Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Oral Multiple Sclerosis Drugs

Date of Review: September 2015
PDL Class: Multiple Sclerosis

Date of Last Review: September 2014
Literature Search: July 2014 – June 2015

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:

- There is insufficient comparative evidence between oral disease modifying drugs for multiple sclerosis (MS) and other oral or injectable disease-modifying therapies.
- Moderate-quality evidence demonstrates the proportion of patients who experience at least one relapse over 2 years is reduced with use of dimethyl fumarate compared to placebo (relative risk [RR] = 0.58; 95% CI, 0.50 to 0.67, p<0.00001) but not when compared to glatiramer acetate (RR=0.91; 95% CI, 0.72 to 1.13);[1] however, the quality of the evidence to support benefit of dimethyl fumarate to slow worsening disability versus placebo is low (RR = 0.66; 95% CI, 0.53 to 0.81).[2]
- According to the National Institute for Health and Clinical Excellence (NICE), there is low quality evidence fampridine (ie, dalfampridine), which is not a disease-modifying drug, may be more effective than placebo in response outcomes to different walking ability parameters are assessed; however, there is low quality evidence that there is no difference in efficacy between fampridine and placebo in time to walk 8 meters and there is insufficient evidence to determine if fampridine improves gait speed versus placebo.[3] In addition, there is low quality evidence that there is no difference in the MS walking scale (MSWS-12) scores with fampridine compared to placebo.[3] The NICE recommends against the use of dalfampridine due to poor cost effectiveness.[3]
- There is low-quality evidence, based on one phase 3 trial, that a daily dose of 7 mg and 14 mg of terflunomide may reduce time to first relapse in patients with a first clinical episode suggestive of MS (14 mg vs. placebo: hazard ratio [HR]=0.574 [95% CI, 0.379-0.869; p=0.0087] and 7 mg vs. placebo: HR=0.628 [95% CI, 0.416-0.949; p=0.0271].[4] It is currently FDA-approved to treat relapsing-remitting forms of multiple sclerosis (RRMS).[5]
- A follow-up phase 3 trial of fingolimod confirms results from previous phase 3 trials, and provides moderate-quality evidence the drug significantly reduces relapse rates versus placebo in patients with RRMS (fingolimod 0.5 mg: rate ratio [RR]=0.52 (95% CI, 0.40-0.66; p<0.0001).[6] It is currently FDA-approved to treat RRMS, to reduce the frequency of clinical exacerbations, and to delay the accumulation of physical disability in these patients.[7]

Recommendations:

- Update clinical prior authorization criteria for oral MS drugs to reflect Guideline Note 95 that restricts coverage to RRMS only (see **Appendix 5**).
- No change to the current PDL recommended at this time.

Previous Conclusions:

- There is moderate strength of evidence that glatiramer 40 mg three times a week (tiw), a recently approved dosage and new formulation, reduced annualized relapses compared to placebo by 34% (mean ARR = 0.331 vs. 0.505; RR 0.66 [95% CI 0.539 to 0.799], $p < 0.0001$) based on one 12-month, good quality study. Limited data suggests similar efficacy to glatiramer 20 mg daily, however, no direct comparisons are available.
- There is low-moderate strength of evidence that fingolimod 0.5 mg reduced the mean annualized relapse rate by 48% in patients with relapsing-remitting multiple sclerosis (MS) compared to placebo, 0.21 versus 0.40, respectively (rate ratio 0.52, 95% CI 0.40 to 0.66; $p<0.001$) as demonstrated by one fair quality study.
- There is moderate strength of evidence from one good-quality study that peginterferon beta-1a significantly reduced relapses in patients with relapsing-remitting MS when given every 14 or 29 days compared to placebo. Annualized relapse rates at 48 weeks were 0.397 for placebo, 0.256 for peginterferon beta-1a every 2 weeks and 0.288 for peginterferon beta-1a every 4 weeks. The most common adverse event with active treatment were injection site reactions which were higher in the peginterferon beta-1a groups receiving injections every 2 weeks.
- There is low strength of evidence indicating dimethyl fumarate 720 mg daily reduced the risk of relapse (RR 0.75, 95% CI 0.59 to 0.96) and improved annualized relapse rate (rate ratio 0.69, 95% CI 0.51 to 0.96) compared with glatiramer 20 mg. This was based on one fair quality 2-year, placebo-controlled trial comparing dimethyl fumarate and glatiramer with placebo. The study was not designed to directly compare dimethyl fumarate with glatiramer and there was no difference in preventing disability progression.
- There is insufficient evidence that dimethyl fumarate is more effective than other treatment options in slowing disability progression in patients with RRMS.
- Based on an indirect study, there is low quality evidence that dimethyl fumarate is associated with more adverse events than glatiramer, but no differences in serious adverse events or withdrawals due to adverse events.
- The evidence supports a benefit of interferon beta-1b SC over interferon beta-1a IM in relapse outcomes (1.51, 95% CI 1.11 to 2.07; NNT 6). There is conflicting evidence on disease progression outcomes.
- Three head to head trials suggest a benefit of interferon beta-1a SC over interferon beta-1a IM in relapse outcomes, with no differences in disease progression.
- There is insufficient evidence to identify any differences between interferon beta-1b SC and interferon beta-1a SC.
- There is no head to head evidence available for teriflunomide and insufficient evidence to determine its efficacy and safety.

Methods:

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, NICE, Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

A systematic review[1] aimed to conduct a meta-analysis after assessing the efficacy and safety of dimethyl fumarate for the treatment of RRMS. Eligible studies were published, blinded RCTs evaluating dimethyl fumarate monotherapy compared to placebo or an active control for the treatment of RRMS in adults (≥18 years of age).[1] Evaluation of efficacy was based on the annualized relapse rate at 2 years, the proportion of patients who relapsed, or proportion of patients who had confirmed progression of disability by 2 years.[1] Safety evaluations were based on the proportion of patients who experienced any adverse event, any serious adverse event, or proportion of patients who discontinued treatment due to adverse events or died from any cause.[1] Only 3 RCTs were identified and eligible for qualitative review; only 2 of these RCTs were eligible for meta-analysis.[1] In brief, the two 96-week studies (n=2,651) included in the meta-analysis were phase 3, double-blind placebo-controlled RCTs which evaluated the effectiveness of dimethyl fumarate 240 mg twice daily and three times daily as monotherapy in adult patients with RRMS; a third arm in one of the studies also assessed a third group of patients who received subcutaneous daily injections of glatiramer acetate.[1] In this review, only the FDA-approved twice daily dose will be discussed.[1] The annualized rate of relapse at 2 years was significantly reduced with dimethyl fumarate when compared to placebo ($p<0.001$).[1] In patients with one or no relapse in the year prior to study entry, the annualized rate of relapse with dimethyl fumarate was reduced by 50%; in patients with 2 or more relapses in the year prior to study entry, the annualized rate of relapse was decreased by 47%.[1] The difference between dimethyl fumarate and glatiramer acetate was not significantly different.[1] In both RCTs, the proportion of patients who had at least 1 relapse of MS by 2 years was significantly reduced with dimethyl fumarate (relative risk [RR] = 0.58; 95% CI, 0.50 to 0.67, $p<0.00001$).[1] However, there was no statistically significant difference in the proportion of patients with a relapse by 2 years between dimethyl fumarate and glatiramer acetate (RR = 0.91; 95% CI, 0.72 to 1.13).[1] Dimethyl fumarate was also associated with reduced risk of confirmed progression of disability over 2 years compared to placebo (RR = 0.66; 95% CI, 0.53 to 0.81).[1] Overall, there was no significant difference in the frequency of any adverse events between dimethyl fumarate and placebo (RR = 1.02; 95% CI, 1.00 to 1.05).[1] Adverse events that occurred more frequently with dimethyl fumarate in both trials compared to placebo included: flushing and gastrointestinal events (e.g., diarrhea, nausea, and upper abdominal pain).[1] However, glatiramer acetate was associated with significantly fewer adverse events compared to dimethyl fumarate (RR = 1.09; 95% CI, 1.04 to 1.14).[1]

A recent systematic review[2] from the Cochrane Collaboration specifically aimed to review the evidence of dimethyl fumarate as monotherapy or combination therapy compared to placebo or other disease modifying therapies for MS. All parallel-group RCTs with a length of follow-up of at least 1 year were included. The 2 placebo-controlled Phase 3 trials previously assessed by Kawalec, et al.[1] were the only trials identified in the Cochrane review; the data from the Cochrane meta-analysis were similar and will not be reported again. The authors concluded there is "moderate-quality evidence to support that dimethyl fumarate at a dose of 240 mg orally three times daily or twice daily reduces both the number of patients with a relapse and the annualized rate over 2 years of treatment in comparison to placebo. However, the quality of the evidence to support the benefit in reducing the number of patients with disability worsening is low."[2]

Both systematic reviews of dimethyl fumarate found flushing and gastrointestinal events to be the most common adverse effects associated with the drug.[1,2] Both lymphocytopenia (abnormally low level of lymphocytes in the blood) and leukopenia (decreased number of white blood cells) were significantly more common with dimethyl fumarate than with placebo.[2] The FDA approved the twice daily regimen because it had similar efficacy and safety as the three times daily regimen in the Phase 3 trials.[8]

New Guidelines:
The NICE updated their clinical guideline for the management of multiple sclerosis symptoms in October 2014.[3] This specific guideline does not address the use of disease-modifying treatments.[3] Relevant outcomes identified by in this guideline to assess management of MS symptoms were: quality of life; changes in disability or impairment scales assessing motor function, fatigue, spasticity, and walking speed; and incidence of adverse events.[3] Dalfampridine was the only drug in the OHP PDL addressed in this guideline. It is an oral drug approved in the U.S. and previously reviewed by this P&T committee. It is formerly known as fampridine,[9] and was specifically evaluated for its efficacy in improving mobility in MS patients. In total, 4 parallel RCTs and 4 crossover RCTs were identified. In terms of assessing walking ability, "low quality evidence from 3 studies (n=738) showed fampridine was clinically effective compared to placebo at obtaining a positive response to treatment. Moderate quality evidence from 1 study (n=8) showed that there was no difference between fampridine and placebo in time to walk 8 meters. Very low quality evidence from 2 studies (n=334) showed there was no difference in clinical effectiveness between fampridine and placebo in terms of gait speed."[3] When the MS walking scale (MSWS-12) was used, there was very low to low quality evidence that there was no difference in MSWS-12 scores between low, medium and high doses of fampridine compared to placebo.[3] Very low quality evidence showed that fampridine was clinically harmful compared to placebo in terms of a higher rate of adverse events, but without a difference in clinical harm between fampridine and placebo in terms of discontinuation due to adverse events.[3] Safety comparisons suffered from serious imprecision and no comparison was made with active controls.[3] The NICE recommends not using fampridine to treat lack of mobility in people with MS because of lack of cost effectiveness from the perspective of the English National Health Service.[3]

The NICE provided guidance on the use of dimethyl fumarate in 2014.[10] Currently, dimethyl fumarate is recommended as an option for treating adults with RRMS if "they do not have highly active or rapidly evolving severe RRMS" and if the manufacturer provides dimethyl fumarate at a discounted cost.[10]

New FDA Drug Approvals:
None identified.

New Formulations/Indications:
None identified.

New FDA Safety Alerts:
Tecfidera (dimethyl fumarate)
The FDA issued new contraindication labeling in December 2014 for patients with known hypersensitivity to dimethyl fumarate or any of its excipients. Reactions have included anaphylaxis and angioedema.[11]

Gilenya (fingolimod)
The FDA issued a drug safety alert in August 2015 that warns about cases of rare brain infection. One confirmed case of progressive multifocal leukoencephalopathy (PML) and one case of probable PML have been reported. These are the first cases of PML reported in patients taking Gilenya who had not previously been treated with an immunosuppressant drug for MS or any other medical condition.[12]

References:

1. Kawalec P, Mikrut A, Wisniewska N, Pilc A. The Effectiveness of Dimethyl Fumarate Monotherapy in the Treatment of Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis. *Current Neuropharmacology*. 2014;12:256-268.

2. Xu Z, Zhang F, Sun F, Gu K, Dong S, He D. Dimethyl fumarate for multiple sclerosis. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD011076. DOI: 10.1002/14651858.CD011076.pub2.

3. Multiple Sclerosis: Management of multiple sclerosis in primary and secondary care; NICE Clinical Guideline 186, October 2014. National Institute for Health and Care Excellence (NICE). Available at guidance.nice.org.uk/cg186. Accessed June 11, 2015.

4. Miller A, Wolinsky J, Kappos L, et al. Oral terflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-986.

5. Aubagio (teriflunomide) [prescribing information]. Cambridge, MA: Genzyme Corporation (Sanofi), October 2014.

6. Clabresi P, Radue E, Goodin D, et al. Safety and efficacy of fingolimid in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:545-556.

7. Gilenya (fingolimod) [prescribing information]. East Hanover, MJ: Novartis Pharmaceuticals, May 2015.

8. Drugs at FDA. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory#apphist. Accessed July 6, 2015.

9. Dalfampridine [application no: 22-250s000]. FDA Summary Review. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022250s000_SumR.pdf. Accessed June 11, 2015.

10. Dimethyl fumarate for treating relapsing-remitting multiple sclerosis. NICE technology appraisal guidance 320, August 2014. National Institute for Health and Care Excellence (NICE). Available at http://www.nice.org.uk/guidance/ta320. Accessed June 11, 2015.

11. MedWatch: The FDA Safety Information and Adverse Event Reporting Program. Safety Information: Tecfidera (dimethyl fumarate) delayed-release capsules, for oral use. The U.S. Food and Drug Administration. http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm429768.htm. Accessed June 12, 2015.

12. Gilyena (fingolimod): Drug Safety Communication. MedWatch, The FDA Safety Information and Adverse Event Reporting System. The U.S. Food and Drug Administration. Available at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm457183.htm. Accessed August 8, 2015.

Author: A. Gibler, Pharm.D. Date: September 2015

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INTRAMUSC	SYRINGEKIT	AVONEX	INTERFERON BETA-1A	Y
INTRAMUSC	KIT	AVONEX	INTERFERON BETA-1A/ALBUMIN	Y
INTRAMUSC	PEN IJ KIT	AVONEX PEN	INTERFERON BETA-1A	Y
INTRAMUSC	SYRINGE	AVONEX	INTERFERON BETA-1A	Y
SUB-Q	SYRINGE	REBIF	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	PEN INJCTR	REBIF REBIDOSE	INTERFERON BETA-1A/ALBUMIN	Y
SUB-Q	KIT	BETASERON	INTERFERON BETA-1B	Y
SUB-Q	KIT	EXTAVIA	INTERFERON BETA-1B	Y
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	Y
INTRAVEN	VIAL	LEMTRADA	ALEMTUZUMAB	
INTRAVEN	VIAL	TYSABRI	NATALIZUMAB	N
INTRAVEN	VIAL	MITOXANTRONE HCL	MITOXANTRONE HCL	N
INTRAVEN	VIAL	NOVANTRONE	MITOXANTRONE HCL	N
INTRAMUSC	PEN INJCTR	AVONEX PEN	INTERFERON BETA-1A	N
SUB-Q	SYRINGE	COPAXONE	GLATIRAMER ACETATE	N
SUB-Q	VIAL	BETASERON	INTERFERON BETA-1B	N
SUB-Q	VIAL	EXTAVIA	INTERFERON BETA-1B	N
SUB-Q	SYRINGE	PLEGRIDY	PEGINTERFERON BETA-1A	N
SUB-Q	PEN INJCTR	PLEGRIDY PEN	PEGINTERFERON BETA-1A	N
ORAL	**TAB ER 12H**	**AMPYRA**	**DALFAMPRIDINE**	**N**
ORAL	**CAPSULE**	**GILENYA**	**FINGOLIMOD HCL**	**N**
ORAL	**TABLET**	**AUBAGIO**	**TERIFLUNOMIDE**	**N**
ORAL	**CAPSULE DR**	**TECFIDERA**	**DIMETHYL FUMARATE**	**N**

Appendix 2: New Clinical Trials

Thirty-once potentially relevant clinical trials were evaluated from the literature search. After further review, only 2 interventional, prospective trials evaluating an oral MS drug were identified. These trials are briefly described in the table below. Full abstracts are included in Appendix 3.

Table 1: Description of Clinical Trials

Study	Comparison	Population	Primary Outcome	Results
Miller AE, et al.[4] MC, DB, PG, PC, RCT, Phase 3 (n=618) 108 weeks Genzyme (Sanofi)	Teriflunomide 14 mg once daily vs. placebo Teriflunomide 7 mg once daily vs. placebo	Adults 18-55 years of age w/ clinically isolated syndrome (first acute or subacute neurological event consistent w/ demyelination (optic neuritis, spinal cord syndrome, or brainstem or cerebellar syndromes)	Time to relapse, indicating conversion to clinically definite MS	Reported as hazard ratios (HR) vs. placebo: Teriflunomide 14 mg: HR=0.574 (95% CI, 0.379-0.869; p=0.0087) Teriflunomide 7 mg: HR=0.628 (95% CI, 0.416-0.949; p=0.0271)
Calabresi PA, et al.[6] MC, DB, PG, PC, RCT, Phase 3 (n=1083) 24 months Novartis	Fingolimod 0.5 mg once daily vs. placebo Fingolimod 1.25 mg once daily vs. placebo	Adults 18-55 years of age diagnosed w/ RRMS, ≥1 confirmed relapses in preceding 1 year, and EDSS score of 0.5-5.5.	Reduction in annualized relapse rates in patients with RRMS	Reported as rate ratios (RR) vs. placebo: Fingolimod 0.5 mg: RR=0.52 (95% CI, 0.40-0.66; p<0.0001) Fingolimod 1.25 mg: RR=0.50 (95% CI, 0.39-0.65; p<0.0001)

Abbreviations: DB = double-blind; EDSS = Expanded Disability Status Scale; MC = multi-centered; PC = placebo-controlled; PG = parallel group; RCT = randomized controlled trial; RRMS = relapsing-remitting multiple sclerosis.

Appendix 3: Abstracts of Clinical Trials

Miller AE, Wolinsky JS, Kappos L, et al. Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13:977-986.

<u>Background</u>: Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing-remitting multiple sclerosis. We aimed to assess the efficacy and safety of teriflunomide in patients with a first clinical episode suggestive of multiple sclerosis.
<u>Methods</u>: In this randomised, double-blind, placebo-controlled, parallel-group study, we enrolled patients aged 18–55 years with clinically isolated syndrome (defined as a neurological event consistent with demyelination, starting within 90 days of randomisation, and two or more T2-weighted MRI lesions ≥3 mm in

diameter) from 112 centres (mostly hospitals) in 20 countries. Participants were randomly assigned (1:1:1) in a double-blind manner (by an interactive voice response system) to once-daily oral teriflunomide 14 mg, teriflunomide 7 mg, or placebo, for up to 108 weeks. Patients, staff administering the interventions, and outcome assessors were masked to treatment assignment. The primary endpoint was time to relapse (a new neurological abnormality separated by ≥30 days from a preceding clinical event, present for ≥24 h in the absence of fever or known infection), which defined conversion to clinically definite multiple sclerosis. The key secondary endpoint was time to relapse or new gadolinium-enhancing or T2 lesions on MRI, whichever occurred first. The primary outcome was analysed for the modified intention-to-treat population; safety analyses included all randomised patients who were exposed to the study drug, as treated. This trial is registered with ClinicalTrials.gov, number NCT00622700.
Findings: Between Feb 13, 2008, and Aug 22, 2012, 618 patients were enrolled and randomly assigned to teriflunomide 14 mg (n=216), teriflunomide 7 mg (n=205), or placebo (n=197). Two patients in each of the teriflunomide groups did not receive the study drug, so the modified intention-to-treat population comprised 214 patients in the teriflunomide 14 mg group, 203 in the teriflunomide 7 mg group, and 197 in the placebo group. Compared with placebo, teriflunomide significantly reduced the risk of relapse defining clinically definite multiple sclerosis at the 14 mg dose (hazard ratio [HR] 0·574 [95% CI 0·379–0·869]; p=0·0087) and at the 7 mg dose (0·628 [0·416–0·949]; p=0·0271). Teriflunomide reduced the risk of relapse or a new MRI lesion compared with placebo at the 14 mg dose (HR 0·651 [95% CI 0·515–0·822]; p=0·0003) and at the 7 mg dose (0·686 [0·540–0·871]; p=0·0020). During the study, six patients who were randomly assigned to placebo accidently also received teriflunomide at some point: four received 7 mg and two received 14 mg. Therefore, the safety population comprised 216 patients on teriflunomide 14 mg, 207 on teriflunomide 7 mg, and 191 on placebo. Adverse events that occurred in at least 10% of patients in either teriflunomide group and with an incidence that was at least 2% higher than that with placebo were increased alanine aminotransferase (40 [19%] of 216 patients in the 14 mg group, 36 [17%] of 207 in the 7 mg group vs 27 [14%] of 191 in the placebo group), hair thinning (25 [12%] and 12 [6%] vs 15 [8%]), diarrhoea (23 [11%] and 28 [14%] vs 12 [6%]), paraesthesia (22 [10%] and 11 [5%] vs 10 [5%]), and upper respiratory tract infection (20 [9%] and 23 [11%] vs 14 [7%]). The most common serious adverse event was an increase in alanine aminotransferase (four [2%] and five [2%] vs three [2%]).
Interpretation: TOPIC is to our knowledge the first study to report benefi ts of an available oral disease-modifying therapy in patients with early multiple sclerosis. These results extend the stages of multiple sclerosis in which teriflunomide shows a beneficial effect.

Calabresi PA, Radue EW, Goodin D, 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;13:545-556.

Background: Fingolimod has shown reductions in clinical and MRI disease activity in patients with relapsing-remitting multiple sclerosis. We further assessed the effi cacy and safety of fingolimod in such patients.
Methods: We did this placebo-controlled, double-blind phase 3 study predominantly in the USA (101 of 117 centres). Using a computer-generated sequence, we randomly allocated eligible patients—those aged 18–55 years with relapsing-remitting multiple sclerosis—to receive fingolimod 0·5 mg, fingolimod 1·25 mg, or placebo orally once daily (1:1:1; stratified by study centre). On Nov 12, 2009, all patients assigned to fingolimod 1·25 mg were switched to the 0·5 mg dose in a blinded manner after a review of data from other phase 3 trials and recommendation from the data and safety monitoring board, but were analysed as being in the 1·25 mg group in the primary outcome analysis. Our primary endpoint was annualised relapse rate at month 24, analysed by intention to treat. Secondary endpoints included percentage brain volume change (PBVC) from baseline and time-to-disability-progression confirmed at 3 months. This trial is registered with ClinicalTrilals.gov, number NCT00355134.
Findings: Between June 30, 2006, and March 4, 2009, we enrolled and randomly allocated 1083 patients: 370 to fingolimod 1·25 mg, 358 to fingolimod 0·5 mg, and 355 to placebo. Mean annualised relapse rate was 0·40 (95% CI 0·34–0·48) in patients given placebo and 0·21 (0·17–0·25) in patients given fingolimod 0·5 mg: rate ratio 0·52 (95% CI 0·40–0·66; p<0·0001), corresponding to a reduction of 48% with fingolimod 0·5 mg versus placebo. Mean PBVC was –0·86 (SD 1·22)

for fingolimod 0·5 mg versus –1·28 (1·50) for placebo (treatment difference –0·41, 95% CI –0·62 to –0·20; p=0·0002). We recorded no statistically significant between-group difference in confirmed disability progression (hazard rate 0·83 with fingolimod 0·5 mg vs placebo; 95% CI 0·61–1·12; p=0·227). Fingolimod 0·5 mg caused more of the following adverse events versus placebo: lymphopenia (27 [8%] patients vs 0 patients), increased alanine aminotransferase (29 [8%] vs six [2%]), herpes zoster infection (nine [3%] vs three [1%]), hypertension (32 [9%] vs 11 [3%]), first-dose bradycardia (five [1%] vs one [<0·5%]), and first-degree atrioventricular block (17 [5%] vs seven [2%]). 53 (15%) of 358 patients given fingolimod 0·5 mg and 45 (13%) of 355 patients given placebo had serious adverse events over 24 months, which included basal-cell carcinoma (ten [3%] patients vs two [1%] patients), macular oedema (three [1%] vs two [1%]), infections (11 [3%] vs four [1%]), and neoplasms (13 [4%] vs eight [2%]).
Interpretation: Our findings expand knowledge of the safety profile of fingolimod and strengthen evidence for its beneficial effects on relapse rates in patients with relapsing-remitting multiple sclerosis. We saw no effect of fingolimod on disability progression. Our findings substantiate the beneficial profile of fingolimod as a disease modifying agent in the management of patients with relapsing-remitting multiple sclerosis.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to June Week 1 2015
1 dalfampridine.mp. 56
2 fingolimod.mp. 1399
3 teriflunomide.mp. 139
4 dimethyl fumarate.mp. 327
5 1 or 2 or 3 or 4 1825
6 exp Multiple Sclerosis/ 46930
7 5 and 6 547
8 limit 7 to (english language and yr="2014 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or guideline or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 31

Oral Multiple Sclerosis Drugs

Goal(s):
- Promote safe and effective use of oral disease-modifying multiple sclerosis drugs
- Promote use of preferred multiple sclerosis drugs.

Length of Authorization:
- Up to 12 months

Requires PA:
- Fingolimod
- Teriflunomide
- Dimethyl Fumarate

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Does the patient have a diagnosis of relapsing remitting Multiple Sclerosis (MS) (ICD10 G35)?	**Yes:** Go to #3	**No:** Pass to RPh; Deny, not funded under the OHP per Guideline NOTE 95.
3. Will the prescriber consider a change to a preferred MS product? Message: • Preferred products do not require a PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #4

Approval Criteria		
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5	**No:** Pass to RPh; Deny, medical appropriateness.
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6	**No:** Pass to RPh; Deny, medical appropriateness.
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta 1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPh; Deny, medical appropriateness.	**No:** Go to #7
7. Is the prescription for teriflunomide?	**Yes:** Go to #8	**No:** Go to #10
8. Is the patient of childbearing potential?	**Yes:** Go to #9	**No:** Approve for up to 1 year.
9. Is the patient currently on a documented use of reliable contraception?	**Yes:** Approve for up to 1 year.	**No:** Pass to RPh; Deny, medical appropriateness.
10. Is the prescription fingolimod?	**Yes:** Go to #11	**No:** Go to #14
11. Does the patient have evidence of macular edema (ICD10 E11311)?	**Yes:** Pass to RPh; Deny, medical appropriateness.	**No:** Go to #12
12. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on anti-arrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13	**No:** Approve up to 1 year.
13. Has the patient had a cardiology consultation before initiation (see clinical notes)?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh; Deny, medical appropriateness.
14. Is the prescription for dimethyl fumarate?	**Yes:** Approve up to 1 year.	**No:** Pass to RPh; Deny, medical appropriateness.

Fingolimod Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs, electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

Teriflunomide Clinical Notes:

- Before starting Terinflunomide, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check BP, obtain a complete blood cell count within the 6 months prior to starting therapy, instruct patients receiving Terinflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Terinfluomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Terinflunomide is given with other potentially hepatotoxic drugs, consider stopping Teriflunomide if serum transaminase levels increase (>3 times the ULN), monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction, stop TER and start accelerated elimination in those with suspected TER-induced liver injury and monitor liver tests weekly until normalized, check BP periodically and manage elevated BP, check serum potassium level in TER-treated patients with hyperkalemia symptoms or acute renal failure, monitor for signs and symptoms of infection.
- Monitor for hematologic toxicity when switching from TER to another agent with a known potential for hematologic suppression, because systemic exposure to both agents will overlap.

P&T / DUR Review: *9/15 (AG); 9/13; 5/13; 3/12*
Implementation: *1/1/14; 6/21/2012*