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New Drug Evaluation: Teriflunomide

Month/Year of Review: May 2013
Generic Name: Teriflunomide
PDL Class: MS Drugs

End date of literature search: December 1, 2012
Brand Name (Manufacturer): Aubagio®
Dossier Received: Yes

FDA Approved Indication:

Teriflunomide (TER) is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).[1]

Research Questions:

- Is TER superior to placebo (PLA) for reducing relapses, disability progression, and lesion activity in subjects with relapsing MS?
- How does the efficacy and safety of teriflunomide compare to that of other DMD?
- Are there important unanswered safety questions associated with TER?

Conclusions:

- At this time, the evidence supporting the TER efficacy is low, due to the lack of a sufficient number of adequately controlled phase 3 studies, as well as issues with internal and external validity. The strongest evidence is in affecting relapse rate and evidence is more robust for the TER 14 mg dose than the 7 mg dose
    - The TEMSO trial demonstrated TER 7 mg and 14 mg compared to PLA resulted in significantly reduced rates of relapse (31.2% for TER 7mg and 31.5% for TER 14 mg), active inflammatory lesions (risk reductions were 39.4% and 67.4% for TER 7 mg and 14 mg, respectively, v PLA), and, in the case of TER 14 mg, risk of disability progression as measured by the proportion of patients with sustained disability progression (27.3% for PLA, 21.7% for TER 7 mg (NS), and 20.2% for TER 14 mg, corresponding to a NNT of 14 for TER 14 mg). The Kaplan-Meier estimated percentage of patients without relapse over 108 weeks were 45.6% for PLA, 53.7% for TER 7 mg, and 56.5% for TER 14 mg, corresponding to a NNTs of 12 and 9.[2] For Study 2001, TER 7 mg and 14 mg were superior to placebo in reducing the number of combined unique (CU) active lesions per MRI scan (the primary endpoint) during the 36-week study; however, they were not significantly superior to PLA for ARR and only TER 14 mg was superior to placebo at preventing disability progression (key secondary endpoints).[3] An interim analysis of the TOWER study revealed the percentages of patients without confirmed relapses were 66%, 76.5%, and 77.1% for PLA, TER 7 mg, and TER 14 mg, corresponding to NNTs of 10 and 9 for TER 7 mg and 14 mg, respectively.[4]

- Due to external validity concerns, one is unable to draw conclusions about the efficacy of TER in populations with secondary progressive (SP) and progressive relapsing (PR) MS, non-Caucasian patients, patients with more advanced disability, and populations who may have greater experience with DMDs, such as those in the U.S. In its review, the FDA noted the treatment effect on relapse tended to be greater among those who began with an EDSS score ≤3.5 at baseline and those with known relapsing remitting (RR) multiple sclerosis (MS).
- No head-to-head trials for TER have been published and therefore insufficient evidence to make comparative conclusions. The TENERE study assessed TER compared to interferon beta-1a, however the primary endpoints were not clinically relevant.[5] In the phase 3 TEMSO trial, both TER doses reduced the risk of relapse by about 31%, which is similar to other first-line disease modifying drugs (DMD). However, cross-trial comparisons should be viewed cautiously, as cross-trial comparisons of DMD efficacy have been found to be misleading and potentially contradictory to head-to-head trials.[6]
- There is low quality evidence for TER in reducing the risk of disability progression. However, the ARR and MRI data indicate TER would have a positive effect on disability progression, because the effect of treatment on relapse and the effect of treatment on disability are significantly correlated.[7]
- Some uncertainty surrounds the extent to which TER is safe and TER is clearly unsafe in pregnancy.
- TER comes with numerous safety concerns including hepatotoxicity and teratogencitiy, considerable monitoring, and an accelerated elimination procedure. Providers and patients may find it difficult to comply with these processes. Nevertheless, options for patients who are unable to self-administer injections or who have conditions precluding them from repeated injections have only fingolimod as an oral option. Because of fingolimod's potential to induce life-threatening bradycardia, cardiovascular monitoring is required following first dose and the drug poses a greater risk to cardiovascular patients. Therefore, TER may be an important option for patients unable to take injectables and fingolimod.

Recommendations:
- Prior authorize teriflunomide to limit use to confirmed patients with documentation of prior failed use of an interferon for MS or glatiramer acetate (Appendix 2).
- Documentation of compliance with requisite laboratory evaluation prior to prescribing
- Add proof of contraception for women of childbearing age to prior authorization criteria.

Background:
Disease modifying drugs (DMD) and symptomatic therapies are the mainstay for managing MS. The disease has no cure; therefore, the primary goals of disease modifying therapy are to prevent relapses, progression of demyelination, and long-term disability. Long-term disability progresses over many years and each patient's course varies widely. Also, patients recover some or all function over the weeks and months following an acute attack. Therefore, studies of MS treatments are limited by their short duration, their population focus, and assessment tools that inadequately predict disease course.[8–10]

MS is a chronic, progressive, immune-mediated disorder characterized by inflammation of the white and gray matter of the central nervous system and destruction of axonal myelin sheaths, resulting in neurodegeneration and gliotic sclerosis. MS affects about 350,000 people in the US and more than 1 million worldwide. MS occurs 2–2.5 times more frequently in women than in men.[11,12]

MS symptoms typically present between the ages of 18 and 45 and include combinations of the following: fatigue; heat sensitivity; weakness; depression; bladder, bowel, or sexual dysfunction; or impaired vision, sensation, coordination or balance.[11,12]

The subtypes of MS are relapsing remitting (RRMS), secondary progressive (SPMS), progressive relapsing (PRMS), and primary progressive (PPMS).

About 85–90% of patients present with RRMS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with RRMS develop SPMS within 20–40 years. SPMS is characterized by steady neurological decline with few or no clinical relapses. The least common form of MS is PRMS, which is progressive from onset and has acute relapses with progression between relapses. About 10–15% of patients present with PPMS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[11–14]

The goal of MS therapy is to prevent the long-term accumulation of irreversible disability. Relapse rate is the most often used primary efficacy endpoint in phase 3 clinical trials of DMD, while disease progression, as measured by change in EDSS score, and MRI-detected lesion activity have been more often used as a secondary efficacy endpoints. Each of these endpoints has limitations. Because of the uncertainty in the correlation of outcome measures and future function, the evidence from clinical trials using a combination of outcome measures—both clinical and MRI—are considered stronger.[8]

Relapse rate is the preferred primary endpoint because evaluating treatment effect on disability progress would require large patient samples sizes that could be followed for several years. A 2010 pooled analysis of published RCTs in RRMS, with treatment durations of 2 to 3 years, has found a significant correlation between the effect of treatments on relapse and the effect of treatment on disability worsening, as measured by EDSS. However, how relapses impact long-term disability is still unclear.[7]

The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored from 0, no neurological abnormality, to 10, death from multiple sclerosis. An EDSS score between 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.[18–21]

The EDSS's shortcomings include the following: (1) the scale is non-linear, so the clinical importance of a 1.0-point change in EDSS varies with the baseline score; (2) the EDSS emphasizes ambulation and poorly measures cognitive and visual impairment; (3) the ratings, which are based on neurological exam, are subjective and subject to within and between rater variability; (4) the EDSS has reduced sensitivity in the mid and upper ranges of scores. Nevertheless, the EDSS is widely accepted as a measure of clinical progression in clinical trials.[22,23]

In most clinical trials of DMA, disease progression has been defined as a sustained 3- or 6-month increase in EDSS of at least 1.0 point recorded in a period when the patient had no exacerbation.[21] Because the EDSS scores for many patients continue to improve for 3 months after relapse, confirming worsening at 6 months may be a better indicator of long-term accrual of disability than assessments performed at 3 months.[22]

MRI-detected lesion activity is a well-accepted endpoint used in MS clinical trials. Often, MRI serves as a primary outcome in phase 2 studies and a secondary outcome in phase 3 studies. MRI is used to evaluate the inflammatory and degenerative aspects of MS. Treatment effects on MRI-detected lesion activity correlate well with relapse activity but only weakly with accumulated disability.[22]

Two categories of MRI measures are used to monitor MS treatment: those that reflect disease activity (new or enlarged T2 lesions, galodinium-enhancing and new enhancing lesion counts, and enhancing lesion volume) and those that reflect burden of disease and are markers of irreversible tissue loss (T2 lesion load, T1-hypointence lesions, and brain atrophy).[20]

Immunomodulatory agents—interferon (IFN)-β-1a, IFN)-β-1b, glatiramer acetate, natalizumab, and fingolimod—are used to reduce the risk of relapse and slow disease progression, but are unable to stop or reverse disability. Anti-inflammatory drugs, such as glucocorticoids are used for acute attacks.[10]

The limitations of these agents, whether delivery or side effect profile, has fueled the search for oral agents. Interferon and glatiramer acetate are first-line agents delivered by self-injection, with 12% of patients citing injection site reactions as one of many reasons patients discontinue these medications. At 30%, perceived lack of efficacy is the most oft cited reason.[9,10]

The FDA approved fingolimod as the first DMA delivered orally. Although fingolimod was approved as a first-line agent, it has been associated with potentially life-threatening bradycardia and requires 6 hours or more of hourly pulse and blood pressure monitoring in every patient and overnight ECGs in high risk cardiovascular patients. For these reasons, some practitioners believe the interferons and glatiramer acetate should be tried before prescribing fingolimod. Natalizumab, a second-line agent for patients uncontrolled on interferon or glatiramer, has been associated with progressive multifocal leukoencephalopathy.[9,10]

Guidelines from the American Academy of Neurology (AAN), National Institute for Health and Clinical Excellence (NICE), and European Federation of Neurological Societies (EFNS) have not been updated since the introduction of TER and fingolimod.[8,14,24] The following is a table for comparing their use, efficacy, and safety; however, cross-trial comparisons of DMD efficacy have been found to be misleading and potentially contradictory to head-to-head trials.[4,6]

Medication 1st or 2nd line	**Indication**	**Maintenance dose/Route of delivery**	**Efficacy**	**Safety concern**
Avonex (IFNβ-1a) 1st line	↓ exacerbations & slows physical disability in relapsing forms	30 mg qWK IM	32% RRR 37% reduction disability	Decreases blood count, hepatic injury, flu-like symptoms
Rebif (IFNβ-1a) 1st line	↓ exacerbations & slows physical disability in relapsing forms	22 mcg tiw SQ 44 mg tiw SQ	29% RRR 32% RRR	Hepatic injury, flu-like symptoms, injection site reaction
Betaseron (IFNβ-1b) 1st line	↓ exacerbations & delay physical disability in relapsing forms	0.25 mg qOD SQ	30% RRR	Injection site necrosis, flu-like symptoms
Copaxone (glatiramer acetate) 1st line	↓ exacerbations In RRMS and includes patients with CIS	20 mg/1 ml qD SQ	29-75% RRR	Transient chest pain, post-injection reaction, skin necrosis
Tysabri (natalizumab) 2nd line	↓ exacerbations & delays physical disability in relapsing forms of MS	300 mg q4WK IV	61% RRR 33% reduction disability progression	PML, immunosuppression, malignant melanoma, hepatic toxicity
Novantrone (mitoxantrone)	↓ exacerbations & neurological disability in SPMS	12 mg/m^3 q3MO IV	60% RRR	Cumulative cardiotoxicity, AML

2nd line	or worsening RRMS		64% reduction disability progression	
Gilenya (fingolimod) 1st line	↓ exacerbations & delays physical disability in relapsing forms of MS	0.5 mg PO qD	55-58% RRR 29-30% reduction disability	AV conduction delay, ↓ in HR with 1st dose, infections, macular edema, ↓ pulmonary functions, increase ↑ in liver enzymes

Clinical Efficacy:

The FDA approved TER based on one phase 3 clinical trial, called TEMSO, that is published, along with supporting, descriptive evidence from one phase 2 clinical trial, called Study 2001, and an interim analysis of a phase 3 clinical trial, called TOWER, that has not been published.[2–4]

The TEMSO trial demonstrated TER treatment resulted in significantly reduced rates of relapse, active inflammatory lesions, and, in the case of TER 14 mg, risk of disability progression. TEMSO compared TER 7 mg once daily and TER 14 mg once daily to PLA in 1088 patients randomized 1:1:1. The subjects were aged 18 to 55, had EDSS scores ≤5.5 (mean 2.68), were predominantly Caucasian (97%), female (72%), and without DMD treatment in the 2 years before randomization (73%). Most subjects had RRMS (91%) and EDSS scores≤3.5 (77%). The primary endpoint for the 108 week study was annualized relapse rate (ARR) and key secondary endpoints were confirmed disability progression and total lesion volume. Confirmed relapse was defined as the appearance of a new clinical sign or symptom (S/S) or clinical worsening of a previous S/S that had been stable for ≥30 days and persisted for ≥24 hours and an increase of 1 point in each of 2 EDSS functional-system scores or 2 points in 1 EDSS functional-system score or 0.5 points in the EDSS score from the previous clinically stable assessment. Disability progression was defined as a ≥1.0 increase in EDSS score for patients with a baseline EDSS score ≤5.5 and ≥0.5 for those with an EDSS score >5.5 that persisted for ≥12 weeks. The adjusted ARRs were 0.54 (CI: 0.47 to 0.62), 0.37 (CI: 0.32 to 0.43, p=0.01), and 0.37 (0.31 to 0.44, p=0.01) for the PLA, TER 7 mg, and TER 14 mg groups, respectively, corresponding to relative reductions v. PLA of 31.2% for TER 7mg and 31.5% for TER14 mg. The Kaplan-Meier estimated percentages of patients without relapse were 45.6% (CI: 40.2 to 51) for PLA, 53.7% (CI: 48.3 to 59.1, p<0.001) for TER 7 mg, and 56.5% (CI: 51 to 62, p=0.003) for TER 14 mg, corresponding to a NNTs of 12 and 9, respectively, to prevent 1 subject from having a relapse over 108 weeks. The percentages of patients with sustained disability progression were 27.3% (CI: 22.3 to 32.3) for PLA, 21.7% (CI: 17.1 to 26.3, NS) for TER 7 mg, and 20.2% (CI: 15.6 to 24, p=0.03) for TER 14 mg, corresponding to a hazard ratio reduction of 29.8% and an NNT of 14 for TER 14 mg. The changes in total lesion volume from baseline were 2.21±7.00 for PLA, 1.31±6.80 for TER 7 mg, and 0.72±7.59 for TER 14 mg, corresponding to relative risk reductions of 39.4% and 67.4% for TER 7 mg and 14 mg, respectively.[2] Subgroup analyses reported to the FDA revealed patients from the Americas (n=245) experienced no benefit for disability progression: hazard ratio (HR) 1.397 (CI: 0.684 to 2.851) TER 7 mg and 1.114 TER 14 mg (CI: 0.523 to 2.371) v. PLA. However, TEMSO was not powered to examine subgroups.[4]

Key limitations of TEMSO trial included the following:

- The study duration was short compared to the lengthy course of disability progression in MS.
- The patient population was less advanced in their disease state; therefore, one is unable to determine how more advanced patients will respond to TER.
- The study population was predominantly Caucasian; therefore, one is unable to determine how non-Caucasians will respond to TER.
- TER was tested only in patients with relapsing forms of MS, predominantly relapsing remitting; therefore, one is unable to draw conclusions about the efficacy of TER in patients with SPMS and PRMS (for example, subgroup analyses reported to the FDA show the relative risk TER14 mg v. PLA in this patient population is 0.985, p=0.9708. However, the n is only 26.).

- Only sustained disability progression for 12 weeks was reported. FDA analysis to estimate the percentage of patients with 24-week sustained disability progression at week 108 revealed neither TER dose had a statistically significant benefit: 25% risk reduction for TER 7 mg (p=0.1459) and 25.1% risk reduction TER 14 mg (p=0.125).[4]
- Most patients (67–77%) had not been treated with a DMD in the two years prior to randomization, only 22% of patients were from the Americas, and a subgroup analysis of patients from the Americas showed no benefit for disability progression. This casts uncertainty on how the U.S. population initially receiving TER will respond.
- The risk of disability progression was not significantly reduced in the TER 7 mg, suggesting the possibility of a dose response and the weaker efficacy of TER 7mg.

For Study 2001, TER 7 mg once daily and 14 mg once daily were superior to placebo in reducing the number of combined unique (CU) active lesions (T1 plus T2 new and persisting active lesions) per MRI scan (the primary endpoint) during the 36-week study; however, they were not significantly superior to PLA for ARR and only TER 14 mg was superior to placebo at preventing disability progression (key secondary endpoints). Disability progression was defined as an EDSS score increase ≥1.0 in patients with baseline EDSS scores ≤5.5 or a score increase ≥0.5 in patients with baseline EDSS scores ≥5.5. Study 2001, a phase 2 PLA-controlled study of TER efficacy and safety, randomized (1:1:1) 179 patients age 18 to 65 with relapsing forms of MS and EDSS scores of ≤6 (median 2.33). Patients primarily had RRMS (88%) and were predominantly female (67% PLA, 75% 7 mg, 79% TER 14 mg). Racial demographics were not reported. The mean number of CU active lesions was less for the TER groups: 1.04±0.37 for TER 7 mg and 1.06±0.38 for TER 14 mg v. 2.68±0.39 for PLA, resulting in relative reductions of –61.1% and –61.3% for TER 7 mg and TER 14 mg, respectively. However, only the TER 14 mg group had a median change in BOD (T2 lesion volume) from baseline that was significantly different from PLA: –4.1 TER 14 mg, 2.9 TER 7 mg, 5.2 PLA ($p<0.02$ for TER 14 mg). The TER groups had lower mean ARRs v. PLA, but not significantly: 0.58±0.85 TER 7 mg and 0.55±1.12 TER 14 mg v. 0.81±1.22 (NS). The TER 14 mg group had a larger proportion of subjects who were relapse-free v. PLA, but not significantly: 65% TER 7 mg and 77% TER 14 mg v. 62% for PLA (NS). The proportion of patients with an increase in disability was only significantly lower for the TER14 mg group v. PLA: 7.4% v. 21.3%, $p<0.04$.[3,4]

Because Study 2001 is a phase 2 trial, its limitations are numerous. Some key limitations include the following: the study size was small and the duration short; the study had imbalanced discontinuation rates; MRI was the primary outcome; no follow-up confirmation of EDSS progression or confirmation of relapse was performed; 6 patients were included who did not meet inclusion criteria; protocol deviations occurred for 30 patients (including the use of corticosteroids prior to MRI in 8 PLA, 7 TER 7 mg, and 10 TER 14 mg patients); the TER groups had a greater percentage of females; several figures were unreported in the published study; inadequate numbers of patients who were non-Caucasian and had SPMS were included in the study; patients with PRMS were not included; and the study did not meet several secondary efficacy measures. According to the FDA Medical Review, Study 2001 "had an inadequate design to be relied on for proving efficacy."

As further evidence of the efficacy of TER, the FDA performed an interim analysis of the TOWER study, a placebo-controlled trial of 1096 subjects randomized 1:1:1 to receive TER 7 mg, TER 14 mg, or PLA once daily. Included were subjects age 18–55 with an EDSS≤5.5 who were ambulatory and had relapsing forms of MS. Most subjects were female (71%), Caucasian (83.5%), and without DMA treatment in the 2 years prior to randomization (67%). Most subjects had RRMS (97%) and EDSS scores ≤3.5 (75%). The primary outcome was confirmed ARR. The median duration of treatment for subjects was 313 days for PLA, 302 for TER 7 mg, and 317.5 for TER 14 mg. About 44% of the three treatment groups received the specified 48 weeks of treatment. The adjusted ARR was 0.531 (CI: 0.444 to 0.634) for PLA, 0.371 (CI: 0.300 to 0.459) for TER 7 mg, and 0.321 (CI: 0.258 to 0.400) for TER 14 mg, corresponding to ARR reductions of 30% for TER 7 mg and 42.7% for TER 14 mg. The percentages of patients without confirmed relapses were 66%, 76.5%, and 77.1% for PLA, TER 7 mg, and TER 14 mg, corresponding to NNTs of 10 and 9 for TER 7 mg and 14 mg, respectively. Subgroup analysis

revealed TER outperformed PLA in all groups except for those previously treated with immunomodulators; however, the FDS noted the study is incomplete and TER was superior to PLA for this group in the TEMSO trial, which was not powered to examine subgroups.[4]

The limitations of the TOWER interim analysis are myriad due to its nature. Based on study population and design, the limitations of the TOWER study at its conclusion would be similar to that of the TEMSO trial.

Clinical Safety:[1]

In PLA-controlled studies of TER in patients with relapsing forms of MS, increased ALT, alopecia, diarrhea, influenza, nausea, and paresthesia were the most frequently reported adverse reactions (ADRs), defined as an ADR with an incidence ≥10% and ≥2% greater than PLA. Alopecia was the most common cause of discontinuation due ADRs: 0.5% and 1.4% of patients on TER 7 mg and 14 mg, respectively, and 0% on PLA). Incidents of peripheral neuropathy (<2% TER v. 0% PLA), acute renal failure (1.2% v. 0%), hyperkalemia (1% v. 0.2%), and hypertension (4% v. 2%) have been reported during TER use.

Hepatotoxicity, hematologic dysfunction, interstitial lung disease, infection, severe skin reactions, and malignancy due to immunosuppression are potential risk factors with TER, as they have been reported with leflunomide, the prodrug of TER. Therefore, TER is contraindicated in those with severe liver impairment, is not recommended in those with severe immune dysfunction, should be avoided in those with unresolved acute or chronic liver disease or infections, and liver function tests (LFTs) should be performed before and after initiating TER. TER has caused birth defects in animals; therefore, the pregnancy category for TER is X and women of childbearing potential should use contraception. TER has been detected in human semen; therefore, men on TER as well as their female partners also should use reliable contraception. In PLA-controlled trials, peripheral neuropathy was reported more frequently in patients taking TER. Clinicians should consider suspending TER and using an accelerate elimination protocol in those who develop infection, symptoms of peripheral neuropathy, or new or worsening pulmonary symptoms. In trials, 1.2% of TER-treated subjects v. 0% of PLA-treated subjects had transient acute renal failure (likely due to TER's ability to cause increased renal uric acid clearance), 1.0% of TER-treated subjects v. 0.2% of PLA-treated subjects developed hyperkalemia, and 4% of patients treated with TER v. 2% on PLA developed hypertension.

TER stays in the body for up to 2 years (8 months average); therefore, an accelerated elimination procedure must be used to rapidly clear the drug from the body when certain patients need to stop the drug. For example, this procedure, involving taking cholestyramine three times daily or charcoal twice daily for 11 days, is recommended in those who are having serious AEs, have become pregnant, are women of childbearing potential, and are men intending to father a child.

Unanswered safety questions include the following:
What are the long-term risks of taking TER? What are the safety concerns for pediatric or geriatric patients? What are the endogenous transporter-based interactions between TER and other drugs? What are the safety concerns for those who are not Caucasian and for those who have more advanced disease? What is the mutagenic potential of TER, as the results of mutagenicity assays were mixed? What are the risks of co-administrating TER with antineoplastic or immunosuppressive therapies used for treating MS has not been evaluated? What are the risks of male-mediated fetal toxicity with TER?

COMPARATIVE CLINICAL EFFICACY[2-4]

Relevant Endpoints:

1) Disability progression
2) Relapse rate
3) Disease activity as measured by MRI
4) Health-related quality of life
5) Serious adverse effects

Primary Study Endpoint:

1) Annualized relapse rate
2) Number of combined CU active lesions/scan

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
1. TEMSO O'Connor Sept 24, 2004– March 13, 2008 Phase 3, DB, PC, EDSS- and site-stratified, RT 127 centers 21 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD Duration: 108 wks	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 38.4, 37.4, 37.8 · Female (%): 75.8, 69.7, 71.0 · White race (%): 98.3, 97.3, 96.9 · Time from 1st MS symptom (yr): 8.6, 8.8, 8.7 · Relapses (no.) in prior year: 1.4±0.7, 1.4±0.7, 1.3±0.7 in prior 2 yrs: 2.2±1.0, 2.3±1.2, 2.2±1.0 · MS subtype (%) RR: 90.6, 91.0, 92.8 SP: 6.1, 4.6, 3.3 PR: 3.3, 4.4, 3.9 · Use of DMD in previous 2 years (%): 24.8, 27.9, 28.4 · mean EDSS: 2.68±1.34, 2.68±1.34, 2.67±1.24 · Total lesion volume (ml): 19.34, 20.37, 18.08 **Inclusion Criteria:** · age 18 to 55 yrs · RR, SP, or PRMS · EDSS ≤5.5 who are ambulatory · ≥1 relapse in the previous yr or ≥2 relapses in the previous 2 yrs · clinically stable in the 30 d before randomization	Modified ITT: 1. 365 2. 358 3. 363 Attrition: 1. 91 2. 95 3. 104	Adjusted annualized relapse rate: 1. 0.37 (0.32 to 0.43; < 0.001) 2. 0.37 (0.31 to 0.44; <0.001) 3. 0.54 (0.47 to 0.62) *relative reduction v. PLA:* *TER 7 mg: 31.2%* *TER 14 mg: 31.5%* Kaplan Meier estimate of absence of relapse during 108 wk: 1. 53.7% (48.3 to 59.1, 0.01) 2. 56.5% (51 to 62, p=0.003) 3. 45.6% (40.2 to 51) Sustained disability progression (≥12 wk): 1. 21.7% (17.1 to 26.3; NS) 2. 20.2% (15.6 to 24.7; 0.03) 3. 27.3% (22.3 to 32.3)	NA 8.1%/12 10.9%/9 NS 7.1%/14	**Serious AEs** TER 7 mg: 14.1% TER 14 mg: 15.9% PLA: 12.8% **AEs leading to D/C of study drug** TER 7 mg: 9.8% TER 14 mg: 10.9% PLA: 8.1%	1 1.3%/77 3.1%/32 1.7%/59 2.8%/36	Quality Rating: Fair Internal Validity: · High but similar D/C rates in all groups: 29% PLA, 25% TER 7 mg, and 27% TER 14 mg · FDA analysis to estimate the percentage of patients with 24-week sustained disability progression at week 108 revealed neither TER dose had a statistically significant benefit: 25% risk reduction for TER 7 mg (p=0.1459) and 25.1% risk reduction TER 14 mg (p=0.125).) · Mean EDSS score on low end of scale: 2.68 External Validity: · Patients predominantly female, Caucasian, and RRMS subtype. Most patients had not taken DMD in previous 2 years. · Patients ambulatory and 77% of patients with EDSS scores <3.5 (% from FDA analysis)

		Exclusion Criteria: · relapses in the 60 days before randomization · systemic diseases · abnormal CBC · pregnant or planned to conceive during the trial · prior or concomitant use of immunosuppressants · prior use of natalizumab, interferons or cytokines in last 4 mo, glatiramer acetate or investigational drugs in preceding 6 mo · liver function impairment or persistent LFT elevations · moderate to severe renal impairment		*hazard ratio reduction v. PLA:* *TER 7 mg 23.7%* *TER 14 mg 29.8%* <u>Total lesion volume (change from baseline):</u> 1. 1.31±6.8 mL (p=0.03) 2. 0.72±7.59 mL (p<0.001) 3. PLA: 2.21±7 mL *relative reduction v. PLA:* *TER 7 mg: 39.4%* *TER 14 mg: 67.4%*				Analysis: · Unable to draw conclusions about the efficacy and safety of TER in more advanced patients. · Unable to draw conclusions about efficacy and safety of TER in non-Caucasian and in patients with SP/PRMS due to inadequate numbers. · The study may not reflect the U.S. MS patient population, who may have more experience with DMDs. · Treatment effect is modest particularly for TER 7 mg. NNTs to prevent relapse over 2 years are 12 and 9 for TER 7 mg and 14 mg, respectively, and to prevent sustained disability progression were NS and 14, respectively. · While TER 14 mg appears to be more effective than 7 mg, there is a greater chance of serious AE on TER 14 mg.
2. Study 2001 O'Connor Phase 2 "proof of concept" study April 2001 to March 2003 DB, PC, RT, EDSS- and site-stratified 16 centers, 2 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD (double dose given the 1st wk) Duration: 36 wks	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 39.2, 40.1, 40.1 · Female (%): 67, 75, 79 · Caucasian (%)*: 96.7, 91.8, 91.2 · Time since diagnosis (yr) 4.4±5.7 6.0±5.6 5.4±6.2 · Disease duration (yr) 8.6±7.9 10.3±8.1 8.5±7.1 · Relapses (no., range): in previous yr 1 (0-3), 1 (0-4), 1 (0-3) in previous 3 yrs 3 (1-9), 2 (2-5), 3 (2-6) · MS subtype (%): RR 86.9, ,88.5, 87.7 SP 13.1, 11.5, 12.3 · median EDSS score*: 2.5, 2.5, 2.0 · MRI assessments	ITT: 1. 61 2. 57 3. 61 Attrition: 1. 2 2. 11 3. 4	**Primary outcome:** No. of combined CU active lesions/scan Median 1. 0.2 2. 0.3 3. 0.5 Mean (± SE) 1. 1.04±0.37 2. 1.06±0.38 3. 2.68±0.39 *mean difference v. PLA:* *TER 7 mg:–1.64 (CI –2.69 to –0.59,*	NA NA NA	**Overall AEs** (at least one adverse event) TER 7 mg: 100% TER 14 mg:100 % PLA: 100% **Serious AEs** (elevated liver enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, trigeminal neuralgia) TER 7 mg: 8.2% TER 14 mg: 12.3%	NA NA NA 0.8/125	Quality Rating: Poor *Figures marked with * were obtained from the FDA Medical Review, as they were not reported in the published study Internal Validity: · Because this is a phase 2 study, there are insufficient patient numbers and study duration and MRI is the primary endpoint · Use of disease-modifying therapy in prior 2 years not reported. However, article states distribution

		· patients w CU active lesions (%): 62.3, 47.5, 61.4 · mean CU active lesions/scan: 2.16±0.63, 1.3±0.60, 2.48±0.62 · mean T2 lesion volume, mm^3: 9119, 10338, 8475 **Inclusion Criteria:** (see protocol) · MS · age 18 to 65 yrs · EDSS ≤6 · 2 relapses in prior 3 yrs and 1 clinical relapse during prior yr · willing to use contraception during and for 24 mos after study drug use · MRI w abnormalities consistent w MS **Exclusion Criteria:** · prior treatment w interferon, γ-globulin, glatiramer acetate, or other noncorticosteroid in the 4 mos before the trial		*p<0.03)* *TER 14 mg: –1.62* *(CI –2.68 to –0.56, p<0.01)* *relative reduction v. PLA* *TER 7 mg: –61.6%* *TER 14 mg: –61.3%* **Secondary outcomes:** Median change in BOD (T2 lesion volume) from baseline (%) at 18 weeks 1. –0.1[NS] 2. –3.8 [NS] 3. 1.1 at 36 weeks 1. 2.9 [NS] 2. –4.1 (p<0.02) 3. 5.2 Mean annualized relapse rate: 1. 0.58±0.85 [NS] 2. 0.55±1.12 [NS] 3. 0.88±1.22 % relapse-free patients 1. 65%* 2. 77% [NS] 3. 62% % patients with increased EDSS score from baseline to endpoint 1. 28.8% 2. 7.4% (p<0.04) 3. 21.3%	NA NA NA NA NS NS NS 13.9/7	PLA: 11.5% AEs leading to D/C of study drug TER 7 mg: 4.9% TER 14 mg: 14% PLA: 6.6%	NA 7.4/14	of previous meds for MS and concomitant meds given during trial were similar across groups. · FIS score not reported · Median EDSS was 2.33.* · No follow-up confirmation of EDSS progression · Relapse confirmation not performed. · 6 patients were included who did not meet inclusion criteria · protocol deviations occurred for 30 patients, including the use of corticosteroids prior to MRI in 8 PLA, 7 TER 7 mg, and 10 TER 14 mg patients · the TER groups had a greater % of females External validity: · Median EDSS was 2.33. · Changes in relapse rates were not significant over 36 weeks for TER v PLA · Change in burden of disease not significant at 36 weeks for TER 7 mg v PLA · Compared to PLA, more than twice as many patients on TER 14 mg dropped out of the study. · PRMS patients not included in study Analysis: Because this is a phase 2 study, it is inadequately designed for proving efficacy of TER and can only serve as descriptive evidence. ·TER was not significantly

								superior to PLA in preventing relapse. TER 7 mg was significantly superior to PLA in preventing disability; however, TER 14 mg was (NNT 7). TER 7 mg also was not significantly superior to PLA in reducing BOD.
3. TOWER (FDA interim analysis) August 26, 2008–February 28, 2011 (interim) DB, PC, RT, EDSS- and site-stratified 190 center, 26 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD Mean treatment duration: 1. TER 7 mg: 302 d 2. TER 14 mg: 317.5 d 3. PLA: 313 d (44% of the 3 treatment groups received the intended 48 weeks of treatment)	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 38.1, 37.4, 38.1 · Female (%): 69.1, 73.9, 69.8 · Caucasian (%): 83.6, 82.1, 84.9 · Asian race (%): 13.7, 13.7, 12.8 · from U.S. (%): 19.1, 18.7, 17.9 · Disease duration (yr): 4.87, 5.3, 5.27 · Time since last attack (mo): 5.28, 5.22, 5.31 · Relapses (no.) in prior year: 1.4, 1.4, 1.7 · MS subtype (%) RR: 97.3, 96.3, 98.9 SP: 1.1, 0.8, 0.6 PR: 1.6, 2.9, 0.6 · Previously treated w DMD (%): 34.2, 30.3, 34.2 · EDSS: 2.66, 2.75, 2.70 · EDSS ≤3.5: 77.5, 74.9, 73.6 **Inclusion Criteria:** · Age 18–55 · EDSS≤5.5 and ambulatory · ≥1 relapse over the preceding 12 mo or 2 relapses over the preceding 24 mo and no relapses 30 d before randomization **Exclusion Criteria:** · Similar to TEMSO trial above · use of natalizumab, IV immunoglobulins, cladribine, glatiramer acetate, mitoxantrone, or other immunomodulatory agents in preceding 6 mo or other interferons or cytokine therapy in prior 4 mo	Modified ITT: 1. 378 2. 349 3. 365 Attrition: 1. 85 2. 74 3. 72	**Primary outcome:** Annualized confirmed relapse rate: 1. 0.371 (0.300 to 0.459; < 0.001) 2. 0.321 (0.258 to 0.400; <0.001) 3. 0.531 (0.444 to 0.636) *Relative risk reduction v. PLA:* *TER 7 mg: 30%* *TER 14 mg 42.7%* % relapse-free patients 1. 76.5% 2. 77.1% 3. 66%	NA 10.5/10 11.1/9	NA	NA	Quality Rating: Poor Internal Validity: Because this is an interim report, insufficient information exists to fully assess internal validity. However, the following are noted: · Protocol violation as of interim analysis 2.5% (n=27). Most frequent protocol violation was treatment compliance <80%: n=8 TER 14mg, 4 TER 7 mg, 2 PLA · Compliance rates 77.6-80.3% (similar in all 3 arms) · Mean EDSS score on low end of scale: 2.68 · High attrition rates: 22.4% TER 7 mg, 21.1% TER 14 mg, 19.7% PLA External Validity: Because this is an interim report, insufficient information exists to fully assess external validity. However, the following are unlikely to change: · Patient population predominantly female and Caucasian and Asian. ·Patients ambulatory and 77% of patients with EDSS≤3.5.

								・Most patients had not taken DMD in previous 2 years. ・18.6% of patients from U.S. Analysis: Based on patient characteristics one would be unable to draw conclusions about efficacy and safety in racial populations other than Caucasian or Asian, in SP/PRMS populations. How U.S. patients would respond to TER has some uncertainty, as the study may not reflect the U.S., which may have an MS population with more experience with DMDs.

DB: double blind, PC: placebo controlled, RT: randomized trial, TER: teriflunomide, PLA: placebo
EDSS: Expanded Disability Status Scale (ranges from 0 to 10, with higher scores indicating greater disability)
RR: relapsing remitting, SP: secondary progressive, PR: progressive relapsing, MS: multiple sclerosis, DMD: disease modifying drug
D/C: discontinuation. AEs: adverse events, NA: not applicable

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1,4]

TER is a novel immunomodulator with anti-proliferative and anti-inflammatory properties. Its exact mechanism of action is unknown; however, it blocks *de novo* pyrimidine synthesis by selectively and reversibly inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase. TER's cytostatic effect on proliferating peripheral T-cells and B-cells may reduce the number of activated lymphocytes entering the central nervous system.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	>99%
Elimination	Biliary excretion of unchanged drug and renal excretion of metabolites (37.5% feces and 22.6% urine over 21 days)
Half-Life	About 18 days*
Metabolism	Unchanged TER (major) Hydrolysis (primary pathway to minor metabolites)

*Without an accelerated elimination procedure, the plasma concentrations of TER fall to <0.02 mg/L after an average of 8 months or as much as 2 years. An accelerated elimination procedure can be used at any time after stopping TER. Elimination can be accelerated by either:

- giving cholestyramine 8 g every 8 hours for 11 days (cholestyramine 4 g three times daily can be used if cholestyramine 8 g three times daily is intolerable) OR
- giving 50 g oral activated charcoal powder every 12 hours for 11 days.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS*
7 mg or 14 mg tablets	Oral	Once daily	7 mg or 14 mg daily	No dosage adjustment	No dosage adjustment for mild and moderate impairment. Contraindicated in severe impairment (PK not established).	Efficacy and safety not established	Clinical studies did not include subjects >65 years	Taken with or without food

* Before starting TER, 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 TER to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.

After starting TER, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when TER is given with other potentially hepatotoxic drugs, consider stopping TER 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.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Hepatotoxicity: Risk of hepatotoxicity is expected with TER because leflunomide has caused severe, including fatal, liver injury. Taking TER concomitantly with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Transaminase and bilirubin levels should be obtained within 6 months before initiating therapy. ALT levels should be monitored at least monthly for 6 months after starting TER. Suspected cases of liver injury should stop TER and start the accelerated elimination procedure. TER is contraindicated in patients with severe hepatic impairment, and, normally, should be avoided in those with pre-existing acute or chronic liver disease or ALT >2 times the upper limit of normal (ULN). Patients with pre-existing liver disease may be at risk of developing elevated transaminase levels.

Teratogenicity: TER is contraindicated in pregnant women or women of childbearing potential not using reliable contraception, because TER has caused major birth defects in pregnant animals. Pregnancy must be excluded before starting TER and avoided during TER treatment or before completing an accelerated TER elimination. Women receiving TER who wish to become pregnant must discontinue TER and undergo accelerated elimination, which includes verifying TER plasma concentrations <0.02 mg/L.

Co-administration of teriflunomide with leflunomide is contraindicated.

Warnings and Precautions:

Risk of pancytopenia, agranulocytosis, and thrombocytopenia may exist for TER as they have been reported postmarketing with leflunomide.

Patients with active acute or chronic infections should not start TER until infections are resolved. Suspending TER treatment and using accelerated elimination in those who develop an infection should be considered. TER is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Vaccination with live vaccines is not recommended.

TER has the potential to be immunosuppression, which could increase the risk of malignancy, particularly lymphoproliferative disorders. No apparent increase in the incidence of malignancies was reported in TER clinical trials, but larger, longer-term studies are needed to determine a risk.

In PLA-controlled trials, peripheral neuropathy was reported more frequently in patients taking TER (1.2% TER 7 mg, 1.9% TER 14 mg, 0% PLA). Age >60 years, concomitant neurotoxic drugs, and diabetes may increase the risk. Consider stopping TER and performing accelerated elimination in patients who develop symptoms of peripheral neuropathy.

In trials, 10 of 844 (1.2%) of TER-treated subjects v. 0 of 421 PLA-treated subjects had transient acute renal failure with a creatinine measurement increased ≥100% above baseline. Seven of the 10 subjects had a nadir CrCl <30 mL/minute. While continuing TER, the 10 subjects had normal serum creatinine levels 6-48 days following the creatinine increase. Acute uric acid nephropathy likely explains the cases of transient acute renal failure, since TER can cause increased renal uric acid clearance.

In trials, treatment-emergent hyperkalemia >7.0 mmol/L occurred in 8/829 (1.0%) of TER-treated subjects v. 1/414 (0.2%) of PLA-treated subjects. Two TER-treated subjects had hyperkalemia >7.0 mmol/L with acute renal failure.

Hypertension was reported as an adverse reaction in 4% of patients treated with 7 mg or 14 mg of TER v. 2% on placebo. In trials, mean change from baseline in systolic BP was 2.9 mmHg and 2.7 mmHg for TER 7 mg and 14 mg, respectively, and -1.3 mmHg for PLA. The change from baseline in diastolic BP was 1.4 mmHg and 1.3 mmHg for TER 7 mg and 14 mg, respectively, and -0.9 mmHg for PLA.

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide. A similar risk would be expected for TER. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason to stop TER.

Co-administration of TER with antineoplastic or immunosuppressive therapies used for treating MS has not been evaluated. No specific safety concerns arose in studies of TER used with other IMA (interferon beta, glatiramer acetate) for up to 1 year. The long-term safety of these combinations in treating MS has not been established.

Drug-Drug Interactions: TER may be an inhibitor of CYP2C8 and the BCRP, OATP1B, and OAT3 transporters, as well as a weak inducer of CYP1A2. A 25% decrease in peak INR is observed when TER is co-administered with warfarin, and about 1.5-fold increases in ethinylestradiol and levonorgestrel Cmax and AUC were observed when TER was coadministered with these contraceptive hormones. Clinicians should monitor patients taking drugs metabolized by CYP2C8 (e.g., repaglinide, paclitaxel, pioglitazone, or rosiglitazone) or CYP1A2 (e.g., duloxetine, alosetron, theophylline, and tizanidine), and warfarin and consider the type or dose of oral contraceptives used with TER. Studies to confirm transporter-based interactions have not been done.

Food-Drug Interactions: None

Allergy/Cross Reactive Substances: TER has the potential to cause SJS or TENs, as rare cases of these skin reactions have been reported in patients taking leflunomide for rheumatoid arthritis.

Pregnancy/Lactation rating: Pregnancy category X. TER is contraindicated in women who are pregnant or are of childbearing potential and not using reliable contraception, because animal studies have demonstrated the drug is teratogenic and embryolethal at doses less than those used clinically. It is unknown whether the drug is excreted in breast milk, but due to the potential for serious adverse reactions in nursing infants, either the drug or nursing should be discontinued. TER has been detected in semen and animal studies have not been performed to evaluate the risk of male-mediated fetal toxicity. Men on TER should use reliable contraception, as well as their female partners, and undergo accelerated elimination before attempting to father a child. TER reduces the epididymal sperm count in male rats at doses less than the maximum recommended human dose (MRHD), but no effects on fertility were observed.

Dose Index (efficacy/toxic):
Studies in mice have shown no evidence of carcinogenicity at plasma exposures corresponding to 3 times the plasma exposure of humans MRHD. Studies in rats were performed at doses producing plasma exposure concentrations below the MRHD. TER and its metabolite were positive for mutagenesis in some in vitro mutagenicity assays, including the chromosomal aberration assay in human lymphocytes. Although TER was negative in the in vitro Ames and HPRT assays and in vivo micronucleus and chromosomal aberration assays, its minor metabolite, 4-trifluoromethylaniline, was positive in the Ames and HPRT assays.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	USP Online	Clinical Judgment
LA/SA for teriflunomide	None	Not updated since drug approval	Flutamide Teriparatide
LA/SA for Aubagio	None	Not updated since drug approval	None

ADVERSE REACTIONS[1]

Table 1 Adverse Reactions in Study 1 (occurring in ≥ 2% of patients, and reported for teriflunomide 7 mg or 14 mg at ≥ 2% higher rate than for placebo)

	Teriflunomide		
PRIMARY SYSTEM ORGAN CLASS **Preferred Term (%)**	**14 mg** **(N=358)**	**7 mg** **(N=368)**	**Placebo** **(N=360)**
INFECTIONS AND INFESTATIONS			
Influenza	12%	9%	10%
Upper respiratory tract infection	9%	9%	7%
Bronchitis	8%	5%	6%
Sinusitis	6%	4%	4%
Cystitis	4%	2%	1%
Gastroenteritis viral	4%	2%	1%
Oral herpes	4%	2%	2%
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Neutropenia	4%	2%	0.3%
Leukopenia	1%	2%	0.3%
IMMUNE SYSTEM DISORDERS			
Seasonal allergy	3%	2%	1%
PSYCHIATRIC DISORDERS			
Anxiety	4%	3%	2%
NERVOUS SYSTEM DISORDERS			
Headache	19%	22%	18%
Paraesthesia	10%	9%	8%
Sciatica	3%	1%	1%
Burning sensation	3%	2%	1%
Carpal tunnel syndrome	3%	1%	0.3%
EYE DISORDERS			
Vision blurred	3%	3%	1%
Conjunctivitis	1%	3%	1%
CARDIAC DISORDERS			
Palpitations	2%	3%	1%
VASCULAR DISORDERS			
Hypertension	4%	4%	2%
GASTROINTESTINAL DISORDERS			
Diarrhoea	18%	15%	9%
Nausea	14%	9%	7%
Abdominal pain upper	6%	5%	4%
Toothache	4%	4%	2%
Abdominal distension	1%	2%	0.3%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	13%	10%	3%
Acne	3%	1%	1%
Pruritus	3%	4%	2%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Musculoskeletal pain	4%	5%	3%
Myalgia	3%	4%	2%
INVESTIGATIONS			
Alanine aminotransferase increased	14%	12%	7%
Gamma-glutamyltransferase increased	3%	5%	1%
Aspartate aminotransferase increased	3%	2%	1%
Weight decreased	2%	3%	1%
Neutrophil count decreased	2%	3%	0.3%
White blood cell count decreased	1%	3%	0%

Appendix 2: Suggested 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)**

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 fingolimod?	**Yes:** Go to #8	**No:** Approve up to one year

8. Does the patient have evidence of macular edema (ICD-9 362.07)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #9
9. Does the patient has preexisting cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #10.	**No:** Approve up to one year
10. Has the patient had a cardiology consultation before initiation?	**Yes:** Approve up to one year	**No:** Pass to RPH; Deny (medical appropriateness)

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.

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Revision(s): 5-30-2013 (MH)
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