

## Multiple Sclerosis, Oral Drugs

### **Goal(s):**

- Promote safe and effective use of oral disease-modifying drugs for multiple sclerosis or ulcerative colitis.
- Promote use of preferred multiple sclerosis drugs.

### **Length of Authorization:**

- Up to 6 months

### **Requires PA:**

- All oral MS therapy including:
  - Sphingosine 1-phosphate receptor modulators (e.g. fingolimod, ozanimod, ponesimod, siponimod, etc.)
  - Teriflunomide
  - Fumarate salts (e.g., dimethyl fumarate, monomethyl fumarate, diroximel fumarate, etc.)
  - Cladribine

### **Covered Alternatives:**

- Current PMPDP preferred drug list per OAR 410-121-0030 at [www.orpdl.org](http://www.orpdl.org)
- Searchable site for Oregon FFS Drug Class listed at [www.orpdl.org/drugs/](http://www.orpdl.org/drugs/)

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for ozanimod to treat moderate-to-severe ulcerative colitis?	<b>Yes:</b> Go to #3	<b>No:</b> Go to #4
3. Has the patient failed to respond or had an inadequate response to at least one of the following conventional immunosuppressive therapies for ≥6 months: <ul style="list-style-type: none"> <li>• Mercaptopurine, azathioprine, or budesonide; <u>or</u></li> <li>• Have a documented intolerance or contraindication these conventional therapies?</li> <li>AND</li> <li>• Has the patient tried and failed a 3-month trial of a Humira® product?</li> </ul>	<b>Yes:</b> Go to #6	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
4. Is the request for an FDA-approved form of multiple sclerosis in the appropriate age range? (see Table 1)	<b>Yes:</b> Go to #5	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

## Approval Criteria

5. Will the prescriber consider a change to a preferred product?  <u>Message:</u> <ul style="list-style-type: none"> <li>Preferred products are reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee and do not require PA.</li> </ul>	<b>Yes:</b> Inform prescriber of covered alternatives in class.	<b>No:</b> Go to #6
6. Is the medication being prescribed by or in consultation with a neurologist or gastroenterologist (if the diagnosis is ulcerative colitis)?	<b>Yes:</b> Go to #7	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
7. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1b, glatiramer acetate, interferon beta-1a, natalizumab, ofatumumab, ocrelizumab, or mitoxantrone)?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #8
8. Is this a request for continuation of therapy?	<b>Yes:</b> Go to <b>Renewal Criteria</b>	<b>No:</b> Go to #9
9. Is there documentation of recommended baseline testing to mitigate safety concerns (Table 2)?	<b>Yes:</b> Go to #10	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
10. Is the prescription for teriflunomide?	<b>Yes:</b> Go to #11	<b>No:</b> Go to #14
11. Is the patient of childbearing potential?	<b>Yes:</b> Go to #12	<b>No:</b> Approve for up to 6 months.
12. Is the patient pregnant or actively trying to conceive?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #13
13. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	<b>Yes:</b> Go to #14	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
14. Is the prescription for a sphingosine 1-phosphate receptor modulator (Table 1)?	<b>Yes:</b> Go to #15	<b>No:</b> Go to #18
15. Does the patient have evidence of macular edema?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #16

Approval Criteria		
16. Does the patient have preexisting cardiac disease, risk factors for bradycardia, or is on an anti-arrhythmic, beta-blocker, or calcium channel blocker?	<b>Yes:</b> Go to #17	<b>No:</b> Go to #21
17. Has the patient had a cardiology consultation before initiation (see clinical notes)?	<b>Yes:</b> Go to #21	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
18. Is the prescription for a fumarate product?	<b>Yes:</b> Go to # 19	<b>No:</b> Go to #20
19. Does patient have a baseline CBC with lymphocyte count greater than 500/ $\mu$ L?	<b>Yes:</b> Approve for up to 6 months.	<b>No:</b> Pass to RPh. Deny; medical appropriateness.
20. Is the request for cladribine?	<b>Yes:</b> Go to #21	<b>No:</b> Go to #24
21. Is the patient of child bearing potential?	<b>Yes:</b> Go to #22	<b>No:</b> Go to #24
22. Is the patient pregnant or actively trying to conceive?	<b>Yes:</b> Pass to RPh. Deny; medical appropriateness.	<b>No:</b> Go to #23
23. Is there documentation that the provider and patient have discussed the teratogenic risks of the drug if the patient were to become pregnant?	<b>Yes:</b> Approve for 6 months	<b>No:</b> Pass to RPh. Deny; medical appropriateness.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement?	<b>Yes:</b> Approve for 12 months.  Document baseline assessment and physician attestation received.	<b>No:</b> Pass to RPh; Deny; medical appropriateness.

**Table 1. Dosing And FDA-Approved Indications for Oral MS Drugs**

Generic Name	FDA Indication (Adults unless otherwise indicated)			
	CIS	RRMS	SPMS	Ulcerative Colitis
Cladribine		X	X	
Fingolimod	X ( $\geq 10$ years)	X ( $\geq 10$ years)	X ( $\geq 10$ years)	
Siponimod	X	X	X	
Ozanimod	X	X	X	X

Ponesimod	X	X	X	
Teriflunomide	X	X	X	
Dimethyl Fumarate	X	X	X	
Monomethyl Fumarate	X	X	X	
Diroximel Fumarate	X	X	X	
Abbreviations: CIS = clinically isolated syndrome; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis				

**Table 2. FDA-recommended Baseline Safety Assessments (see clinical notes for details)**

	Negative Pregnancy Test	LFTs	CBC with lymphocyte count	Ophthalmic Exam	Varicella Zoster Antibodies	CYP2C9 genotype	Other Screening
Fumarate salts		X	X (>500)				
Fingolimod*	X	X	X	X	X		
Ozanimod*	X	X	X	X	X		
Ponesimod*	X	X	X	X	X		
Siponimod*	X	X	X	X	X	X	
Teriflunomide	X (box warning)	X (box warning)	X				
Cladribine	X (box warning)	X	X (WNL)		X		TB; HBV; HIV; HCV; MRI for PML
Abbreviations: HBV = hepatitis B; HCV = hepatitis C; HIV = human immunodeficiency virus; MRI = magnetic resonance imaging; PML = progressive multifocal leukoencephalopathy; TB = tuberculosis; WNL = within normal limits							

\* sphingosine 1-phosphate receptor modulators

**Sphingosine 1-Phosphate Receptor Modulators (fingolimod, ozanimod, ponesimod, siponimod) Clinical Notes:**

- Because of bradycardia and atrioventricular conduction, patients must be observed for 4 to 6 hours after initial dose in a clinically appropriate area (fingolimod, ponesimod, siponimod).
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with risk factors for bradycardia (h/o MI, age >70 yrs., electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod, ozanimod, ponesimod, or siponimod with caution. A cardiology evaluation should be performed before considering treatment.
- An ophthalmology evaluation should be repeated 3-4 months after fingolimod, ozanimod, ponesimod, or siponimod initiation with subsequent evaluations based on clinical symptoms.
- Patients starting on siponimod therapy must be tested for CYP2C9 variants to determine CYP2C9 genotype before starting siponimod. Siponimod is contraindicated in patients with a CYP2C9\*3/\*3 genotype. The recommended maintenance dosage in patients with a CYP2C9\*1/\*3 or \*2/\*3 genotype is 1 mg. The recommended maintenance dosage in all other patients is 2 mg.

**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 individuals of childbearing potential, check blood pressure, and obtain a complete blood cell count within the 6 months prior to starting therapy. Instruct patients to report symptoms of infection 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. Consider additional ALT monitoring when teriflunomide is given with other potentially hepatotoxic drugs. Consider stopping teriflunomide if serum transaminase levels increase (>3-times the upper limit of normal). Monitor serum transaminase and bilirubin particularly in patients who develop symptoms suggestive of hepatic dysfunction. Discontinue teriflunomide and

start accelerated elimination in those with suspected teriflunomide-induced liver injury and monitor liver tests weekly until normalized. Check blood pressure periodically and manage hypertension. Check serum potassium level in teriflunomide-treated patients with hyperkalemia symptoms or acute renal failure. Monitor for signs and symptoms of infection.

- Monitor for hematologic toxicity when switching from teriflunomide to another agent with a known potential for hematologic suppression because systemic exposure to both agents will overlap.

#### **Fumarate Salts (Dimethyl Fumarate, Monomethyl Fumarate, Diroximel Fumarate) Clinical Notes:**

- Fumarate salts may decrease a patient's white blood cell count. In the clinical trials the mean lymphocyte counts decreased by approximately 30% during the first year of treatment with dimethyl fumarate and then remained stable. The incidence of infections (60% vs. 58%) and serious infections (2% vs. 2%) was similar in patients treated with dimethyl fumarate or placebo, respectively. There was no increased incidence of serious infections observed in patients with lymphocyte counts  $<0.8 \times 10^3$  cells/mm<sup>3</sup> (equivalent to  $<0.8$  cells/ $\mu$ L). A transient increase in mean eosinophil counts was seen during the first 2 months of therapy.
- Fumarate salts should be held if the WBC falls below  $2 \times 10^3$  cells/mm<sup>3</sup> or the lymphocyte count is below  $0.5 \times 10^3$  cells/mm<sup>3</sup> (cells/ $\mu$ L) and permanently discontinued if the WBC did not increase to over  $2 \times 10^3$  cells/mm<sup>3</sup> or lymphocyte count increased to over  $0.5 \times 10^3$  cells/mm<sup>3</sup> after 4 weeks of withholding therapy.
- Patients should have a CBC with differential monitored every 6 to 12 months.

#### **Cladribine Clinical Notes:**

- Cladribine is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile.
- Prior to initiating cladribine follow standard cancer screening guidelines because of the risk of malignancies.
- Obtain a CBC with differential including lymphocyte count. Lymphocytes must be: within normal limits before initiating the first treatment course and at least 800 cells per microliter before initiating the second treatment course. If necessary, delay the second treatment course for up to 6 months to allow for recovery of lymphocytes to at least 800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine.
- Infection screening: exclude HIV infection, perform TB and hepatitis screening. Evaluate for active infection; consider a delay in cladribine treatment until any acute infection is fully controlled.
- Administer all immunizations according to immunization guidelines prior to starting cladribine. Administer live-attenuated or live vaccines at least 4 to 6 weeks prior to starting cladribine.
- Obtain a baseline (within 3 months) magnetic resonance imaging prior to the first treatment course because of the risk of progressive multifocal leukoencephalopathy (PML).

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*P&T/DUR Review:* 10/22 (DM); 10/21(DM); 8/21 (DM); 6/21 (DM); 8/20 (DM); 6/20; 11/17; 11/16; 9/15; 9/13; 5/13; 3/12  
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