Guidance for Disease Modifying Therapy Selection in Multiple Sclerosis

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The number of drug classes available to treat Multiple Sclerosis (MS) has grown over the last decade. While new therapies are welcome, it has added to the challenge and complexity of managing MS. This document is intended to complement the ***Criteria for Use*** **documents** (vaww.pbm.va.gov) and to assist in prioritizing the selection of oral disease modifying therapies used in the treatment of relapsing MS (RMS)and primary progressive MS (PPMS).

The content of this document will be dynamic and revised as new information becomes available. The clinician will be expected to use and interpret the final version of this guidance in the clinical context of the individual patient. These are general recommendations and suggestions, and should not supersede the clinical judgment of the treating provider.

Patients must meet the McDonald Criteria 2010 for diagnosis of MS (**Figure 1**)

These patient characteristics should be reviewed as they could impact the choice of DMT agent.

- Cardiac, Pulmonary risk factors or macular edema
- Desire or potential for pregnancy
- Elevated liver enzymes, hepatic disease
- Elevated wbc, evidence of infection
- Tuberculosis
- History of varicella zoster infection
- Baseline wbc below 500 µL
- Positive for JC virus

Initial Therapy selection- RMS

Glatiramer acetate

Interferon beta 1B

Interferon beta 1A

Teriflunomide

Initial Therapy Selection- PPMS

Ocrelizumab

Alternate Initial Therapy Selection- highly active disease[1] RMS

Dimethyl fumarate#

Fingolimod#

Natalizumab#

Ocrelizumab

Preferred Agents when DMT Switch is Needed[2] RMS

Alemtuzumab#

Daclizumab

Dimethyl fumarate #(improved efficacy if patient is treatment naïve)

Fingolimod#

Natalizumab#

Ocrelizumab

[1] Signs of Highly Active MS

- Onset with significant disabling symptoms (motor, sphincter, cerebellar)
- Significant MRI findings (enhancing, tumefactive lesions and/or overall lesion burden)
- Onset refractory to relapse suppression with poor recover from relapse
- Significant recurrent or breakthrough disease over a short period of time
- MS that has quick progression to disability

[2] Considerations for Switching DMT agents

- Relapse while on current DMT
- Development of neutralizing antibodies (while on interferon)
- Conversion to JC positive status
- Adverse events limit therapy (e.g.; injection site reactions, lipoatrophy,
- MRI activity characterized by
    - ≥1 enhancing lesion
    - ≥2 or more new T2 lesions in 12 months
    - MRI activity on consecutive MRI over a 3-12 month period
    - >2 Gd enhancing lesions in first 12 months on therapy

Cases of PML reported with use in MS and/or other disease states. JC virus infection resulting in PML has been observed in patients treated with anti-CD20 antibodies (Ocrelizumab).

For more information on dosing, special considerations, monitoring and adverse events please refer to **Table 1 DMT agents used in Multiple Sclerosis**

Please refer to **Figure 2: Comparative Safety and Efficacy of the DMT Agents**

Figure 1 McDonald Criteria

Clinical (Attacks)	Objective Lesions	Additional requirements to make diagnosis
2 or more	2 or more	None; additional evidence desirable but must be consistent with MS
2 or more	1	Dissemination in space by 1 or more MRI lesions consistent with MS ***or*** further clinical attack involving different site
1	2 or more	Dissemination in time by MRI lesions ***or*** await second clinical attack
1 (clinically isolated syndrome)	1	Dissemination in space by 1 or more MRI lesions consistent with MS **and** Dissemination in time by MRI lesions ***or*** second clinical attack
1 (progression from onset)	1	Continued progression for 1 year **AND** **2 of 3 of the following:** Dissemination in space by 1 or more MRI lesions consistent with MS in the brain ***or*** 2 or more MRI lesions consistent with MS in the cord ***or*** positive CSF

Definition of MRI evidence of dissemination in space	T2 lesion in at least 2 of 4 MS-typical regions (peri-ventricular, juxtocortical, infra-tentorial, or spinal cord) Note: Gd-enhancing lesions are not required
Definition of MRI evidence of dissemination in time	Simultaneous presence of Gd-enhancing and non-enhancing MRI lesions at any time New T2 and/or Gd-enhancing lesion on follow-up MRI
Gd, gadolinium; MS, multiple sclerosis	

Polman CH, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol. 2011 Feb;69(2):292-302

Figure 2: Comparative Safety and Efficacy of the DMT Agents

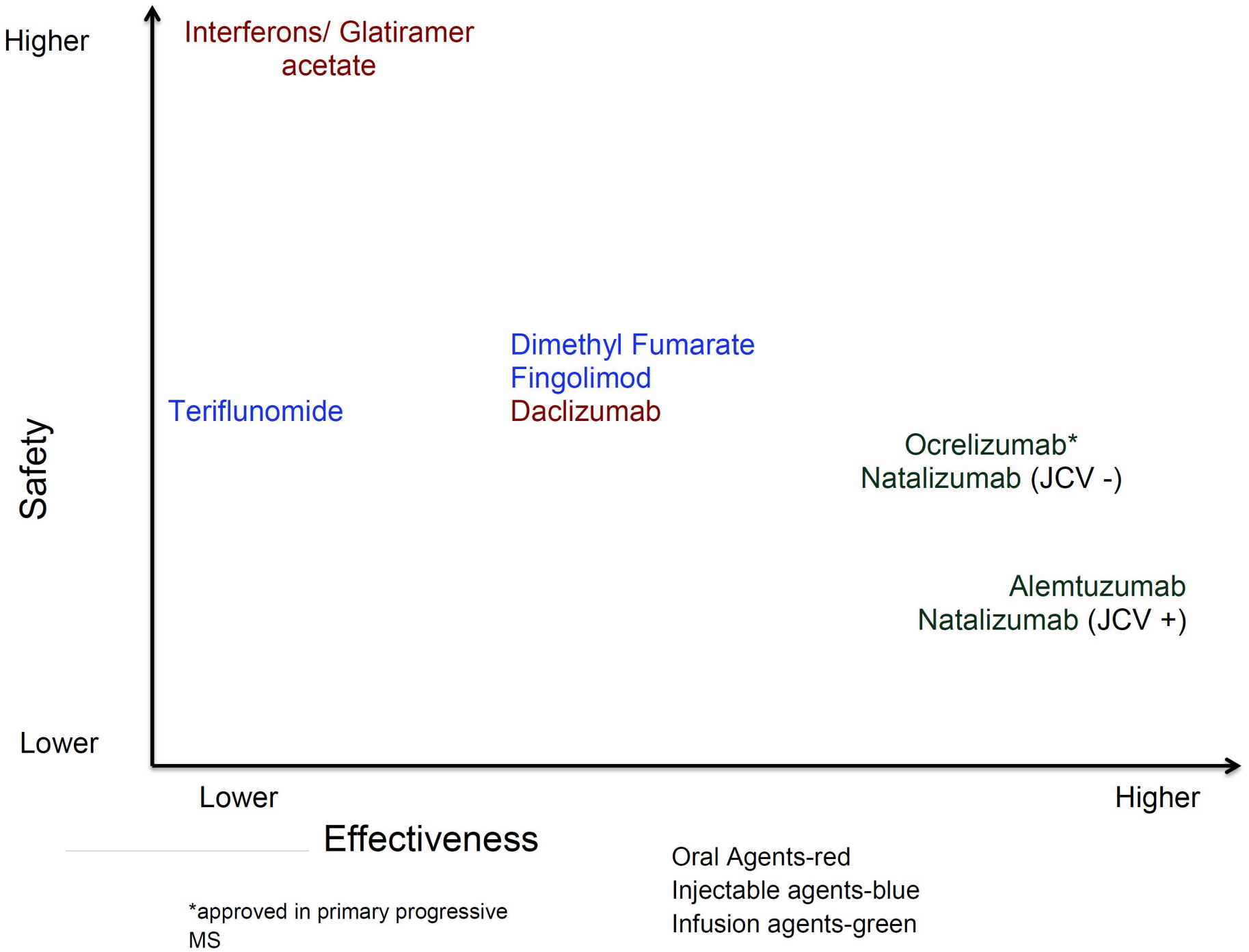

Table 1 DMT agents used in Multiple Sclerosis

Drug * indicates nonformulary	Dosing	storage/ autoinjector	avoid in	baseline monitoring	on therapy monitoring	DC due to lab results	special consideration	potentially serious AE	common AE	pregnancy category
INJECTABLE										
interefron beta 1a										
subcutaneous (SQ) ***Rebif***	22-44mcg 3 times weekly	autoinjector, can be at room temp for one week	hypersensitivity to albumin	CBC with differential, LFT, thyroid	CBC with differential, LFT, thyroid every 3 months for 6 months then annually			anemia, leukopenia, depression, CHF, seizure, autoimmune disorders	injection site reaction (ISR), flu like symptoms, fatigue, myalgia	C
intramuscular (IM) ***Avonex***	30 mcg once weekly	autoinjector, can be at room temp for one month		CBC with differential, LFT, thyroid	CBC with differential, LFT, thyroid every 3 months for 6 months then annually			anemia, leukopenia, depression, CHF, seizure, autoimmune disorders	flu like symptoms, fatigue, myalgia	C
interferon beta 1b										
Betaseron	Initiate at 0.0625 mg and titrate up to 0.25 mg SQ every other day	autoinjector, can be at room temp for a month		CBC with differential, LFT, thyroid	CBC with differential, LFT, thyroid every 3 months for 6 months then annually		development of neutralizing antibodies		ISR, flu like symptoms, fatigue, myalgia	C
Extavia	Initiate at 0.0625 mg and titrate up to 0.25 mg SQ every other day	autoinjector, can be at room temp for a month		CBC with differential, LFT, thyroid	CBC with differential, LFT, thyroid every 3 months for 6 months then annually				ISR, flu like symptoms, fatigue, myalgia	C
glatiramer acetate										
20 mg QD ***Copaxone***	20 mg SQ daily	autoinjector, can be at room temp for a month	hypersensitivity to mannitol	none	none		post injection hypersensitivity reaction, flushing, tightness of chest, shortness of breath, sweating	lipoatrophy and skin necrosis	ISR, lipoatrophy, vasodilation, rash	B

40 mg TIW ***Copaxone***	40 mg SQ 3 times weekly	autoinjector, can be at room temp for a month	hypersensitivity to mannitol	none	none		post injection hypersensitivity reaction, flushing, tightness of chest, shortness of breath, sweating	lipoatrophy and skin necrosis		B
20 mg QD (generic) ***Glatopa***	20 mg SQ daily	autoinjector, can be at room temp for a month		none	none		post injection hypersensitivity reaction, flushing, tightness of chest, shortness of breath, sweating	lipoatrophy and skin necrosis		B
pegylated interferon beta 1a***** ***Plegridy***	125 mcg SQ every other week	prefilled pen or syringe, may be at room temp for one week		CBC with differential, LFT	CBC with differential, LFT, thyroid every 3 months for 6 months then annually				flu like reaction, ISR, depression	
daclizumab***** ***Zinbryta***	150 mcg SQ monthly	Prefill syringe	pre-existing liver disease or history of autoimmune hepatitis	LFT, bilirubin	LFT, bilirubin monthly and for 6 months after drug discontinuation	if LFT increase 2X ULN	REMS	fatal liver injury, autoimmune hepatitis, hypersensitivity (anaphylaxis, angioedema)	rash, dermatitis, lymphadenopathy eczema, throat pain, URI	C
ORAL										
fingolimod ***Gilyena***	0.5 mg daily			CBC, LFT, Varicella titer, Optical coherence tomography (OCT)	CBC with differential, LFT every 3-6 months		first dose bradycardia, AV block. Must undergo first dose monitoring	risk for infection and PML Increase in liver enzymes. Development of macular edema. Caution if using in asthmatics as it may cause PFT changes	diarrhea, mild BP increase, headache, back pain, cough,	C

dimethyl fumarate ***Tecfidera***	Initiate at 120 mg twice daily and titrate up to 240mg twice daily			CBC, LFT	CBC including lymphocyte count quarterly	discontinue if WBC falls below 2000/m^3 or lymph count < 500/uL for > 4 weeks	can manage GI side effects by taking dose with high fat, high protein food and use of H1 and H2 blockers	PML, decreased WBC	flushing, abdmoninal pain, diarrhea, nausea, puristis	C
teriflunomide ***Aubagio***	14 mg once daily		acute or chronic infection pregnancy severe hepatic impairment concurrent therapy with leflunomide	CBC, LFT, PPD, pregnancy test	monthly LFT monthly for 6 months		If pregnancy or liver injury occurs (increase of total bilirubin, ALT or AST greater than 2 times the upper limit of normal), immediately stop teriflunomide and initiate an accelerated elimination procedure with cholestyramine 8 grams given every 8 hours for 11 days (if this regimen is not well tolerated, 4 gram given 3 times a day can be used) or oral activated charcoal powder 50 grams every 12 hours for 11 days should be initiated.	hepatotoxicity, risk of teratogenicity, risk of infection, acute renal failure, SJS, peripheral neuropathy, increased K+	alopecia, diarrhea, influenza, nausea, headache, paresthesia, may increase blood pressure	X
INFUSIBLE										

natalizumab ***Tysabri***	300mg IV monthly		JC virus positive	CBC, LFT, JC virus titer	monthly checklist as part of TOUCH Online and CBC, LFT prior to each dose, JCV Antibody testing every 3-6 months	consider risk benefit if patient develop s JCV antibody	REMS	PML, other infections, antibody formation, melanoma, hepatic injury, hypersenitivity	headache, fatigue, UTI, uticaria, vaginitis, depression, diarrhea	C
alemtuzumab* ***Lemtrada***	12 mg IV daily for 5 days then 1 year later, 12 mg daily for 3 days		Patients must be evaluated for varicella zoster titers. I vaccination is required , alemtuzumab should not be given till 6 weeks after the second dose of Varivax	CBC with differential, serum creatinine, urinalysis, TSH, varicella zoster titer, skin exam for melanome	HPV screening annually, CBC with differential, serum creatinine, monthly for 48 months after last infusion. TSH every 3 months till 48 months after infusion		REMS Premedication 1000mg IV methylprednisilone first 3 days, herpes antiviral prophylaxsis on day one and for 2 months or until CD4+ lymph count is > 200 cells/ml	autoimmune diseases, infusion reactions, malignancy	infusion reaction, monitor for 2 hrs post infusion	C
ocrelizumab* ***Ocrevus***	Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion. Subsequent doses: single 600 mg intravenous infusion every 6 months.		contraindicate d in patients with active HBV confirmed by positive results for HBsAg and anti-HBV tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of	CBC with differential, HBV testing			Prior to every infusion determine whether there is an active infection. Pre-medicate with 100 mg of methylprednisol one (or an equivalent corticosteroid) administered intravenously approximately 30 minutes prior to infusion and with an antihistamine	infusion reactions. Observe patients for at least 1 hour post infusion increased risk of malignancy may exist	Respiratory infections, herpes infections	no adequate data on the developme ntal risk associated with use in pregnant women. However, transient peripheral B-cell depletion and lymphocyto penia have been reported in infants

			HBV [HBsAg+], consult liver disease experts before starting and during treatment				(e.g., diphenhydramine) approximately 30-60 minutes prior to infusion			born to mothers exposed to other anti-CD20 antibodies during pregnancy

Further information regarding pregnancy and teratogenicity risk can be found at http://va.reprotox.us/

Criteria for use for the DMT agents can be found at National PBM Criteria for Use

Special Handling Documents and Policies can be found at Special Handling Drugs