as opposed to non-indexed ones. Only a proportion of research projects get published in indexed journals and thus become easily identifiable for systematic reviews.

Appendix M. Specific biases in each study

Table M.1. Biases in the study by Imani *et al.*

Pre-trial phase	Narrow perspective: payer Inappropriate comparator: intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b *vs.* placebo as control Some costs were left unmeasured, such as the cost of managing adverse events associated to the therapy Intermittent data collection: the data collection method is not clearly described No sensitivity analysis was performed
Trial phase	Inappropriate discount: a discount of 7.2% was selected in an unjustified way
Post-trial phase	No

Table M.2. Biases in the study by Montgomery *et al.*

Pre-trial phase	Narrow perspective: payer
Trial phase	No
Post-trial phase	Sponsored by Novartis Pharmaceuticals, manufacturer of fingolimod, with favorable analytical results

Table M.3. Biases in the study by Maruszczak *et al.*

Pre-trial phase	Narrow perspective: payer
Trial phase	No
Post-trial phase	Sponsored by Novartis Pharmaceuticals, manufacturer of fingolimod, with favorable analytical results

Table M.4. Biases in the study by Montgomery *et al.*

Pre-trial phase	Narrow perspective: payer Inappropriate comparator: alemtuzumab vs. fingolimod as control in highly active disease
Trial phase	No
Post-trial phase	Sponsored by Novartis Pharmaceuticals, manufactured by fingolimod, with favorable analytical results

Apéndice M ***(cont.).*** Specific biases in each study

Table M.5. Biases in the study by Mauskopf *et al.*

Pre-trial phase	Narrow perspective: payer
Trial phase	No
Post-trial phase	Sponsored by Biogen Idec, manufacturer of dimethyl fumarate, with favorable analytical results

Table M.6. Biases in the study of Su *et al.*

Pre-trial phase	Narrow perspective: payer
Trial phase	No
Post-trial phase	Sponsored by Biogen Idec, manufacturer of dimethyl fumarate, with favorable analytical results

Table M.7. Biases in the study by Bin Sawad *et al.*

Pre-trial phase	Narrow perspective: payer Some costs were left unmeasured, such as the cost of managing adverse events associated to the therapy
Trial phase	No
Post-trial phase	No

Table M.8. Biases in the study by Noyes *et al.*

Pre-trial phase	Narrow perspective: payer Inappropriate comparator: intramuscular interferon beta-1a, subcutaneous interferon beta-1a, interferon beta-1b, glatiramer acetate vs. symptomatic control (placebo) as control Some costs were left unmeasured, such as the cost of managing adverse events associated to the therapy Intermittent data collection: information extracted from surveys
Trial phase	Inappropriate discount: discount was not specified
Post-trial phase	Sponsored by Biogen Idec, manufacturer of intramuscular interferon beta-1a. Analytical results were not favorable

Table M.9. Biases in the study by Soini *et al.*

Pre-trial phase	Narrow perspective: payer
Trial phase	No
Post-trial phase	Sponsored by Sanofi/Genzyme, manufacturer of teriflunomide, with favorable analytical results