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

Class Update: Disease Modifying Agents for Multiple Sclerosis

Month/Year of Review: September 2014
PDL Classes: Neurologic– MS Drugs (Disease modifying agents)
New Drug(s): Peginterferon beta-1a (Plegridy®)

Date of Last Review: September 2013
Source Document: OSU College of Pharmacy

Current Status of PDL Class:

- **Preferred Agents:** INTERFERON BETA-1A IM (AVONEX®/AVONEX PEN®, AVONEX ®ADMINISTRATION PACK), INTEFERON BETA-1A SUBQ (REBIF®), INTERFERON BETA-1B SUBQ (BETASERON® AND EXTAVIA®), GLATIRAMER ACETATE 20mg/ml (COPAXONE®)
- **Non-Preferred Agents:** NATALIZUMAB IV (TYSABRI®), MITOXANTRONE IV, FINGOLIMOD (GILENYA®), TERIFLUNOMIDE (AUBAGIO®), DIMETHYL FUMARATE (TECFIDERA®), GLATIRAMER ACETATE 40mg/ml (COPAXONE®)

Current PA: Prior authorization criteria is currently in place for dalfampridine and the oral drugs, fingolimod, teriflunomide and dimethyl fumarate, to ensure appropriate drug use and limit its use to patient populations in which the drug has been shown to be effective and safe (Appendix 2).

Research Questions:

- Is there any new comparative evidence for disease-modifying treatments, in long-term clinical outcomes such as relapse and disease progression in adult patients being treated for multiple sclerosis (MS)?
- Is there any new evidence about comparative harms of disease-modifying treatments in adult patients being treated for MS?
- Are there subpopulations of patients with MS for which one disease-modifying treatment is more effective or associated with less harm?
- Is peginterferon beta- 1a effective and safe for the treatment of MS and/or offer safety or efficacy advantages over currently available therapies for the treatment of MS?
- Are there certain patient subgroups which would benefit from peginterferon beta-1a?

Conclusions:

- There is moderate strength of evidence that glatiramer 40mg 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 20mg daily, however, no direct comparisons are available.[1]
- There is low-moderate strength of evidence that fingolimod 0.5mg 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.[2]

- 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.[3] 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.[3]

Recommendations:

- Limited evidence suggests glatiramer 40mg tiw is effective in preventing relapses in patients with RRMS. Evaluate costs in executive session.
- Recommend requiring a prior authorization for peginterferon beta-1a (Appendix 1).
- No changes are recommended to PDL as a result of this review. Evaluate comparative costs in executive session.

Reason for review:

The class of MS treatments was last reviewed in September of 2013. Annual updates of the class allow for incorporation of new literature and to ensure recommendations are relevant and accurate. Since the last review one new drug and one new formulation has been approved. New primary literature and guidelines will be reviewed and evaluated.

Previous Conclusions and Recommendation:

- There is low strength of evidence indicating dimethyl fumarate 240 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 20mg.[4] Dimethyl fumarate is available by PA to patients who have tried and failed first line agents including beta interferons and/or glatiramer.
- 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).[5] There is conflicting evidence on disease progression outcomes. The committee recommended that all interferons be included on the PDL.

Background:

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system affecting approximately 250,000 to 400,000 people in the United States.[4] MS is usually diagnosed in patients between the ages of 15 and 45 years, with the peak incidence in the fourth decade of life. MS is a diagnosis of exclusion and presents in a variety of ways.[6] Diagnosis begins with patients presenting with neurological symptoms or signs suggestive of demyelination (such as optic neuritis and transverse myelitis) and should be clinically determined on the basis of history and examination.[7] The McDonald criterion is a tool used to help in the diagnosis of MS and is based upon number of clinical attacks, lesions, and dissemination in time and space.[8]

There are four main types of MS: relapsing-remitting, secondary progressive, primary progressive, and progressive relapsing. About 85% of patients have RRMS at diagnosis of disease and is defined by acute relapse of neurological symptoms followed by full or partial recovery.[5] Some patients with RRMS will develop secondary progressive MS, which is associated with rapid neurological damage.

Acute exacerbations or relapses of MS can be disabling. Treatment of MS includes corticosteroids for acute relapse, symptom management, and disease modification.[5] Use of disease-modifying drugs (DMD) in patients with RRMS has been shown to have many beneficial effects including reducing annual relapse rate, lessening severity of relapses, and slowing progression of disability.[6] Treatment with these agents should not be delayed in patients with a definite

diagnosis of MS with active, relapsing disease. Goals of treatment include decreasing exacerbations, hospitalizations, slowing disease progression, and disability.[6]

There are currently ten DMDs approved by the U.S. Food and Drug Administration (FDA) for use in RRMS.[9] Disease modifying treatments are the preferred choice, however, optimal treatment is dependent upon patient characteristics and response. Interferons (interferon beta-1a and interferon beta-1b) and glatiramer were the first available disease modifying treatments and are often considered first-line options despite the need for injectable administration.[10] Natalizumab, a monoclonal antibody, is also an approved for the treatment of MS, however, its association with progressive multifocal leukoencephalopathy limits its use to patients that have failed other therapies.[10] Three oral agents have been approved for treatment of MS; fingolimod, teriflunomide and dimethyl fumarate.[11] Efficacy and safety data beyond two years and adverse events, such as hepatotoxicity and cardiovascular risks, have resulted in many of the oral therapies being second line treatment options.[10-12]

Progression of MS is measured by the disability caused by the disease. The Expanded Disability Status Scale (EDSS) is a single-item scale used to assess disability and progression of disability and frequently used to measure disability progression in clinical trials.[13] The scale ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments based on eight function system scales (FSS).[13,14] This tool is used primarily in clinical trials and less frequently by clinicians. Limitations to this scale include difficulty interpreting change or group differences due to a 1-point difference in one part of the scale not representing the same interval as a 1-point difference in another part of the scale, and evidence that the EDSS lacks adequate sensitivity to fluctuations in MS-related impairment. Additionally, this outcome may not accurately measure long-term and irreversible disease progression.[15] Due to treatment length "sustained disease progression" is often used instead of hitting a long-term disease progression milestone.[14] Sustained disease progression is an increase in EDSS score that is sustained over several months. In clinical trials, disability progression is often defined as at least 1 point EDSS increase or a 0.5 point increase if the EDSS was greater than or equal to 5.5.

A newer tool to assess disability is the Multiple Sclerosis Functional Composite (MSFC), which was developed by a special Task Force on Clinical Outcomes Assessment appointed by the National Multiple Sclerosis Society's Advisory Committee on Clinical Trials of New Agents in Multiple sclerosis in 1999.[16] This is a three-part, standardized, quantitative, assessment instrument. The MSFC can produce scores for each of the three individual measures as well as a composite score. In addition, there are a variety of ways to calculate scores depending on the nature of the study and sample. The MSFC has rarely been used as an outcome measure in clinical trials.

Relapse rate is a clinically relevant outcome to both the patient and provider. Since, RRMS is characterized by periods or relapse, the goal is to diminish any signs or symptoms of relapse. Confirmed relapse is defined as the occurrence of new symptoms or worsening of previously stable or improving symptoms and signs not associated with fever or infection that occurs at least 30 days after the onset of a preceding relapse and lasts more than 24 hours.[9] This is generally studied after one or more years of treatment. However, the frequency of relapses in the general population is highly variable.[17] According to data from the Marshfield Multiple Sclerosis Center in Wisconsin, 1,078 RRMS patients had a mean of 2.4 relapses per patient, with a range of 1-11 relapses over 1-15 years with an average follow-up of 7.4 years.[18]

MS causes demyelination of neuronal axons which form lesions of the central nervous system on a magnetic resonance imaging (MRI).[5] MRI assessment is used to assess lesions due to MS. MRI changes seen in MS are nonspecific. Therefore, the AAN recommends always using the information derived from imaging in the context of the specific clinical situation presented by an individual patient.[8] T2-weighted lesions at onset appear to correlate with the development of disability. Gadolinium contrast material enhances the lesions and help identify new lesions and disruption of the blood-brain barrier, but do not correlate well over time

with progression of disability.[6] In July 2013, a meta-analysis explored the potential of MRI lesions being used as a surrogate for effect of treatment on relapses.[16] Results suggested that MRI lesions can accurately predict the effect of a treatment on relapses and will enhance further trials by reducing the number of patients needed in a study. In most cases, MRI alone adds little to the clinical outcomes.

Methods:
A Medline literature search beginning August 2013 and ending July 2014 for new systematic reviews and randomized controlled trials (RCTs) that compared disease modifying medications for the treatment of MS was done. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Guidelines:

National Institute for Health and Clinical Excellence
A NICE technology appraisal on teriflunomide for the treatment of RRMS was released in January of 2014.[19] Recommendations were to consider teriflunomide therapy in adults with active RRMS if there is no evidence of highly active or rapidly evolving severe relapsing-remitting MS. Recommendations were based on three, phase III studies, Study 2001, TEMSO and TOWER. A meta-analysis of placebo controlled comparison of the trials showed a reduction in annualized relapse rate (RR: 0.66, 95% CI 0.59 to 0.75).[19]

New FDA Safety Alerts:
In April 2014, the FDA added a safety warning to interferon Beta-1a adverse reaction section.[20] The warning included the following: injection site reactions and cases of pseudo-relapses erythema multiforme and Steven-Johnson syndrome, suicide and hepatic injury, reports of thrombotic thrombocytopenic purpura and hemolytic uremia syndrome, retinal vascular disorders and convulsive disorders and systemic lupus erythematosus, autoimmune hepatitis and pancytopenia.

A FDA warning and subsequent label change was issued for fingolimod (Gilenya®) in April 2014 for the risk of posterior reversible encephalopathy syndrome (PRES).[21] Fingolimod should be discontinued if PRES is suspected.

New drugs/formulations/indications:
A new dosing regimen was approved for glatiramer 40mg tiw in January of 2014 as an alternative option to daily injections.[22] The glatiramer three times weekly dosing regimen was shown to be effective in one good quality study.[1]

Khan, et al studied the use of subcutaneous glatiramer 40mg tiw compared to placebo in a randomized, double-blind study in 2,928 patients with RRMS (GALA). Included patients had a least one relapse within the last year and an EDSS of ≤ 5.5. Patients were ineligible if they had previously used glatiramer and/or were being treated with immunomodulators. Included patients were a mean age of 38 years, majority were female (67.5%) and a mean EDSS score of 2.75. The primary endpoint was the number of confirmed relapses in the 12-month placebo controlled phase. Relapses included changes from baseline in functional

system (FS) and Kurtzke's EDSS assessment in addition to neurologic abnormalities. Secondary endpoints were cumulative GdE T1 lesions at 6 and 12 months, cumulative new or newly enlarging T2 lesions at 6 and 12 months and percentage change in brain volume at 12 months.

There is moderate strength of evidence that glatiramer was shown to reduce annualized relapses compared to placebo by 34% (mean ARR = 0.331 vs. 0.505; RR 0.66 [95% CI 0.539 to 0.799], $p < 0.0001$). Changes assessed by the EDSS score demonstrated similar rates of no progression in those receiving glatiramer (95.5%) and placebo (96.3%). Secondary endpoints were significantly reduced for cumulative GdE T1 lesions in the glatiramer group (0.905) compared to placebo (1.639) and for cumulative new or newly enlarging T2 lesions in patients randomized to glatiramer compared to placebo, 3.650 versus 5.592, respectively. Patients in the glatiramer group showed less reduction in brain volume compared to placebo but not significantly so.

Discontinuations were similar in glatiramer and placebo groups, 8.9% and 6.7%, respectively. The most common adverse event was injection site reactions in the glatiramer group (35%) compared to placebo (5%). Serious adverse events were similar between groups (4.5%) and discontinuations due to adverse events occurred in 3.1% of glatiramer patients and 1.3% of those in the placebo group.

Patients included in GALA were predominately white females with low levels of disability. Extrapolation of results to other populations should be done with caution. Annualized relapse rates were similar to 20mg once daily glatiramer injections which have been shown to have an approximate 30% reduction in relapses.[9] Injection site reactions and systemic immediate post injection reactions were lower, in indirect comparisons, with glatiramer 40mg tiw compared with those reported with glatiramer 20mg daily. An open-label phase of this trial is ongoing.

New Primary Literature:

Fingolimod

Calabresi, et al studied the use of fingolimod 0.5mg or 1.25mg compared to placebo in a double-blind, randomized, phase 3 study in 1083 patients with RRMS (FREEDOMS II).[2] The data safety monitoring board recommended that all patients be switched to fingolimod 0.5mg dose on November 12, 2009. This group was still analyzed as the fingolimod 1.25mg group. Patients were a mean age of 40 years (18-55 years) The primary endpoint was annualized relapse rate at month 24. Secondary endpoints were percentage of brain volume change from baseline and time-to-disability-progression at 3 months.

There is low-moderate strength of evidence that fingolimod 0.5mg reduced the mean annualized relapse rate by 48% in patients with RRMS compared to placebo, 0.21 versus 0.40, respectively (rate ratio 0.52, 95% CI 0.40 to 0.66; $p<0.001$). Percentage of patients free from disability at month 6 was significantly greater in fingolimod 1.25mg and fingolimod 0.5mg groups compared to placebo, NNT of 21 and 25, respectively. Mean percent brain volume change was significantly less in both fingolimod groups compared to placebo, $p= 0.0002$. Disability progression was similar between groups.

Common adverse events were upper respiratory tract infections, nasopharyngitis, urinary tract infection and sinus infections. Hypertension, bronchitis, influenza and herpes viral infection were more common in the fingolimod groups. Fingolimod was associated with increased liver function tests compared to placebo (10% with fingolimod 1.25mg, 8% with fingolimod 0.5mg and 2% in placebo group). Serious adverse events included macular edema and lymphopenia. More patients in the fingolimod groups compared to placebo developed basal-cell carcinomas, 2% in the fingolimod 1.25 mg group, 3% in the fingolimod 0.5mg group and 1% in the placebo group. No abnormal findings were found related to valve disease onset or stenosis. Bradycardia following the administration of the first dose was reported in 27 patients, however, most did not require treatment and resolved within 24 hours.

Author: Kathy Sentena, Pharm.D.

Small sample size and high attrition rates are limitations of this study. Applicability of results to patients naïve to disease-modifying treatment is low since a majority (75%) of study patients had been previously treated with these therapies. Most patients were of limited disability with a mean EDSS score of 2.45.

New Drug Evaluation – Peginterferon beta-1a (Plegridy®)

FDA Indication: Peginterferon beta-1a was approved in August 2014 for the treatment of patients with relapsing forms of multiple sclerosis.[23] Peginterferon beta-1a is a subcutaneous formulation requiring administration once every 14 days in contrast to other forms of interferon bet-1a which require subcutaneous administration three times a week (Rebif®) or intramuscularly once a week (Avonex®).[24, 25]

Clinical Efficacy (see evidence table below):
One good-quality study was used for the approval of peginterferon beta-1a (ADVANCE). ADVANCE was a double-blind, placebo-controlled, parallel group, phase 3, randomized trial of 1516 patients.[3] Patients were randomized to placebo, peginterferon beta-1a every 2 weeks (PG2) or peginterferon beta-1a every 4 weeks (PG4) for 48 weeks. A majority of patients were female with relapsing-remitting MS, mean age of 36 and mean EDSS score of 2.46. Them primary endpoint was annualized relapse rate at 48 weeks. Important secondary endpoints were proportion of patients with relapse at 48 weeks and disability progression at 48 weeks (≥1 point increase on the EDSS from baseline score of ≥1 sustained for 12 weeks or at least a 1.5 point increase from baseline score of 0 sustained for 12 weeks).

There is moderate strength of evidence that PG2 and PG4 significantly decreased relapses compared to placebo. The adjusted annualized relapse rate per patient-year was 0.397 for placebo, 0.256 for PG2 and 0.397 for PG4 at week 48 (rate ratio for PG2 vs. placebo: 0.644 [95% CI 0.500 to 0.831, p=0.0007] and PG4 vs placebo: 0.725 [95% CI 0.565 to 0.930, p=0.0114]).[3] The number of patients with 12 weeks of sustained disability progression at 48 weeks and proportion of patients with a relapse at 48 weeks were both significantly reduced with peginterferon beta-1a compared to placebo, NNT of 25 for both groups and NNT of 10 for PG2 and 14 for PG4, respectively. The number of T1 hypointense and gandolinium-enhancing lesions were less in the peginterferon beta-1a group compared to placebo. This study is ongoing, with the placebo phase ending at 48 weeks with those patients randomized to one of the active treatment groups for an additional year.

Clinical Safety:
The most common adverse reactions associated with peginterferon beta-1a were injection site reactions, influenza-like symptoms, pyrexia, and headache. Injection site reactions were more common in the PG2 group compared to the PG4 group, 62% and 56%, respectively.[3] Serious adverse reactions were relapse, pneumonia and urinary tract infections with relapse being the most common. Discontinuations due to adverse events were higher in both the peginterferon beta-1a groups with influenza-like illness being the most common cause. Hepatic enzyme elevations and reduced hematologic parameters were more common in the peginteferon beta-1a groups compared to placebo but most did not result in treatment discontinuation. Less than 1% of patients in the active treatment groups developed neutralizing antibodies. Results of a 2-year safety extension study suggest similar findings as the ADVANCE trial.

In conclusion, PG2 and PG4 were found to be effective in reducing relapse rates in patients with relapsing-remitting MS. Reductions in relapses were similar to other interferon beta-1a treatments but no head to head comparisons are available. Study limitations include short duration and small number of patients on previous MS therapy limiting applicability of results to those with less severe disease.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Relapse Rate
2) Disability Progression
3) Withdrawals due to adverse events
4) Quality of Life

Primary Study Endpoint:

1) Annualized relapse rate
2) Percent change in brain volume/ number of brain lesions
3) Relapse free / free of disability progression

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns

GALA trial Khan, et al[1] Phase III, RCT, DB, PC 142 sites and 17 countries	1. Glatiramer 40mg/mL tiw (GL) 2. Placebo Duration: 12 months	Mean age: 38 Age range: 18-55 yrs. Mean EDSS: 2.75 Females: 68% White: 98% <u>Inclusion Criteria:</u> age 18-55 years, confirmed diagnosis of RRMS, baseline EDSS ≤5.5, relapse free for ≥30 days at least 1 relapse within the 12 months prior to screening, ≥2 relapses within 24 months prior to screening, or one relapse between 12 and 24 months prior to screening with at least 1 T1 Gd enhancing lesions within previous 12 months. <u>Exclusion Criteria:</u> progressive relapsing MS, previous glatiramer treatment, treatment with immunomodulators within previous 2 months immunosuppressive agents, cytotoxic agents, chronic corticosteroid treatment within previou 6 months, monoclonal antibody treatment within 2 years of screening, Gd or mannito sensitivity or not able to undergo MRI scanning.	1. n= 1524 2. n= 943	<u>Annualized relapse rate at 12 months</u> GL: 0.331 P: 0.505 RR: 0.656 (95% CI 0.539 to 0.799), P<0.0001 <u>Relapse-Free at 12 months</u> GL: 726 (77%) P: 306 (66.5%) OR: 1.9 (95% CI 1.5 to 2.5), p<0.0001 <u>Cumulative GdE T1 lesions at 6 and 12 months</u> GL: 0.905 P: 1.639 RR: 0.55 (95% CI 1.300 to 2.066), p<0.0001 <u>Cumulative new or newly enlarging T2 lesions at 6 and 12 months</u> GL: 3.650 P: 5.592 RR: 0.653 (95% CI 0.546 to 0.780), p<0.0001	N/A ARR: 11.5% NNT: 9 N/A N/A	<u>Serious adverse events</u> GL: 42 (4.5%) P: 21 (4.6%) <u>Discontinuations due to adverse event</u> GL: 29 (3.1%) P: 6 (1.3%)	N/A N/A	Quality rating: Good Internal validity: <u>Selection:</u> Constrained blocks stratified by center was used for randomization. Baseline characteristics were similar. <u>Performance:</u> Placebo and active treatment identical. All providers involved in patient management were blinded to treatment assignment. <u>Detection:</u> data management was blinded to treatment. <u>Attrition:</u> Overall attrition was 13% in both groups. A modified ITT was used that included all patients randomized. External validity: <u>Setting:</u> From 142 sites in 17 countries. <u>Patient characteristics:</u> Age range representative of general population. Primarily white patients (98%). Mean EDSS score suggests minimal disability. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.

FREEDOMS II[2] Calabresi P, et al Phase III, RCT, DB, PC 117 centers	1. Fingolimod 0.5mg daily (F0.5) 2. Fingolimod 1.25mg daily (F1.25) 3. Placebo (P) Duration: 24 months *Patients in the 1.25mg group were switched to the 0.5mg dose 11/12/09	Mean age: 40 years Females: 78% Mean EDSS score: 2.45 Inclusion Criteria: patients 18-55 years old with RRMS, EDSS score of 0 -5.5, at least 1 relapse within the 12 months prior to screening (or two or more relapses within the previous 2 years), and no relapse or steroid treatment within 30 days before randomization. Previously treated patients were included if interferon beta or glatiramer was discontinued at least 3 months prior to randomization and natalizumab treatment was stopped at least 6 months before randomization. Exclusion Criteria: Patients with significant systemic disease, malignancy, diabetes, cardiac, pulmonary, or hepatic disorders and active infection or macular edema.	1. n= 358 2. n= 370 3. n= 355	<u>Annualized relapse rate at 2 years:</u> F0.5:0.21 F1.25: 0.20 P: 0.40 Rate Ratio for F0.5 vs.P: 0.52 (95% CI 0.40 to 0.66) P<0.0001 Rate Ratio for F1.25 vs.P: 0.50 (95% CI 0.39 to 0.65) P<0.0001 <u>Percentage of patients free of disability progression at 6 months</u> F0.5: 309 (86.2%) F1.25:319 (86.9%) P: 291(82.2%) HR for F0.5 vs. P: 0.72 (95% CI, 0.48 to 1.07) P = 0.101 HR for F1.25 vs P: 0.72 (95% CI 0.48 to 1.08) p= 0.113 <u>Mean Percent Change in Brain Volume from Baseline to month 24:</u> F0.05: -0.858% F1.25: -0.595% P: -1.279% F0.5 vs P: p=0.0002 F1.25 vs P: p<0.0001	N/A F0.5 vs.P: ARR: 4% NNT: 25 F1.25 vs. P: ARR: 4.7% NNT: 21 NA	<u>Serious adverse events</u> F0.5: 53 (14%) F1.25: 53 (15%) P: 45 (13%) <u>D/c of study drug due to adverse event</u> F0.5: 66 (18%) F1.25: 72 (20%) P: 37 (10%)	N/A N/A	Quality rating: Fair Internal validity: <u>Selection:</u> Randomization done via automated system. <u>Performance:</u>. Placebo and active treatments identically packaged. <u>Detection:</u> independent data board. <u>Attrition:</u> Overall attrition was high and varied between groups (32% for fingolimod 1.25mg, 24% for fingolimod 0.5mg and 28% for placebo. ITT analysis was used for all randomized patients. External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Patients with major comorbidities were excluded. Majority (75%) of patients had previously used disease-modifying treatments. <u>Setting:</u> Included 117 centers (101 US sites). Sponsored by Novartis Pharma AG. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.

ADVANCE[3] Calabresi, et al PC, DB, PG, Phase 3, RCT 183 sites	1. Peginterferon beta-1a every 2 weeks (PB2) 2. Peginterferon beta-1a every 4 weeks (PB4) 3. Placebo * Patients assigned to peginterferon beta-1a groups underwent dose escalation over first 4 weeks * Duration 48 weeks	Mean age: 36 years Females: 71% Mean EDSS score: 2.46 Inclusion Criteria: patients 18-65 years old with RRMS, EDSS score of 0 -5.0, at least 2 relapses within the previous 3 years, with at least one having occurred within the past 12 months. Exclusion Criteria: Patients with progressive forms of MS, pre-specified laboratory abnormalities, and previous treatment with interferon for MS for more than 4 weeks or discontinuation less than 6 months before baseline	N= 512 N= 500 N= 500	<u>Annualized relapse rate at 48 weeks:</u> PB2: 0.256 PB4: 0.288 P: 0.397 Rate Ratio for PB2 vs.P: 0.644 (95% CI 0.500 to 0.831) P=0.0007 Rate Ratio for PB4 vs.P: 0.725 (95% CI 0.565 to 0.930) P=0.0114 <u>Disability progression at 48 weeks:</u> PB2: 31 (6%) PB4: 31 (6%) P: 50 (10%) HR for PB2 vs. P: 0.62 (95% CI, 0.40 to 0.97) P = 0.0383 HR for PB4 vs P: 0.62 (95% CI 0.40 to 0.97) p= 0.0380 <u>Proportion of patients with a relapse at 48 weeks:</u> PB2: 90 (18%) PB4: 105 (21%) P: 142 (28%) HR for PB2 vs P: 0.61 (95% CI 0.47 to 0.80) p= 0.0003 HR for PB4 vs P: 0.74 (95% CI 0.57 to 0.95) p=0.02	NA For PB2 vs. P and PB4 vs. P: ARR: 4% NNT: 25 PB2 vs P: ARR: 10% NNT: 10 PB4 vs. P: ARR: 7% NNT: 14	<u>Serious adverse events</u> PB2: 55 (11%) PB4: 71 (14%) P: 76 (15%) <u>D/c of study drug due to adverse event</u> PB2: 25 (5%) PB4: 24 (5%) P: 7 (1%)	NA NA	Quality rating: Good Internal validity: <u>Selection:</u> Randomization done via interactive voice response or web system. <u>Performance:</u>. Placebo and active treatments identically packaged in pre-filled syringe. All study management and site personnel, investigators, and patients were masked to treatment assignment. Separate examining and treating neurologists were at each site. <u>Detection:</u> blinded independent data and safety monitoring board. <u>Attrition:</u> Overall attrition was 9% for the placebo group, 14% for the PB2 group and 12% for the PG4 group. ITT analysis was used for all randomized patients. External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Patients had moderate disability and only seventeen percent had previously used treatments for MS. <u>Setting:</u> Included 183 centers and 26 countries (approximately 3.5% from North America). Sponsored by Biogen Idec. <u>Outcomes:</u> Clinically relevant efficacy and safety endpoints.

Abbreviations: RCT=randomized controlled trial, DB=double blind, PC=placebo controlled, BID = twice daily, TID = three times daily, ARR= absolute risk reduction, NNT = number needed to treat, NS – non-significant, N/A = not applicable, HR = hazard ratio, RRMS = relapsing-remitting multiple sclerosis, TIW = three times a week, EDSS = Expanded Disability Status Scale,

References:

1. Khan, O., Rieckmann, P., Boyko, A., Selmaj, K., Zivadinov, R. and GALA Study Group (2013), Three times weekly glatiramer acetate in relapsing–remitting multiple sclerosis. Ann Neurol., 73: 705–713. doi: 10.1002/ana.23938.
2. Calabresi P, Radue E, Goodin D, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomized, placebo-controlled, phase 3 trial. Lancet Neurol 2014;13:545-56. doi:10.1016/S1474-4422(14)70049-3.
3. Calabresi P, Kieseier B, Arnold D, et al. Pegylated interferon beta-1a for relapsing-remitting multiple sclerosis (ADVANCE): a randomised, phase 3, double-bind study. Lancet Neurol 2014;13:657-65.
4. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087–1097. doi:10.1056/NEJMoa1206328.
5. Selph S, Thakurta S, McDonagh M. Drug Class Review: Disease-modifying Drugs for Multiple Sclerosis. Draft Update 2 Report. *Drug Effectiveness Review Project Paciric Northwest Evidence-based Practice Center*. 2013.
6. Dipiro J. Multiple Sclerosis. In: *Pharmacotherapy*. 8th Edition. McGraw-Hill Companies; 2011:Ch 64.
7. National Institute for Health and Clinical Excellence (NICE). Multiple sclerosis: management of multiple sclerosis in primary and secondary care. London (UK): National Institute for Health and Clinical Excellence; 2003 November. Clinical guidelines; no 8). Available at: http://www.nice.org.uk/. Accessed August 6, 2013.
8. Frohman EM, Goodin DS, Calabresi PA, et al. The utility of MRI in suspected MS: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2003;61(5):602–611.
9. He D, Xu Z, Dong S, et al. Teriflunomide for multiple sclerosis. *Cochrane Database Syst Rev*. 2012;12:CD009882. doi:10.1002/14651858.CD009882.pub2.
10. Canadian Agency for Drugs and Technologies in Health. CADTH Therapeutic Review. Recommendations for Drug Therapies for Relapsing-Remitting Multiple Sclerosis. 2013. Available at: http://www.cadth.ca/en/products/therapeutic-reviews/relapsing-remit-multiple-sclerosis.
11. Cross, A, Naismith R. Established and novel disease-modifying treatments in multiple sclerosis. J of Intern Med 2014;275:350-363. doi:10.1111/joim.12203.
12. National Multiple Sclerosis Society. The MS disease-modifying medications. 2013. Available at: nationalMSsociety.org/DMD.
13. National Multiple S. Functional systems score (FSS) and expanded disability status scale (EDSS).
14. Healy BC, Engler D, Glanz B, Musallam A, Chitnis T. Assessment of definitions of sustained disease progression in relapsing-remitting multiple sclerosis. *Mult Scler Int*. 2013;2013:189624. doi:10.1155/2013/189624.
15. U.S. National Institutes of Health. Dimethyl fumarate. Available at: http://clinicaltrials.gov.
16. National Multiple Sclerosis Society. Multiple sclerosis function composite (MSFC). Available at: http://www.nationalmssociety.org/ms-clinical-care-network/researchers/clinical-study-measures/msfc/index.aspx.
17. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *Lancet Neurol*. 2013;12(7):669–676. doi:10.1016/S1474-4422(13)70103-0.
18. Bejaoui K, Rolak LA. What is the risk of permanent disability from a multiple sclerosis relapse? *Neurology*. 2010;74(11):900–902. doi:10.1212/WNL.0b013e3181d55ee9.
19. National Institute for Health and Care Excellence (NICE). Teriflunomide for treating relapsing-remitting multiple sclerosis. London (UK): National Institute for Health and Care Excellence (NICE); 2014 Jan. 57p. (Technology appraisal guidance; no.303).
20. Food and Drug Administration. Safety labeling changes; Rebif (Interferon Beta-1a). April 2014. Accessed on July 1, 2014. Available at: ww.fda.gov/safety/medwatch/safetyinformation/ucm351803.htm.
21. Food and Drug Administration. FDA Drug Safety Communication: FDA investigating rare brain infection in patients taking Gilenya (fingolimod). Accessed July 1, 2014. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm366529.htm.
22. Teva Neuroscience, Inc. Label – Glatiramer (Copaxone®). 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020622s089lbl.pdf. Accessed July 13, 2014.
23. Biogen Idec Inc. Label – Peginterferon beta-1a (Plegridy®). 2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125499s000lbl.pdf. Accessed August 21, 2014.
24. Biogen Idec, Inc. Label – Inerferon beta-1a (Rebif®).2014. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/103780s5178s5179lbl.pdf. Accessed July 13, 2014.
25. Biogen Idec, Inc. Label – Interferon beta-1a (Avonex®). 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/103628s5206lbl.pdf. Accessed July 13, 2014.

Author: Kathy Sentena, Pharm.D.

Appendix 1: Suggested PA Criteria

Peginterferon Beta-1a (Plegridy®)

Goal(s): Approve therapy for covered diagnoses which are supported by the medical literature.

Length of Authorization:
Up to 12 months

Requires PA:
- Non-preferred drugs

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

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing-remitting Multiple Sclerosis?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a Preferred MS product?	**Yes:** Inform Provider of covered alternatives in the class. Additional information can be found at www.orpdl.org	**No:** Go to #4
4. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #5	**No:** Pass to RPH; Deny (medical appropriateness).
5. Does the patient have any of the following: - Adherence issues necessitating less frequent administration - dexterity issues limiting ability to administer subcutaneous injections	**Yes:** Approve for up to one year.	**No:** Pass to RPH; Deny (medical appropriateness)

P&T Action: 9/23/14 (KS)
Revision(s):
Initiated:

Author: Kathy Sentena, Pharm.D.

Appendix 2: PA criteria

Oral MS Drugs

Goal(s):

- To ensure appropriate and safe drug use drugs
- Promote preferred drugs

Length of Authorization: One year

Requires PA:

- **Fingolimod (Gilenya)**
- **Teriflunomide (Aubagio)**
- **Dimethyl Fumarate (Tecfidera)**

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness).
3. Will the prescriber consider a change to a Preferred MS product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml.	**No:** Go to #4.
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.

Author: Kathy Sentena, Pharm.D.

8. Is the patient of childbearing potential?	**Yes:** Go to #9.	**No:** Approve for up to one year.
9. Does the patient currently on a documented use of reliable contraception?	**Yes:** Approve up to one year.	**No:** Pass to RPH; Deny (medical appropriateness)
10. Is the prescription for fingolimod?	**Yes:** Go to #11.	**No:** Go to #14.
11. Does the patient have evidence of macular edema (ICD-9 362.07)?	**Yes:** Pass to RPH; Deny (medical appropriateness).	**No:** Go to #12.
12. Does the patient has preexisting cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #13.	**No:** Approve up to one year.
13. Has the patient had a cardiology consultation before initiation?	**Yes:** Approve up to one year.	**No:** Pass to RPH; Deny (medical appropriateness).
14. Is the prescription for dimethyl fumarate?	**Yes:** Approve up to one 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 Teriflunomide, 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 Teriflunomide to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.
- After starting Teriflunomide, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when Teriflunomide 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 Action: 3-29-2012
Revision(s): 5-30-2013 (MH)
Initiated: 6/21/2012

Author: Kathy Sentena, Pharm.D.

Dalfampridine (Ampyra)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which the drug has been shown to be effective and safe.

Length of Authorization: One year.

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is the request for continuation of therapy? (Patient has completed two month trial)	**Yes:** Go to "Continuation of Therapy"	**No:** Go to #5
5. Does the patient have a history of seizures (ICD-9 345.00-345.51, 345.80, 345.81, 780.33-780.39)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #6
6. Does the patient have moderate to severe renal impairment (CrCl <50 ml/min)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Is the patient ambulatory with a walking disability requiring use of a walking aid OR with moderate ambulatory dysfunction who do not require a walking aid AND • Is able to complete the baseline timed 25 foot walk between 8 and 45 seconds	**Yes:** Approve initial fill for 2 month trial.	**No:** Pass to RPH; Deny (medical appropriateness)

Author: Kathy Sentena, Pharm.D.

Continuation of Therapy		
1. Has the patient been taking dalfampridine for 2 months or longer and has demonstrated that walking speed has improved while on dalfampridine (documentation of ≥20% improvement in timed 25 foot walk).	**Yes:** Go to #2	**No:** Pass to RPH; Deny (medical appropriateness)
2. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Approve for 12 months	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

- Because fewer than 50% of MS patients respond to therapy and therapy has risks, a trial of therapy should be used prior to beginning ongoing therapy.
- The patient should be evaluated prior to therapy and then 4 weeks to determine whether objective improvements which justify continued therapy are present (i.e. at least a 20% improvement from baseline in timed walking speed).
- Dalfampridine is contraindicated in patients with moderate to severe renal impairment.
- Dalfampridine can increase the risk of seizures; caution should be exercised when using concomitant drug therapies known to lower the seizure threshold.

P&T Action: 3-29-2012
Revision(s):
Initiated:

Appendix 3: Drug Information

NDE: Peginterferon beta-1a (Plegridy®)

Pharmacology: The mechanism in which peginterferon beta-1a exerts its effects in patients with multiple sclerosis is unknown.

Table 1. Pharmacokinetics

Parameter	Peginterferon beta-1a	Parameter	Peginterferon beta-1a
Half-Life	78 hours	**Renal Dose Adjustment**	Monitor for adverse reactions in severe renal impairment due to increased drug exposure.
Elimination	Renal		
Metabolism	Catabolism and excretion	**Hepatic Dose Adjustment**	No recommendation.

Author: Kathy Sentena, Pharm.D.

Contraindications/Warnings:

- **Contraindications:** Peginterferon beta-1a should not be used in patients with a history of hypersensitivity to natural or recombinant interferon beta or peginterferon or any other component of the formulation.
- **Warning:** Prescribing peginterferon beta-1a has been associated with hepatic injury (monitoring recommended), seizures, anaphylaxis, other allergic reactions, and injection site reactions. Symptoms of depression or suicide should be reported to provider and consider discontinuing peginterferon beta-1a if appropriate. Monitor patients with congestive heart failure for worsening of symptoms. Consider discontinuing peginterferon beta-1a if a new autoimmune disorder occurs.

Dose

The recommended dose of peginteferon beta-1a is 125 micrograms (mcgs) every 14 days. The dose should be titrated, starting with 63 mcgs on day one and 94 mcgs on day 15 and 125 mcgs on day 29. Patients should be consulted on correct technique for self-administering subcutaneous injections using the prefilled pen or syringe. Analgesics and/or antipyretics may be given to help with flu-like symptoms associated with peginterferon beta-1a use.

Author: Kathy Sentena, Pharm.D.