

Class Update: Disease Modifying Agents for Multiple Sclerosis

Month/Year of Review: September 2013

PDL Classes: Neurologic– MS Drugs (Disease modifying agents)

New Drug Evaluation: Dimethyl Fumarate

Manufacturer: Biogen Idec

Date of Last Review: Drug March 2012

Source Document: OSU College of Pharmacy

Brand Name: Tecfidera®

Dossier Received: Pending

Current Status of PDL Class:

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

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

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 dimethyl fumarate more effective or safer than other disease modifying treatments in reducing relapse rate or slowing disease progression in patients with relapsing remitting multiple sclerosis (RRMS)?

Conclusions:

- 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 20mg. 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 relative to other therapies.
- The efficacy and risk-benefit profile of all treatments remains uncertain beyond two years

Recommendations:

- Include dimethyl fumarate on the Oral MS drug Prior authorization criteria to ensure appropriate and safe drug use and limit to patients who have tried and failed first line agents including beta interferons and/or glatiramer.
- Make all interferons preferred due to evidence demonstrating improved efficacy of interferon beta-1a subQ and interferon beta-1b SubQ compared to interferon beta-1a IM in relapse related outcomes.
- Evaluate costs in executive session for further decision-making.

Reason for review:

Since the last review in March 2012, the class of MS treatments has been changing rapidly. While current treatments may slow disease progression, the disease has no cure and there has been an attempt to develop more effective treatments, as well as expand the number of oral options for patients. There are now 3 disease modifying oral agents FDA approved for the treatment of MS; fingolimod, teriflunomide, and dimethyl fumarate. Dalfampridine (Ampyra®) is not a disease modifying treatment, but it may improve impairment of walking associated with MS. In addition, the Pacific Northwest Evidence-based Practice Center's Drug Effectiveness Review Project (DERP) has completed a draft drug class review evaluating disease-modifying drugs for MS and the Canadian Agency for Drugs and Technologies in Health (CADTH) has released draft guideline recommendation for the treatment of RRMS. The new evidence will be reviewed and synthesized here.

Previous Conclusions and Recommendation:

- Due to similar efficacy and potential differences in relapse outcomes between the interferon products, evaluate costs of interferon beta-1a SC (Rebif®), interferon beta-1b SC (betaseron® and Extavia®), and interferon beta-1a IM (Avonex®) for further decision making
- Include dalfampridine as a non-preferred agent on the PDL and include clinical criteria for use including:
 - Has a walking disability that requires the use of a walking aid.
 - Be able to complete the T25FW in 8-45 seconds
 - Does not have renal impairment or a history of seizure disorder or epileptiform activity on an EEG.
- Include fingolimod as a non-preferred disease modifying medication for MS and develop clinical criteria to restrict based on the following:
 - Prescribed by or in consultation with a neurologist
 - Patient has relapsing remitting MS
 - Is not currently on therapy with an injectable disease modifying drug
 - Has failed or cannot tolerate a full course of a first line interferon or glatiramer
- Designate interferon alfacon-1 as a non-preferred agent due to the lack of recommendations for use in current treatment guidelines.

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- The evidence supporting teriflunomide efficacy is low. The strongest evidence is in affecting relapse rate and evidence is more robust for the 14 mg dose than the 7 mg dose. Teriflunomide comes with numerous safety concerns including hepatotoxicity and teratogenicity, considerable monitoring, and an accelerated elimination procedure. It may be an important option for patients unable to take injectables and fingolimod.
- Prior authorize teriflunomide to limit use to confirmed RRMS patients with documentation of prior failed use of an interferon for MS or glatiramer acetate. Documentation of compliance with requisite laboratory evaluation prior to prescribing.

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.¹ 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.² 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.³ Patients should be under the care of a specialized neurological doctor. The McDonald criterion is a tool used to help in differential diagnosis and is based upon number of clinical attacks, lesions, and dissemination in time and space.⁴

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 relapses of neurological symptoms followed by full or partial recovery.¹ Some patients with RRMS will develop secondary progressive MS, which is a progressive form of the disease.

Acute exacerbations or relapses of MS can be disabling.² Treatment of MS includes corticosteroids for acute relapse, symptom management, and disease modification.¹ 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.² Treatment with these agents should not be delayed in patients with a definite diagnosis of MS with active, relapsing disease.² Goals of treatment include decreasing exacerbations, hospitalizations, slowing disease progression, and disability.² There are currently ten DMD's approved by the U.S. Food and Drug Administration (FDA) for use in RRMS.⁵ These medications come in a variety of dosage forms, including injectable and oral agents.

Most of the currently available DMD's require regular and frequent parenteral administration, which is inconvenient to the patient.⁵ Due to many patients not responding adequately to available treatments and drug side effects, there is a need for more treatment options, including oral agents.⁵ The newest oral DMD is dimethyl fumarate (Tecfidera®), which was approved March 2013.⁶ A variation of the drug was approved in Germany in 1994 for the treatment of psoriasis. This drug's proposed mechanism of action is activation of the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcriptional pathway that is involved in the cellular response to oxidative stress and which reduces inflammation and promotes cytoprotection.⁶ Previously approved oral DMD's have also been associated with serious side effects. Teriflunomide carries a black box warning of hepatotoxicity and major birth defects due to either the mother or father.⁷ Fingolimod is associated with cardiovascular risk such as bradycardia upon first dose and its use requires extensive cardiac monitoring.

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.⁸ 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).^{8,9} 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

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impairment. Additionally, this outcome may not accurately measure long-term and irreversible disease progression.¹⁹ Due to treatment length “sustained disease progression” is often used instead of hitting a long-term disease progression milestone.⁹ 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 1999.¹⁰ 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 of 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.⁵ This is generally studied after one or more years of treatment. However, the frequency of relapses in the general population is highly variable.¹² According to data from the Marshfield Multiple Sclerosis Center in Wisconsin, 1,078 RRMS pts 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.¹¹

MS causes demyelination of neuronal axons which form lesions of the central nervous system on a magnetic resonance imaging (MRI).¹ 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.⁴ 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.² In July 2013, a meta-analysis explored the potential of MRI lesions being used as a surrogate for effect of treatment on relapses.¹² 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 January 2013 (since the literature search from the recent DERP report) and ending August 2013 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.

Systematic reviews:

Drug Effectiveness Review Project:

A recent systematic review from the Drug Effectiveness Review Project (DERP) compared the effectiveness and safety of disease-modifying drugs for the treatment of MS.¹ A streamlined approach was used which focused on only head to head studies and natalizumab and mitoxantrone were not included in the report. Intermediate MRI outcomes were not included as they are surrogate markers. After applying exclusion criteria, a total of 37 publications were included in the review; including 10 trials, 17 observational studies, and 4 systematic reviews. A following is a summary of the comparative evidence:

Alemtuzumab:

- There is moderate strength evidence that alemtuzumab 12mg is superior to interferon beta-1a SC in sustained disability at 6 months (RR 0.59, 95% CI 0.40 to 0.86), risk of relapse (RR 0.61, 95% CI 0.52 to 0.71), disease free survival (RR 1.38, 95% CI 1.23 to 1.54), and annualized relapse rate (rate ratio 0.42, 95% CI 0.31 to 0.56), and low strength evidence for alemtuzumab 24 mg.
- There was moderate strength evidence that treatment with alemtuzumab increased the risks of thyroid disease but decreased the probability of withdrawing from the study due to an adverse event (RR 0.31, 95% CI 0.17 to 0.55) compared with interferon beta-1a SC, and low strength evidence of reduced liver toxicity but increased risk of any infection (RR 1.32, 95% CI 1.10 to 1.58).

Dimethyl fumarate

- 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 20mg. 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.
- Low strength evidence indicates that treatment with dimethyl fumarate increased the risk of experiencing any adverse event compared with glatiramer (480mg: RR 1.09, 95% CI 1.04 to 1.14; 720mg: RR 1.06, 95% CI 1.01 to 1.12).

Teriflunomide

- There is no direct, head to head evidence available
- Moderate strength evidence indicated that teriflunomide reduced annualized relapse rate compared to placebo and low strength evidence that teriflunomide 14 mg reduced sustained disability progression (RR 0.74, 95% CI 0.57 to 0.96).
- There is moderate strength evidence that teriflunomide increases alanine aminotransferase levels compared to placebo (RR 1.58, 95% CI 1.05 to 2.37).

Fingolimod

- There is moderate strength evidence that fingolimod 0.5 mg daily and 1.25 mg daily resulted in lower annualized relapse rates than interferon beta-1a (0.16, 0.20, and 0.33 respectively; $p < 0.001$), and in more patients having no confirmed relapse at 1 year compared with interferon beta-1a (82.5%, 80.5%, and 70.1% respectively). There was no difference in disease progression.
- The benefit of fingolimod over interferon beta-1a was greater in the subgroup of patients who had prior exposure to a disease-modifying drug than in patients who had no prior exposure.

- Fingolimod was associated with higher rates of increased alanine aminotransferase levels (RR 3.52, 95% CI 1.66 to 7.50) and herpes virus infections when compared to interferon beta-1a, while interferon beta-1a was associated with higher rates of pyrexia, influenza-like illness, and myalgia.
- Discontinuations due to adverse events and serious adverse events occurred more frequently with fingolimod 1.25 mg than with fingolimod 0.5 mg or interferon beta-1a (RR 2.69, 95% CI 1.55 to 4.69; NNT 16).
- After the first dose of fingolimod, dose-dependent bradycardia and atrioventricular block occurred in the first 6 to 8 hours.

Glatiramer acetate

- There is low strength of evidence of no difference in relapse related outcomes comparing glatiramer and interferon beta-1a and 1b and moderate strength evidence that glatiramer results in similar disease progression as treatment with interferon beta-1b and interferon beta-1a.

Beta interferons

- 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 with only 1 trial finding a significant benefit of interferon beta-1b SC over interferon beta-1a IM (RR 0.44; 95% CI 0.25 to 0.79; NNT 6). Despite a trend toward benefit, there was no statistically significant difference in mean change in EDSS score.
- 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.
- Interferon beta-1a IM appeared to have the lowest immunogenicity, with rates of development of neutralizing antibodies of 2% to 8.5% reported. Antibodies occurred somewhat later with interferon beta-1a SC with rates of immunogenicity as low as 12% and as high as 46%. Neutralizing antibodies appeared as early as 3 months with interferon beta-1b SC and in 30-40% of patients.
- Evidence indicated that consistent positive neutralizing antibody status with high titer adversely affected the impact of these drugs on relapse rates, by one half to two thirds on longer follow up (greater than 2 years). There is insufficient evidence to conclude that there is an impact on disease progression.
- Although generally well tolerated, differences in adverse events between the products were seeming.
- Based on pooled trial rates, there were 7.5% of discontinuations due to adverse events with interferon beta-1b SC, 6.1% with interferon beta-1a SC = and 3.6% with interferon beta-1a IM =
- Interferon beta-1a IM had higher rates of flu-like syndrome, fatigue, and depression, while interferon beta-1b SC = had higher rates of fever and overall withdrawal.

Cochrane Collaboration

In June 2013, a Cochrane systematic review was published that evaluated the relative efficacy of interferon beta-1b (Betaseron), interferon beta-1a (Rebif and Avonex), glatiramer, natalizumab, mitoxantrone, cyclophosphamide, azathioprine, and long-term corticosteroids to provide a ranking of the treatments according to their effectiveness and risk-benefit balance.¹³ A total of 44 trials contributed to results with interferon, glatiramer, and natalizumab evaluated in the majority of the studies. Of the included studies, 11% were considered low risk of bias, 48% had moderate risk of bias, and 41% had high risk of bias. The two primary outcomes considered were clinical relapses (proportion of participants who experienced new relapses over 12, 24, or 36 months) and disability progression (proportion of participants who experienced disability progression over 24 or 36 months).

Results of a meta-analysis demonstrated high quality evidence that natalizumab and interferon beta-1a were more effective than interferon beta-1a in recurrence of relapse at 24 months (OR 0.28, 95% CI 0.22 to 0.36; OR 0.19, 95% CI 0.06 to 0.60, respectively). There was insufficient evidence to compare glatiramer with interferon beta-1b or interferon beta-1a. Disability progression was based on surrogate markers in the majority of studies and beyond two to three years, disability outcome data were unavailable or dropouts compromised interpretation. For disability progression over 24 months, natalizumab and interferon beta-1b were significantly more effective (OR 0.62, 95% CI 0.49 to 0.78; OR 0.35, 95% CI 0.17 to 0.70, respectively) than interferon beta-1a for RRMS and mitoxantrone appeared to be the most effective agents at two years, but this was based on very low evidence. None of the agents were effective in preventing disability worsening over two or three years in patients with progressive MS. Compared to placebo, the most effective drug appeared to be natalizumab, followed by interferon beta-1a mitoxantrone, glatiramer, interferon beta-1b. A lack of strong efficacy data shows that interferon beta-1a, intravenous immunoglobulins, cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.

There were no significant differences in withdrawals in direct comparison trials of the interferons compared to each other or to glatiramer. Treatment with natalizumab is associated with an increased risk of progressive multifocal leukoencephalopathy (PML). The efficacy and risk-benefit profile of all treatments remains uncertain beyond two years for a disease of 30 to 40 years duration. More than 70% of included studies were sponsored by pharmaceutical companies. More studies on the long-term efficacy and safety of immunotherapies for MS are needed.

Horizon Scan:

A recent AHRQ Horizon Scan report identified 5 agents that are currently in Phase III trials for the treatment of MS.¹⁴ Alemtuzumab (Lemtrada®) is a monoclonal antibody that will target a new mechanism of action for treating RRMS. FDA accepted the new drug application in January 2013 and there are completed phase III trials. This drug is given as a once-yearly intravenous treatment regimen. In addition, there are 3 other agents currently in Phase III trials; 1 oral tyrosine kinase inhibitor, 1 oral monoclonal antibody, and one IV treatment.¹⁴ NICE guidance is currently in progress for teriflunomide and dimethyl fumarate.

New Guidelines:

Canadian Agency for Drugs and Technologies in Health

At the time of this report, a CADTH draft recommendations report on drug therapies for the management of relapsing-remitting multiple sclerosis was available for feedback from all interested stakeholders and alemtuzumab and teriflunomide were not approved by Health Canada for the treatment of RRMS.¹⁵ The following is a summary of recommendations:

- The committee recommends glatiramer acetate or interferon beta-1b as the initial pharmacotherapies of choice for patients with RRMS.
- Patients who have failed to respond to, or have contraindications to, glatiramer as the initial treatment, be treated with interferon beta-1b and patients who have failed interferon-beta 1b as initial treatment, be treated with glatiramer.
 - Interferon beta-1b and glatiramer have similar efficacy based on the annualized relapse rate from direct and indirect evidence and are the most cost-effective initial therapies for the treatment of RRMS.
 - SubQ interferon beta-1b is available as more than one branded product, and choice should be based on price.
 - IM interferon beta-1a was considered to be less efficacious, as assessed by the annualized relapse rate, compared with interferons beta-1b and subQ beta-1a based on both direct and indirect evidence.
- Subsequent pharmacotherapies should be selected from dimethyl fumarate, fingolimod, and natalizumab. The selection should be based on cost and individual safety concerns.

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- There was insufficient data to determine relative efficacy of sequential treatments.
- Evolving safety considerations may influence the choice of subsequent pharmacotherapies.
- Combination therapy for treatment of RRMS should not be used.

National Institute for Health and Clinical Excellence

Currently, NICE limits fingolimod as an option for the treatment of highly active RRMS, only if: they have unchanged or increased relapse rate or ongoing severe relapses compared with the previous year despite treatment with beta interferon, AND the manufacturer provides fingolimod with the discount agreed as part of the patient access scheme.¹⁶

New FDA Safety Alerts:

In July 2012, the FDA released a drug safety communication of the risk of seizures in patients with MS who are starting dalfampridine (Ampyra) based on postmarketing case reports. The majority of seizures happened within days to weeks after starting therapy and in patients without a history of seizures.¹⁷ The communication also warned of the increased risk of seizures in those with kidney impairment as dalfampridine is eliminated from the body through the kidneys. Dalfampridine should not be used in patients with a history of seizures or who have moderate to severe renal impairment (CrCl less than or equal to 50 ml/min).

New drugs/formulations/indications:

Teriflunomide (Aubagio[®]) was FDA approved in September 2012 for the treatment of patients with RRMS. This was reviewed by the P&T committee in May and a prior authorization was implemented to limit its use to confirmed patients with documentation of prior failed use of an interferon for MS or glatiramer acetate. Only placebo controlled studies are available for teriflunomide and no direct, head to head evidence is available at this time. The recent DERP report concluded there was moderate strength evidence that teriflunomide reduced annualized relapse rate compared with placebo and low strength evidence that teriflunomide 14 mg reduced sustained disability progression and was not associated with worse EDSS scores compared with placebo. There was no difference in disability progression between teriflunomide 7 mg and placebo. This was based on 3 fair-quality published and 2 fair-quality unpublished placebo-controlled trials.

New Drug Evaluation: Dimethyl Fumarate (Tecfidera)

FDA approved indications: Dimethyl fumarate is indicated for the treatment of patients with relapsing forms of MS.¹⁸

Clinical Efficacy Data:

ClinicalTrials.gov identified seven dimethyl fumarate trials: one Phase I, two Phase II, one of which was published, and 2 published Phase III trials. There are two additional long-term studies that are ongoing.¹⁹ Based on published studies, the FDA approved dimethyl fumarate with an initial dose of 120 mg orally twice daily for seven days, followed by maintenance dose of 240 mg twice a day.

In addition to the pivotal phase III trials included in the evidence table, a study by Kappos et al.²⁰ was a fair quality phase IIb, 24 week dose-ranging trial that randomized patients to dimethyl fumarate 120 mg once daily (n=64), 120 mg three times a day (n=64), 240 mg three times a day (n=63), and matching placebo (n=65). The primary endpoint was total number of new gadolinium enhancing (GdE) lesions on brain MRI scan, which is an intermediate outcome. In patients

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treated with dimethyl fumarate 120 mg once daily, 120 mg three times daily, and 240 mg three times daily there were non-significant results in number of patient that relapsed by 24 weeks (17%, 31%, 19% vs 25% placebo). Interestingly, a trend toward increased relapse was seen in the 120 mg three times daily group. Furthermore, only the 240 mg three times daily group had a significantly lower number of new GdE lesions compared to placebo at 24 weeks (2.2 vs 4.2 placebo; $p=0.0006$).

Gold et al.²¹ was a fair quality phase III trial (DEFINE) that randomized patients to 240 mg dimethyl fumarate twice daily ($n=410$), dimethyl fumarate 240 mg three times daily ($n=416$), and matching placebo ($n=408$). Fox et al.²² was a fair quality phase III trial (CONFIRM) that randomized 359 patients to blinded 240 mg dimethyl fumarate twice daily, 345 patients to blinded 240 mg dimethyl fumarate three times a day, and 363 patients to matching placebo. Additionally, 350 patients were randomized to open-label glatiramer acetate, 20 mg subcutaneous daily injections, as a reference comparator. In both studies, all patients could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks. Randomization and allocation concealment was adequate and described in both phase III trials. Overall attrition was high in both studies, 23% and 21.2%, respectively. However, all groups had similar attrition rates and was mostly due to adverse events in the study groups and withdrawal of consent in the control group. There is a low risk of detection bias in studies due to requiring separate study personnel to treat patients and assess drug efficacy. However, there was a possibility of unblinding in all 3 trials due to the high incidence of flushing associated with dimethyl fumarate. Authors corrected for this by having patients take the study drug at least 4 hours before study visit. However, the authors do not address the patient telling the care provider or how the patient is blinded from this side effect.

Relapse rate at 2 years was similar across studies and was significantly better in the dimethyl fumarate groups compared to placebo.^{21,22} Relapse rate in patients treated with dimethyl fumarate 240 mg twice daily and three times daily was 27% and 26% vs. 46% placebo ($p<0.001$), giving an NNT of 5 for both comparisons in Gold et al.²¹, compared to 29% and 24% vs. 41% ($p\leq 0.01$, $p<0.001$), giving an NNT of 8 and 6, respectively, in Fox et al.²² The glatiramer group had 32% of patients relapse at 2 years, with an NNT of 11 when compared to placebo.²² This study was not designed to directly compare dimethyl fumarate to glatiramer. Disability progression with dimethyl fumarate 240 mg twice daily and three times daily was statistically significant in Gold et al.²¹ (16%, 18% vs. 27% placebo; $p=0.005$ and $p=0.01$; NNT of 9 and 11), while Fox et al.²² showed no significance (13% in both groups vs. 17% placebo; p -value not provided) compared to placebo or glatiramer.

Mean age range in all three trials was 37 years old and patients were primarily female, which is representative of the RRMS population. However, the study population was predominately white. At baseline, most study patients had an EDSS score of 2.0-2.5, which corresponds to minimal disability in one to two items of the FSS. Furthermore, in the Phase III trials only approximately one-third of patients had received prior treatment with any approved DMD. Therefore, it appears study population had less severe forms of RRMS, and study outcomes may not correspond to patients with further stages of RRMS. Published subgroup analyses of DEFINE and CONFIRM showed that the benefits of treatment were consistent across subgroups of patients, irrespective of demographics, treatment history, and disease characteristics at baseline.^{23,24}

There is currently a 5-year extension study of the 2 phase 3 trials underway (A Dose-Blind, Multicenter, Extension Study to Determine the Long-Term Safety and Efficacy of Two doses of BG12 Monotherapy in Subjects with Relapsing-Remitting Multiple Sclerosis [ENDORSE] trial).²⁵

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Clinical Safety:

According to the FDA Summary Review safety data of 3,424 subjects in clinical trials of healthy volunteers, MS patients, psoriasis, and RA were submitted by the sponsor.⁶ Flushing and GI related side effects were most common, and occurred most frequently early in treatment. Flushing was not dose dependent. In patients treated with dimethyl fumarate 240 mg twice daily and three times daily flushing was reported in 38% and 32% vs. 5% placebo in Gold et al.²¹, compared to 31% and 24% vs. 4% in Fox et al.²² Flushing resulted in 3% of patients stopping therapy. GI effects included diarrhea (11%), vomiting (5%), and abdominal pain (10%).¹⁰ Serious side effects had low occurrence. Labeling includes risk of lymphopenia, due to decrease in lymphocyte count during the first year, which is followed by a plateau. A decrease in the lymphocyte count occurred in approximately 6% of patients in clinical trials with a decrease of up to 30% during the first year of therapy, with levels remaining stable after that. However, no serious infections or opportunistic infections were reported. Likewise, increases in hepatic enzymes and proteinuria are included on labeling. Safety data is from relatively short-term clinical trials. Two studies are ongoing to assess long-term safety profile.¹⁹

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) Relapse rate at 2 years
- 2) Annualized relapse rate
- 3) Total number of new GdE lesions on MRI scan (Phase IIb trial)

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
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<p>DEFINE trial Gold R, et al</p> <p>Phase III, RCT, DB, PC</p>	<p>1:1:1 ratio to 1 of 3 groups: 1. 240 mg dimethyl fumarate BID 2. 240 mg dimethyl fumarate TID 3. placebo</p> <p>Duration: 2 years*</p> <p>*All pts could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks.</p>	<p>198 sites in 28 countries January 2007 – February 2011</p> <p>Mean age: 38 Age range: 18-56 yrs Females %: 73.4% White %: 78.5%</p> <p><u>Inclusion Criteria:</u> age 18- 55 yo; confirmed diagnosis of RRMS; baseline EDSS between 0.0-5.0; at least 1 relapse within the 12 months with a prior brain MRI demonstrating lesion(s) consistent with MS, or show evidence of Gd- enhancing lesion(s) of the brain on an MRI performed within 6 week prior to randomization</p> <p><u>Exclusion Criteria:</u> progressive relapsing MS; history of malignancy, severe allergic or reactions; history of abnormal lab results; history of significant cardiovascular, pulmonary, GI, dermatologic, psychiatric neurologic disease; HIV; drug or alcohol abuse; MS relapse within 50 days; hepatitis C or B; ALT, AST, or GGT $\geq 2 \times$ ULN, leukocytes $< 3500/\text{mm}^3$, eosinophils > 0.7 GI/L; proteinuria, hematuria; prior treatment with any monoclonal antibody; tx w/n 1 year with mitoxantrone or cyclophosphamide</p>	<p>1. n= 410 2. n=416 3. n=408</p>	<p><u>Annualized relapse rate at 2 years (adjusted)</u> 1. 0.17 2. 0.19 3. 0.36 p=0.01 in both comparisons</p> <p><u>Relapse by 2 years</u> 1. 111 (27%) 2. 108 (26%) 3. 188 (46%) p<0.001 in both comparisons</p> <p><u>Disability progression (1.0 point increase on the EDSS sustained for at least 12 weeks)</u> 1. 65 (16%); p=0.005 2. 75 (18%); p=0.01 3. 110 (27%)</p> <p><u>Mean number of Gadolinium- enhancing lesions</u> 1. 0.1 2. 0.5 3. 1.8 p=0.01 in both comparisons</p>	<p>N/A</p> <p>1. ARR: 19% NNT: 5 2. ARR: 20% NNT: 5</p> <p>1. ARR: 11% NNT: 9 2. ARR: 9% NNT: 11</p> <p>N/A</p>	<p><u>Serious adverse events</u> 1. 74 (18%); p=0.291 2. 65 (16%); p=0.048 3. 86 (21%)</p> <p><u>D/c of study drug due to adverse event</u> 1. 65 (16%); p=0.374 2. 68 (16%); p=0.851 3. 55 (13%)</p>	<p>2. ARR: 5% NNH: 20</p> <p>NS</p>	<p>Quality rating: Fair Internal validity: <u>Selection:</u> Randomization and allocation concealment were performed with the use of a centralized IVRS and was stratified according to site. Baseline characteristics were similar. <u>Performance:</u> low/moderate risk; Pts took the study drug at least 4 hours before study visit due to flushing side effect, which helped blind care givers. Did not address pt telling care provider about side effect. Unclear how patients were blinded from this side effect, may compromise blinding. Placebo drug packaged in the same manner as the study drug. <u>Detection:</u> low risk; each study center used separate examining and treating neurologist <u>Attrition:</u> moderate risk; Overall attrition was high at 23% (952/1237), however, all groups had similar attrition rates (1. 23.4%, 2. 23.1%, 3. 22.7%). A modified ITT was used that included all pts that received at least one dose (did not include 3 pts that underwent randomization). All data before patient switched to alternative medication was used in the analysis. For analysis of MRI in these patients after they switched a constant rate assumption was used.</p> <p>External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Primarily white pts (78%). Healthy pt population, most having minimal disability. Only 40% had received DMD for MS before study entry. <u>Setting:</u> Included 198 sites in 28 countries. Sponsored by Biogen Idec. <u>Outcomes:</u> Efficacy: clinically relevant endpoints Safety: relevant endpoints reported, did not include p-values or CI</p>
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<p>CONFIRM trial Fox R, et al Phase III, RCT, DB, PC</p>	<p>1:1:1:1 ratio to 1 of 4 groups: 1. 240 mg dimethyl fumarate 2. 240 mg dimethyl fumarate TID 3. 20 mg glatiramer daily SC injections 4. placebo Duration: 2 years *All pts could switch to alternative MS therapy if they had completed 48 weeks of blinded treatment and experienced at least 1 confirmed relapse after 24 weeks, or at any time if they had experienced disability progression sustained for 12 weeks.</p>	<p>200 sites in 28 countries June 2007-August 2011 Mean age: 37 Females %: 70.1% White %: 84.1% Inclusion Criteria: same as previous trial Exclusion Criteria: same as previous trial, except for including pts with prior treatment with glatiramer</p>	<p>1. n= 359 2. n= 345 3. n= 350 4. n= 363</p>	<p><u>Annualized relapse rate at 2 years</u> 1. 0.22; p<0.001 2. 0.20; p<0.001 3. 0.29; p<0.05 4. 0.40 <u>Proportion of patients with relapse at 2 years</u> 1. 104 (29%); p≤0.01 2. 83 (24%); p<0.001 3. 112 (32%); p≤0.01 4. 149 (41%) <u>Disability progression at 2 years (sustained for at least 12 weeks)</u> 1. 47 (13%); p=0.25 2. 45 (13%); p=0.20 3. 56 (16%); p=0.70 4. 62 (17%) <u>Gadolinium-enhancing lesions at 2 years</u> 1. 0.5 2. 0.4 3. 0.7 4. 2.0 p<0.001 in all comparisons</p>	<p>N/A 1. ARR: 12% NNT: 8 2. ARR: 17% NNT: 6 3. ARR: 9% NNT: 11 NS N/A</p>	<p><u>Serious adverse events</u> 1. 61 (17%); p=0.110 2. 54 (16%); p=0.43 3. 60 (17%); p=0.130 4. 79 (22%) <u>D/c of study drug due to adverse event</u> 1. 44 (12%); p=0.483 2. 41 (12%); p=0.553 3. 35 (10%); p=0.902 4. 38 (10%)</p>	<p>NS NS</p>	<p>Quality rating: Fair Internal validity: <u>Selection:</u> Randomization and allocation concealment were performed with the use of a centralized IVRS and was stratified according to site. Baseline characteristics were similar. <u>Performance:</u> moderate risk; Pts took the study drug at least 4 hours before study visit due to flushing side effect, which helped blind care givers. Did not address pt telling care provider about side effect. Unclear how patients were blinded from this side effect, may compromise blinding. Glatiramer was open-label. Placebo drug packaged in the same manner as the study drug. <u>Detection:</u> low risk; each study center used separate examining and treating neurologist <u>Attrition:</u> moderate risk; Overall attrition was high at 21.2% (1127/1430), however, all groups had similar attrition rates (1. 21.5%, 2. 20.9%, 3. 18.9%, 4. 23.4%). A modified ITT was used that included all pts that received at least one dose (did not include 13 pts that underwent randomization). Analyses of endpoints were based on all observed data before patients switched to alternative MS medications, with missing MRI end points imputed using the constant-rate assumption. External validity: <u>Recruitment:</u> Not provided. <u>Patient characteristics:</u> Age range representative of general population. Primarily white pts (84.1%). Healthy pt population, most having minimal disability. Only 30% had received DMD for MS before study entry. <u>Setting:</u> Included 200 sites in 28 countries. Sponsored by Biogen Idec. <u>Outcomes:</u> Efficacy: clinically relevant endpoints Safety: relevant endpoints reported</p>
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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

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY²¹: The mechanism of action of dimethyl fumarate is unknown. Dimethyl fumarate and the metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist in vitro.

PHARMACOKINETICS²¹

Parameter	Result
Oral Bioavailability	Unknown
Protein Binding	27-45%
Elimination	Exhalation of CO ₂ (60%), renal (16%), fecal (1%)
Half-Life	1 hr
Metabolism	Rapid presystemic hydrolysis by esterases to active metabolite, monomethyl fumarate (MMF), which is further metabolized by the TCA cycle

DOSE & AVAILABILITY²¹

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
120 mg and 240 mg	Delayed-release	Oral	Initial dose: 120 mg twice a day After 7 days: 240 mg twice a day	None	None	Unknown	Has not been studied in patients >55	<ul style="list-style-type: none">A high-fat, high-calorie meal did not affect the AUC, but decreased its C_{max} by 40%. T_{max} was delayed from 2.0 hours to 5.5 hours. Flushing was reduced by ~25% in the fed state.Do not chew, crush, or open capsule

DRUG SAFETY²¹

Serious (REMS, Black Box Warnings, Contraindications): None

Warnings and Precautions:

- Mean lymphocyte counts decreased by approximately 30% during the first year of treatment and then remained stable. The incidence of infections (60% vs 58%) and serious infections (2% vs 2%) was similar with dimethyl fumarate and placebo, respectively. Before initiating treatment, a recent CBC (within 6 months) should be available, and is recommended annually and as clinically indicated. Treatment should be withheld in patients with serious infections until infection is resolved.
- 40% of dimethyl fumarate treated patients experienced flushing. Flushing begin soon after initiation and usually improve over time. Administration of dimethyl fumarate with food may decrease flushing.

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Unanswered safety Questions: Further evaluation in ongoing long-term safety studies

Look-alike / Sound-alike (LA/SA) Error Risk Potential: None identified

Adverse Reactions Table²¹

In clinical trials, the most commonly observed adverse reactions, incidence $\geq 2\%$ higher than placebo, reported in the prescribing information.

Adverse Reaction	Placbo (n=771)	Dimethyl fumarate (n=769)
Flushing	6%	40%
Abdominal pain	10%	18%
Diarrhea	11%	14%
Nausea	9%	12%
Albumin urine present	4%	6%
Vomiting	5%	9%
AST increased	2%	4%
Dyspepsia	3%	5%
Pruritus	4%	8%
Rash	3%	8%
Erythema	1%	5%
Lymphopenia	<1%	2%

Allergies/Interactions:

Drug-Drug: Live vaccines

Food-Drug: None known

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 remitting 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

8. Is the patient of childbearing potential?	Yes: Go to #9	No: Approve for up to one year
9. Is 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.

DUR Board Action: 3-29-2012
 Revision(s): 5-30-2013 (MH)
 Initiated: 6/21/2012

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 <ul style="list-style-type: none"> • 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)

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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 $\geq 20\%$ 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.

DUR Board Action: 3-29-2012

Revision(s):

Initiated:

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