Preparation Voting Panel Meeting 6 September 2021

Distribution list: CSC & ASC & VP

Consensus Group on Follow-on DMTs: Systematic Literature Review

Date: 20 August 2021

Background and scope of this document

The "Follow on DMTs in MS" Consensus Initiative aims

- to empower people with MS (PwMS) and MS healthcare providers to critically evaluate and differentiate the evidence available for any given FO-DMT, i.e., to help them to select products based on quality, and
- to avoid unintended harm (nocebo conditioning) by providing knowledge and re-assurance to PwMS and healthcare providers when directed by third-party decision makers to use such FO-DMTs

The initiative shall result in a peer-reviewed publication.

In this short document, we summarize the results of our systematic literature research on the subject conducted in preparation of the voting meeting on 6 September 2021. Performing and documenting a literature search (i.e. a systematic search) is an essential part of a modern consensus guideline development process.

Systematic literature search

Method

A modified Delphi process [Dalkey et al., 1963] was used to formulate specific questions to help guide a systematic Medline search strategy, as well as draft consensus statements. These were as follows:

- How frequently is information on phase I trials (PK/PD data) accessible and which assays were used in PK/PD studies?
- Feasibility of PK/PD studies for MS DMTs.
- Immunogenicity: what types of assays have been used to assess anti-drug antibodies? Is there a correlation with adverse reactions and clinical efficacy? What similarity or differences of immunogenicity are there between FO-DMTs and reference products?
- What equivalence margins have been used in clinical trials?
- Is there any evidence for:
  I. a loss of efficacy and/or
  II. an increase in immunogenicity and/or
  III. a change in safety if PwMS are switched from one drug to another? What is known about multiple switches? Has the nocebo effect of switching been explored?

- What has been the trial design of switching trials? What is the level of harmonisation of:
  I. efficacy
  II. toxicity and
  III. immunogenicity data in current registries? (Note: we would need to ask the registries whether they register this information on FO-DMTs)
- How frequently is information on long-term follow-up and/or pharmacovigilance accessible?
- How frequently is information on cost effectiveness accessible?

The general PubMed search string used was: ((Multiple sclerosis) OR (glatiramer acetate OR copaxone) OR (interferon beta OR extavia) OR (nocebo)) AND (generic OR generic drugs OR hybrid OR biosimilar OR follow-on drugs OR non-complex biological drug OR NCBD OR subsequent entry drug OR therapeutic equivalence), using the following search filters: clinical trials, clinical studies, comparative studies, controlled clinical trial, meta-analysis, systematic review, observational studies. The complete PubMed search string is shown in Table 1. The inclusion and exclusion criteria applied to the search results was as follows. (1) Participants: included adult PwMS, or healthy volunteers. (2) Interventions: included FO generic products for the treatment of MS, including glatiramer acetate and any FO-DMT (e.g. interferon beta), hybrid drug, NBCDs or biosimilar; excluded small molecule follow-on generic products. (3) Comparisons: included placebo, baseline, and comparator-controlled studies. (4) Outcomes: included efficacy, immunogenicity, safety and tolerability. (5) Study design: included systematic literature reviews and meta-analyses, randomised clinical trials, observational studies, PK/PD studies; excluded animal studies, retrospective studies. Global and regional multiple sclerosis and neurological conference abstracts were also searched manually for information that met the systematic review search criteria. Publications were graded according to Oxford Centre for Evidence-based Medicine Levels of Evidence 1. [OCEBM Levels of Evidence Working Group, 2009]

Table 1. Complete PubMed search string used (10 March 2021).

(("multiple sclerosis"[MeSH Terms] OR ("multiple"[All Fields] AND "sclerosis"[All Fields]) OR "multiple sclerosis"[All Fields]) OR ("glatiramer acetate"[MeSH Terms] OR ("glatiramer"[All Fields] AND "acetate"[All Fields]) OR "glatiramer acetate"[All Fields]) OR (("interferon-beta"[MeSH Terms] OR "interferon-beta"[All Fields] OR ("interferon"[All Fields] AND "beta"[All Fields]) OR "interferon beta"[All Fields]) OR ("interferon beta-1b"[MeSH Terms] OR ("interferon"[All Fields] AND "beta-1b"[All Fields]) OR "interferon beta-1b"[All Fields] OR "extavia"[All Fields])) OR ("nocebo effect"[MeSH Terms] OR ("nocebo"[All Fields] AND "effect"[All Fields]) OR "nocebo effect"[All Fields] OR "nocebo"[All Fields])) AND (("drugs, generic"[MeSH Terms] OR ("drugs"[All Fields] AND "generic"[All Fields]) OR "generic drugs"[All Fields] OR "generic"[All Fields]) OR ("drugs, generic"[MeSH Terms] OR ("drugs"[All Fields] AND "generic"[All Fields]) OR "generic drugs"[All Fields] OR ("generic"[All Fields] AND "drugs"[All Fields])) OR ("chimera"[MeSH Terms] OR "chimera"[All Fields] OR "hybrid"[All Fields]) OR ("biosimilar pharmaceuticals"[MeSH Terms] OR ("biosimilar"[All Fields] AND "pharmaceuticals"[All Fields]) OR "biosimilar pharmaceuticals"[All Fields] OR "biosimilar"[All Fields]) OR (follow-on[All Fields] AND ("pharmaceutical preparations"[MeSH Terms] OR ("pharmaceutical"[All Fields] AND "preparations"[All Fields]) OR "pharmaceutical preparations"[All Fields] OR "drugs"[All Fields])) OR (non-complex[All Fields] AND ("biological factors"[MeSH Terms] OR ("biological"[All Fields] AND "factors"[All Fields]) OR "biological factors"[All Fields] OR ("biological"[All Fields] AND "drug"[All Fields]) OR "biological drug"[All Fields])) OR NCBD[All Fields] OR (subsequent[All Fields] AND entry[All Fields] AND drug[All Fields]) OR (("therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapeutic"[All Fields]) AND equivalence[All Fields])) AND (Clinical Study[ptyp] OR Clinical Trial[ptyp] OR Meta-Analysis[ptyp] OR Observational Study[ptyp] OR systematic[sb] OR Comparative Study[ptyp])

Results

The search strategy identified 193 publications in Medline, as of 10 March 2021. After the selection process had been applied, 20 full-text papers were included. A flow chart details the search results (Figure 1). A total of four conference abstracts were also included as these met the selection process criteria but did not duplicate information subsequently published as full papers. The combined results of the literature search are presented in tabular format (Table 2).

Figure 1. Search results.

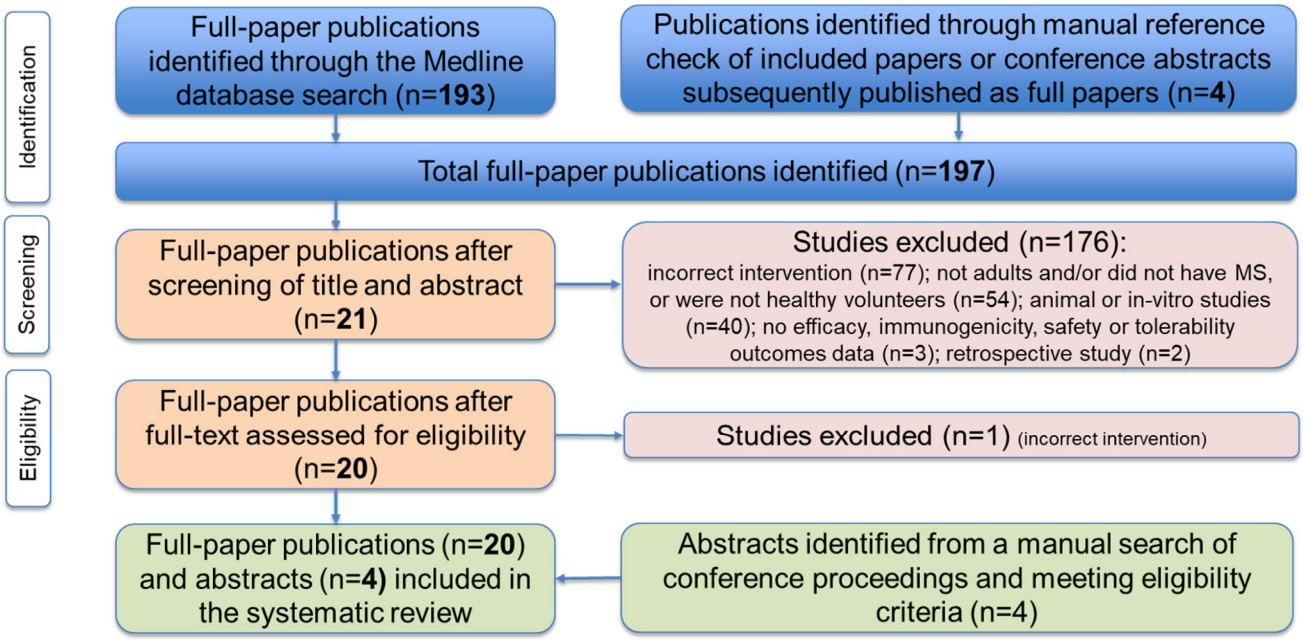

Table 2. Combined results of the literature search, including full-text papers (n=20) conference abstracts (n=4)[a] meeting the selection criteria.

Full published papers: FO-DMTs		
Publication	**Type of study/main results**	**Level of evidence[b]**
Cohen J, Belova A, Selmaj K, et al.; glatiramer acetate clinical trial to assess equivalence with Copaxone (GATE) study group. Equivalence of generic glatiramer acetate in multiple sclerosis: a randomized clinical trial. *JAMA Neurol* 2015; **72(12)**: 1433–41.	Randomised, double-blind, active- and placebo-controlled phase-3 trial. Patients were GA (20mg; n=353), brand GA (20mg; n=357), or placebo (n=84), by daily subcutaneous injection or 9 months. For gadolinium-enhancing lesions, the estimated ratio of generic drug to brand drug was 1.095 (95% CI, 0.883–1.360), which was within the predefined equivalence margin of 0.727 to 1.375. The incidence and severity of adverse events was similar in the generic drug and brand drug groups. Thus, the generic and brand drug had equivalent efficacy, safety, and tolerability.	1b

Selmaj K, Barkhof F, Belova AN, et al.; GATE study group. Switching from branded to generic glatiramer acetate: 15-month GATE trial extension results. *Mult Scler* 2017; **23(14)**: 1909–17.	Open-label 15-month follow-up of the double-blind, placebo-controlled GA clinical trial to assess equivalence with Copaxone (GATE) trial. A total of 729 patients received generic GA. Efficacy and safety generic GA was maintained over 2 years, and switching from GA to generic GA was safe and well tolerated.	2b
Boyko AN, Lashch NY, Sharanova SN, et al. [Comparative, placebo-controlled clinical study of efficacy and safety of glatiramer acetate 20mg in patients with relapsing-remitting multiple sclerosis: results of the first year of the study]. *Zh Nevrol Psikhiatr Im S S Korsakov*a 2016; **116(10 Pt 2)**: 61–7. Russian.	International multicentre randomised double-blind, active and placebo-controlled, comparative phase 3 trial. The goal of the study was to demonstrate non-inferiority of BCD-063 (GA, manufactured by JSC BIOCAD, Russia) to Copaxone in participants with RRMS. PwMS (n=158) were randomly assigned into three groups: BCD-063, Copaxone and placebo, at a ratio of 2:2:1, respectively. After 48 weeks of therapy the BCD-063 and Copaxone groups were similar in terms of both MRI parameters and frequency of relapses. Both drugs had a favourable safety profile.	2b
Boyko AN, Bosenko LP, Vasilovskiy VV, et al. [A comparative placebo-controlled clinical study on the efficacy and safety of interferon beta-1a for subcutaneous injections in patients with remitting multiple sclerosis: results of the first year of observations]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2017; **117(2. Vyp. 2)**: 107–13. Russian.	Double-blind placebo-controlled comparative randomized III phase study included 163 patients with RRMS. PwMS in Russia were randomised into three equal groups (Teberif, Rebif or placebo). After 52 weeks, the equivalent efficacy of Teberif and Rebif was shown. Teberif was shown to have a favourable safety and tolerability profile comparable to that of Rebif. The results suggest the therapeutic equivalency of the drugs in this population.	2b
Boyko AN, Bosenko LP, Vasilovskiy VV, et al. [Efficacy, tolerability and safety of the treatment with teberif: the results of a 2-year randomized clinical trial of treatment naïve patients with remitting multiple sclerosis, who have not received DMT, after switching from other interferon β-1a]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2019; 119(2. Vyp. 2): 73–85. Russian.	First period was a blinded RCT; second period was an open-label comparison. During the first period of the study, PwMS were randomised treatment with Teberif for 52 weeks, or Rebif for 52 weeks, or placebo for 16 weeks. After the first study period, PwMS were group-independently switched to take open-label Teberif over the next 48 weeks. Teberif and Rebif demonstrated equivalent efficacy with no significant for safety and tolerability parameters.	2b
Popova EV, Boĭko AN, Vasil'ev AV, et al.[Results of a comparative clinical trial of the Russian B – interferon-	This was a controlled, randomised, multicenter, parallel group open-label trial of the Russian interferon-1b bioanalogue (infibeta) or control (Extavia) in 122 PwMS. This study did not reveal any essential distinctions	2b

1b bioanalogue (infibeta)]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2012; **112(5)**: 56–61. Russian.	regarding efficiency and safety parameters between these two groups.	
Nafissi S, Azimi A, Amini-Harandi A, Salami S, Shahkarami MA, Heshmat R. Comparing efficacy and side effects of a weekly intramuscular biogeneric/biosimilar interferon beta-1a with Avonex in relapsing remitting multiple sclerosis: a double blind randomized clinical trial. *Clin Neurol Neurosurg* 2012; **114(7)**: 986–9.	Randomised double-blind trial in which Iranian participants with RRMS (n=84) were enrolled for a 24-month study period. PwMS were assigned randomly to receive either Avonex or CinnoVex, and efficacy and side effects compared over the 24-month period. There were no significant differences between groups after 24 months in parameters such as EDSS, number of T2-enhanced lesions or gadolinium-enhancing lesions. There were no significant differences between 2 groups regarding frequency and duration of most considerable side effects.	2b
Shahkarami MA, Vaziri B, Salami S, Harandi AA, Oger J. Neutralizing antibodies in multiple sclerosis patients on weekly intramuscular Avonex and biosimilar interferon beta-1a (CinnoVex): comparing results of measurements in two different laboratories. *J Immunol Methods* 2013; **388(1–2)**: 46–8.	Randomised double-blind trial in which Iranian participants with RRMS (n=84) were enrolled for a 24-month study period. PwMS were assigned randomly to receive either Avonex or CinnoVex, and neutralising antibodies assayed every 6 months. Similar results were obtained from CinnoVex and Avonex, suggesting that both drugs have a similar immunogenetic profile.	2b
Pakdaman H, Abbasi M, Gharagozli K, Ashrafi F, Delavar Kasmaei H, Amini Harandi A. A randomized double-blind trial of comparative efficacy and safety of Avonex and CinnoVex for treatment of relapsing–remitting multiple sclerosis. *Neurol Sci* 2018; **39(12)**: 2107–13.	Patients with RRMS (n=186) randomised to receive either Avonex or CinnoVex and were followed-up for four-and-a-half years. The patient population experienced a steady increase in EDSS during follow-up, with a mean increase of 1.03. ANOVA revealed no statistically significant difference between Avonex and CinnoVex (p=0.78). The most common adverse events were headache, myalgia, fatigue, fever, flu symptoms, injection site pain, and depression. There was no statistically significant difference in MRI activity and clinical activity between the two groups. Avonex and CinnoVex had similar efficacy and safety outcomes in patients with RRMS.	2b
Di Girolamo G, Kauffman MA, González E, et al. Bioequivalence of two subcutaneous pharmaceutical products of interferon beta Ia. *Arzneimittelforschung* 2008; **58(4)**: 193–8.	Blastoferon is an interferon beta-1a biosimilar to the innovator interferon beta-1a product (referred to as the reference product). Thirty-six healthy volunteers were enrolled. Twelve were included in an absolute bioavailability study, whereas 24 volunteered to participate in the relative bioavailability study. Both were open-label, blinded (for laboratory determinations), randomised, single-dose, two-period, cross-over studies. The absolute bioavailability assay involved i.v. and s.c. injection of Blastoferon, and the formal relative bioavailability study involved s.c. injections of both products. Blood samples for pharmacokinetic and pharmacodynamic profiling were	2b or 4 (t.b.c.)

	taken at intervals after injection. Results showed similar bioavailability of interferon beta-1a for both pharmaceutical products.	
Greenberg B, Hall S, Grabner M, Balu S, Zhang X, Kantor D. Multiple sclerosis relapse rates and healthcare costs of two versions of glatiramer acetate. *Curr Med Res Opin* 2020; **36(7)**: 1167–75.	Retrospective observational study comparing relapse rates and healthcare costs in patients treated with Glatopa and Copaxone in a managed-care population in the US. Patients (identified from the HealthCore Integrated Research claims Database). Cohorts were matched using exact and propensity score matching. Relapse rates (calculated using a validated algorithm) were compared using Chi-square tests, while costs (sum of plan-paid and patient-paid amounts) were compared using Wilcoxon tests. 633 Glatopa and 5586 Copaxone patients were identified; 158 per cohort were retained after matching. PwMS treated with Glatopa had similar health outcomes and costs compared with those treated with Copaxone.	4
Melnikov M, Sharanova S, Sviridova A, et al. The influence of glatiramer acetate on Th17-immune response in multiple sclerosis. *PLoS One* 2020; **15(10)**: e0240305.	Open-label controlled study in 25 PwMS and 25 healthy volunteers in Russia, to investigate the effects of Copaxone and generic GA (Timexone) on Th17- and Th1-type cytokine production. Original and generic GA demonstrated comparable modulation of inflammatory cytokine production.	4
Kasatkin DS, Spirin NN, Boiko AN, Stepanov IO, Spirina NN, Baranova NS. [The results of an open prospective study of β-interferon biosimilars (an Yaroslavl' cohort)]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2016; **116(2 Pt 2)**: 68–73. Russian.	Prospective non-randomised open-label long-term study of PwMS in the Yaroslavl oblast (an Yaroslavl' cohort). The study included 203 PwMS treated with DMT biosimilars (Cinnovex, Genfaxon Ronbetal/Interferon, or Infibeta) over 30 months. There was a significant decrease in the frequency of relapses in patients treated with biosimilars compared with baseline. For all biosimilars, with the exception of Infibeta, EDSS scores increased significantly. MRI results revealed an increase in the number of lesions in patients treated with cinnovex (+16.6%), genfaxon (+14.4%) and ronbetal (+10.6%) and a decrease of lesions on T2-WI in patients treated with infibeta (-14.5%). The most marked generalizsed responses were in the Cinnovex group (flu-like syndrome - 66% of the patients), local reactions were most marked in the Genfaxon group (82%). Thus, there were differences between some biosimilars and original DMTs regarding safety and efficacy, requiring further study.	4
Popova EV, Boĭko AN, Davydovskaia MV, et al. [The first experience of the use the Russian B-interferon-1b biosimilar (infibeta) in the daily practice of the Moscow Center of Multiple Sclerosis]. *Zh Nevrol Psikhiatr Im S S Korsakova* 2013; **113(10 Pt 2)**: 93–6. Russian.	Summary of the 1-year experience of using the Russian beta-interferon-1b biosimilar (Infibeta) in 123 PwMS, including 65 patients with RRMS and 58 patients with SPMS. A significant decrease in the frequency of exacerbations per year was seen, and stabilisation of disability without a rise in EDSS scores in more than 50% of PwMS. Good tolerability comparable to that of the original drug was observed.	4
Abolfazli R, Pournourmohammadi S,	A non-interventional open-label cohort study to evaluate the safety, tolerability and efficacy of a brand-generic GA	4

Shamshiri A, Samadzadeh S. Tolerability and safety profile of a new brand-generic product of glatiramer acetate in Iranian patients with relapsing-remitting multiple sclerosis: an observational cohort study. *Curr Ther Res Clin Exp* 2018; **88**: 47–51.	product (Copamer, 40mg/mL) in Iranians with RRMS (n=185) over a 12-month period. Copamer was well tolerated in this group of Iranian PwMS and patient adherence was favourable over a 1-year period.	
Shokrollahi Barough M, Ashtari F, Sadat Akhavi M, et al. Neutralizing antibody production against Rebif® and ReciGen® in Relapsing-Remitting Multiple Sclerosis (RRMS) patients and its association with patient's disability. *Int Immunopharmacol* 2018; **62:** 109–13.	Comparing two groups of PwMS taking Rebif (n=37) and ReciGen (n=34) regarding neutralising antibody development against recombinant IFN-β, and neutralising antibody status correlation with EDSS score of patients from diagnosis to the end of the study. The type of IFN-β used had no significant effect on neutralising antibody positivity. Both groups had comparable EDSS score changes, and neutralising antibody status of PwMS correlated with EDSS scores.	4
Abolfazli R, Hosseini A, Gholam K, Javadi MR, Torkamandi H, Emami S. Quality of life assessment in patients with multiple sclerosis receiving interferon beta-1a: a comparative longitudinal study of Avonex and its biosimilar Cinnovex. *ISRN Neurology* 2012; **2012**: 786526.	30-month non-randomised longitudinal study in Iranian patients with RRMS (n=92), categorised to receive interferon beta-1a (Avonex or Cinnovex), assessing quality of life. The results of the study revealed no significant difference between the two groups with regard to physical health, health perception, energy, and role limitations due to physical problems, pain, sexual and social function, and physical health distress scores. Furthermore, interferon therapy did not significantly affect patients' quality of life after a year of treatment with either Avonex or Cinnovex.	4
Naser Moghadasi A, Darki A, Masoumi P, Hashemi SN, Ghadiri F. Evaluating the efficacy and safety of Zytux™ (Rituximab, AryoGen pharmed) in Iranian multiple sclerosis patients: an observational study. *Mult Scler Relat Disord* 2019; **36**: 101419.	The files of 100 PwMS, who received Zytux (Rituximab) at Sina MS Clinic in Tehran, Iran, were analysed in this hospital-based observational study. Participants had relapsing remitting MS (RRMS, n=20), primary progressive MS (PPMS, n=20), and secondary progressive MS (SPMS, n=60). Results revealed that the Zytux could have a positive and significant effect on all types of MS.	4
Full published papers: Studies evaluating nocebo effects		
Publication	**Type of study**	**Level of evidence[a]**
Gklinos P, Papadopoulos D, Mitsikostas DD. Nocebo in multiple sclerosis trials: a meta-analysis on oral and newer injectable disease-modifying treatments. *Mult Scler Relat Disord* 2019; **36**: 101389.	Systematic review and meta-analysis based on RCTs. This study concluded that oral DMTs may be associated with higher nocebo incidence and severity rates than newer injectables.	1a
Spanou I, Mavridis T, Mitsikostas DD. Nocebo in	Systematic review, not limited to RCTs, included observational studies, but required a comparator arm.	3a

biosimilars and generics in neurology: a systematic review. *Front Pharmacol* 2019; **10**: 809.	Concluded that the true burden of the nocebo response and its effect cannot be estimated accurately in existing studies with generics and biosimilars in neurological diseases.	
Abstracts		
Publication	**Type of study**	**Level of evidence[a]**
Oberye J, van den Tweel E, Mulder M, Voortman G, Hooftman L. Randomised, double-blind, cross-over trial of GTR (generic glatiramer acetate) in healthy volunteers shows similar tolerability and safety to Copaxone. *J Neurol* 2012; **259:** 1–236. P477. (Abstract.)	Randomised, double-blind, cross-over trial of generic GA and Copaxone in healthy volunteers (n=20), conducted to compare occurrence of local injection site reactions and adverse events. Volunteers were randomised to receive each injection separated by 4 days as sequence 1: generic GA–Copaxone–generic GA–Copaxone, or sequence 2: Copaxone–generic GA–Copaxone–generic GA. Local tolerance and gross safety profiles were similar between groups.	2b
Boyko A, Zakharova M, Kotov S et al. Efficacy and safety of generic glatiramer acetate Timexon®: results of the 12-month extension of BCD-063-1 international double-blind randomized placebo-controlled clinical study of efficacy and safety of Timexon® in comparison with Copaxone®. ECTRIMS 2017; P698.	The efficacy and safety of generic glatiramer acetate Timexon was compared with the originator glatiramer acetate (Copaxone) or placebo during a 48-week double-blind period (n=158), followed by a 1-year open-lable observational period in which all patients were switched (or maintained on) Timexon. According to results of the first study period, Timexon and Copaxone did not differ by the number of combined unique active lesions and other key MRI outcomes, relapse-related outcomes, or safety parameters. Both glatiramer acetate showed superiority over the placebo group. During the whole study period (96 weeks), groups did not differ by EDSS, multiple sclerosis functional composite, SF-36 or Beck's depression scores; or frequency, nature, or severity of adverse events. Overall, Timexon demonstrated stable efficacy and a good safety and tolerability profile during the 96-week study period, and when switching from Copaxone.	2b
Ramirez D, Verdi D, Wu Y, Gandhi S, Grossman I, Zeskind B, Flores J, Grinspan A. Rates of adverse events and multiple sclerosis relapses before and after introduction of a purported generic glatiramer acetate in Mexico: a 3-year update from a large patient support program in Mexico. *Mult Scler J* 2016; **23(1**): 142. P-63. (Abstract.)	Patient-reported data on adverse events, relapses, for patients receiving and generic GA or branded GA were collected through the branded GA Patient Support Program (PSP) in Mexico. Outcomes reported in 2012 (when only branded GA was available) were compared with those reported in 2013, 2014, and 2015 (when both products were dispensed). The total number of adverse events and relapses reported in 2013 was significantly higher (p<0.05) than in 2012. The increase in adverse events and relapses in PwMS in Mexico during 2013 raise questions about the interchangeability and comparability of generic GA to branded GA regarding treatment safety and efficacy.	4
Alexander J, Kasturi J, Melamed-Gal S, Ariely R, Vardi M, Su Z, Brecht T, Bryant A. Real-world switching patterns among US generic glatiramer acetate multiple sclerosis	Adult PwMS with ≥1 pharmacy claim or written prescription for FOGA (Glatopa, 20mg/mL) between 1 June 2015 and 30 September 2017 (n=1957) were analysed from OM1, a US health claims database. The majority of FOGA-treated patients who discontinued did so within a relatively short time period. The majority who switched to another DMT switched to branded GA.	4

patients. *Neurology* 2019; **92(Suppl 15)**: P3.2-099. (Abstract.)		

[a]The following meetings abstract records were searched: AAN (American Academy of Neurology), ACTRIMS (Americas Committee for Treatment in Multiple Sclerosis), EAN (European Academy of Neurology), ECTRIMS (European Committee for Treatment and Research in Multiple Sclerosis), EFNS (European Federation of Neurological Societies), ENS (European Neurological Society), LACTRIMS (Latin American Committee for Treatment and Research in Multiple Sclerosis), MENACTRIMS (Middle-East North Africa Committee for Treatment and Research in Multiple Sclerosis), PACTRIMS (Pan-Asian Committee for Treatment and Research in Multiple Sclerosis).

[b]OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). 2009 https://www.cebm.ox.ac.uk/resources/levels-of-evidence (accessed 13 May 2021).

For therapy/prevention/aetiology/harm:

1a, systematic review of randomised controlled trials (RCTs);

1b, individual RCT; 2a, systematic review of cohort studies;

2a, systematic review of cohort studies;

2b, individual cohort study (including low quality RCTs, e.g. <80% follow-up);

2c, 'outcomes' research, ecological studies;

3a, systematic review of case–control studies;

3b, individual case–control study;

4, case series (and poor-quality cohort and case–control studies);

5, expert opinion without explific critical appraisal, or based on physiology, bench research or 'first principles'.

References

- Dalkey N, Helmer O. An experimental application of the Delphi method to the use of experts. Manag Sci 1963; 9(3): 458–67.
- OCEBM Levels of Evidence Working Group. Oxford Centre for Evidence-based Medicine – Levels of Evidence (March 2009). Available from: https://www.cebm.ox.ac.uk/resources/levels-of-evidence (accessed 25 May 2021). – Direct link to the 2009 criteria: Direct link to 2009 criteria: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009