Disease Modifying Therapies in Multiple Sclerosis
National Clinical Recommendations
June 2024

VA Pharmacy Benefits Management Services and the National Formulary Committee
In collaboration with the VA Multiple Sclerosis Centers of Excellence

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and may be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. THE CLINICIAN SHOULD USE THESE CLINICAL RECOMMENDATIONSAND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT.

This document should also be used within the context of each DMT's respective Prescribing Information

Abbreviations: AAN: American Academy of Neurology; ADR: adverse drug reaction; AE: adverse event; ARR: annualized relapse rate; BID: twice daily; BP: blood pressure; CBC (w/diff): complete blood count (with differential); CDP: confirmed disability progression (CDP-3: at three months; CDP-6: at six months); CFU: Criteria for Use; CIS: clinically isolated syndrome; CMP: complete metabolic panel; CV: cardiovascular; DMT: disease modifying therapy; EDSS: expanded disability status scale; EKG: electrocardiogram; FDA: Food and Drug Administration; Gd: gadolinium; GI: gastrointestinal; HIV: Human Immunodeficiency Virus; IM: intramuscular; IV: intravenous; IVP: intravenous push; JCV: John Cunningham Virus; LFT: liver function tests; MRI: magnetic resonance imaging; MS: multiple sclerosis; OSA: obstructive sleep apnea; PA-F: facility-level prior authorization; PI: prescribing information; PML: progressive multifocal leukoencephalopathy; PO: by mouth; PPMS: primary progressive multiple sclerosis; REMS: Risk Evaluation and Mitigation Strategy; RRMS: relapsing-remitting multiple sclerosis; S1PR: sphingosine 1-phosphate receptor; SJS: Stevens-Johnson Syndrome; SPMS: secondary progressive multiple sclerosis; SubQ: subcutaneous; TB: Tuberculosis; TEN: toxic epidermal necrolysis; TSH: thyroid stimulating hormone; UA: urinalysis; VZV: Varicella Zoster Virus

Introduction

This document is intended to provide clinical recommendations to providers in selecting an initial DMT for relapsing forms of MS (includes RRMS and active SPMS) and PPMS. Also, it is to provide considerations regarding when to switch, escalate, de-escalate, and discontinue DMT based on the current level of evidence and expert opinion.

The selection of DMT should consider the Veteran's initial and current levels of MS disease activity category, age, and other comorbid conditions.

Use of DMT for MS

Basic principles of DMTs:

- DMTs reduce but do not eliminate rate of relapses and disability accumulation.
- DMTs have not been shown to treat progression independent of relapse activity in people with RRMS and SPMS.
- DMTs do not treat chronic MS symptoms. The goal is to prevent relapses.
- Consider patient-specific factors when choosing a DMT: beliefs about disease and treatment approach, DMT route of administration, frequency, side effects, pregnancy planning, self-administration abilities, etc.
- DMT does not eliminate the need to treat MS symptoms. Approaches to symptom management may include pharmacologic and nonpharmacologic interventions (e.g., healthy diet, regular exercise/physical therapy, sleep optimization, and management of co-morbid diseases).
- Most DMTs have a positive correlation between efficacy and risk. This means low efficacy DMTs tend to have a low level of risk, whereas high efficacy DMTs have a high level of risk associated with them. See

Figure 1. Thus, making decisions about starting and switching DMTs include the need to balance patient-specific risks and benefits.

- De-escalation and discontinuing DMT is a shift of focus from relapse control to risk reduction and symptomatic management.
- MS relapses tend to become less frequent with age. De-escalation and/or discontinuation of DMT may reduce risk of side effects for older patients.
- There is no consensus regarding timing for DMT discontinuation, but older patients with prolonged stability on lower efficacy therapies are more likely to discontinue DMT without subsequent disease activity.
- Providers should remain vigilant in monitoring for disease activity following DMT discontinuation or de-escalation.

Starting or Switching a DMT for MS

Determine Relapsing MS Activity Category[1-5]

There are no standard definitions of MS disease activity categories. "Highly" and "minimally" active disease are commonly used terms to define severity of relapsing MS. That said, disease activity is widely variable and exists on a spectrum of more and less active. Providers will need to take into account many aspects (clinical symptoms, imaging, relapse history, etc.) to determine if a patient with relapsing MS is closer to "highly" or "minimally" active.

Criteria below are drawn from clinical practice guidelines, clinical trial entry criteria, natural history studies, and expert opinion. Determine a patient's MS activity category at first presentation and again periodically for switching, escalating, de-escalating, and discontinuing considerations as patients may change activity categories over time.

Table 1. MS Activity Categories and Characteristics for Relapsing Forms of MS.

MS Category	Category Definition

Highly active relapsing MS	• ≥ 1 clinical* and/or 1-2 radiographic+ relapses per year while on low- to moderate-efficacy DMT
	OR
	• Presenting within 5 years since disease onset with initial high-risk features:
	  ○ Myelopathic relapses (motor/sphincter involvement, significant impairment from motor/)
	  ○ Infratentorial (brainstem / cerebellar) signs
	  ○ Incomplete recovery from initial relapses within 6 months
	  ○ ≥ 1 clinical* and/or radiographic+ relapse per year
	  ○ High burden brain/spinal cord T2 lesions at disease onset
	  ○ High (≥ 3) accumulation of brain/spinal T2 lesions over first year of disease or ≥ 5 over 2 years

Minimally to Non-active relapsing MS / non-active SPMS	• Does not otherwise meet criteria for "highly active" MS • Overlap in characteristics of "minimally" and "non-active" categories can exist as determining "non-active" status requires a retrospective review of clinical and radiographic activity • No clinical* or radiographic+ relapses > 5 years#

* Clinical relapse defined as new or worsening neurologic symptoms developed over a short period of time and are not associated with fever or infection

\+ Radiographic relapse defined as new or enlarged T2 lesions or presence of contrast enhancing lesions

\# age at which non-active SPMS may occur varies. Per 2018 AAN guidelines, relapses tend to occur in ages younger than 55 years.

DMT Prescribing Considerations[1-7]

Use Tables 2-3 and Figure 1 as guides for initiating, switching, de-escalating, and stopping DMT based on MS Activity Category and General Considerations described below. Providers should reassess MS Activity Level (See Table 1) at least annually as part of a comprehensive DMT assessment.

When initiating or switching to a new DMT, consider monitoring brain MRI (adding spine MRI if cord lesions present) annually for 5 years. If no relapsing activity, imaging frequency may be decreased to every 3-5 years as clinically indicated. If a patient opts to not be on a DMT or a DMT has been discontinued, monitor brain MRI (adding spine if cord lesions present) annually for at least 5 years and then as clinically indicated. More frequent MRIs may be needed for safety monitoring of some DMTs (e.g., natalizumab)

There may be many factors to consider with the patient when initiating or switching a DMT. These can include the patient's disease activity, adherence to medication, amenability to route of administration, required lab monitoring, presence, or risk of adverse events (e.g., persistent lab abnormalities, JCV index >0.9, infections), ability to travel (for in-clinic administered DMTs), and childbearing potential.

De-escalation may include evidence-based dose reduction (e.g., rituximab 1000 mg to rituximab 500 mg), extending the dosing interval (e.g., natalizumab IV every 4 weeks to natalizumab IV every 8 weeks), or switching to a higher safety DMT.

Table 2. DMT Selection Recommendations for Relapsing Forms of MS and PPMS.

MS ACTIVITY LEVEL	Initiating DMT	Escalating / Switching DMT	De-escalating / Stopping DMT
HIGHLY ACTIVE relapsing forms of MS	**Efficacy is prioritized** • Favor high efficacy DMT. • A moderate efficacy DMT may be considered if there are significant concerns regarding safety of high efficacy DMT options. • If a low efficacy DMT is chosen, monitor for clinical and MRI relapses at least every 6 months to determine adequacy of disease control.	After reaching full efficacy of a DMT, if there is ongoing/increase in disease activity in 6 months or less: • Moderate or low efficacy DMT: ○ Escalate to a higher efficacy DMT. • High efficacy DMT: ○ Switch to a high efficacy DMT with a different mechanism of action, AND/OR ○ Obtain MS specialist 2nd opinion.	If a patient is in highly active disease, de-escalation or discontinuation is inadvisable due to relapse risk. If a patient opts to discontinue DMT, monitor for clinical and radiographic progression at least every 6 months. People planning or who are pregnant or breastfeeding may need to de-escalate DMT based on drug-specific risks (See Table 4).
MINIMALLY ACTIVE relapsing forms of MS	**Efficacy is prioritized** • Favor moderate efficacy DMT. • There is some evidence to support high efficacy DMTs are more effective than moderate efficacy DMTs. However moderate efficacy DMTs tend to be safer. • If on a lesser efficacy DMT, monitor for clinical/MRI relapses at least every 6	After reaching full efficacy of a moderate efficacy DMT, if there is ongoing/increase in disease activity in 3 months or less: • Escalate to high efficacy DMT.	If a patient is in minimally active disease, discontinuation is inadvisable due to relapse risk. If a patient opts to discontinue DMT, monitor for clinical and radiographic progression at least every 6 months. People planning or who are pregnant or breastfeeding may need to de-escalate DMT based on drug-specific risks (See Table 4). De-escalating DMT may be considered to prioritize safety as needed. If de-escalating, monitor with

MS ACTIVITY LEVEL	Initiating DMT	Escalating / Switching DMT	De-escalating / Stopping DMT
	months to determine adequacy of disease control.		MRI every 6 months x2, then yearly x2-4, then PRN. Monitor clinically at least annually.
NON-ACTIVE relapsing forms of MS	**Safety is prioritized** • Monitoring with no DMT (i.e., "watch and wait") may be an option. • No DMT is indicated for non-active MS. • Favor low risk DMT if de-escalating (see de-escalating section). • Careful monitoring to verify clinical subtype.	If increase in disease activity: • Reassess activity level and treat based on level. • Consider if benefits outweigh risks of initiating / escalating DMT in older patients.	Consider de-escalating over stopping if: • No relapse activity > 5 years AND > 55 years* and stopping is not ideal based on prior MS activity, comorbid diseases, or the current DMT has evidence for elevated relapse risk after discontinuation (see Table 4) Consider de-escalating or stopping if: • No relapse activity > 5 years AND > 55 years* If de-escalating or stopping, monitor with MRI yearly x2-4, then PRN. Monitor clinically at least annually.
Clinically isolated syndrome (CIS)	• Favor moderate to high efficacy DMT if high risk features (e.g., ≥ 2 brain lesions on MRI, others Table 1). • Favor low risk DMT if low-risk features (<2 brain lesions on MRI, does not have high-risk features). • Monitoring without DMT may be an option with brain MRI at least every 6 months to assess for development of new lesions.	If new clinical or radiographic relapses, reassess diagnosis and related disease activity level. Consider switching DMT accordingly.	• Consider de-escalating moderate and high efficacy DMT after at least 10 years since CIS without conversion to relapsing MS. • Consider stopping lower efficacy DMT after a total of 10 or more years without conversion to relapsing MS.
PPMS	Offer clinically appropriate DMT (see Table 4) for < 55 years and EDSS ≤ 6.5, or for anyone with PPMS if benefits outweigh risks. Clinical response demonstrated as slowed clinical worsening.	No alternative DMT with a different mechanism of action for PPMS currently exists.	Consider stopping if > 55 years, EDSS >5.5, no MRI relapses > 5 years, lack of clinical response, adverse events.

The following figure depicts the overall positive correlation between efficacy and risk that most DMTs have. This means low efficacy DMTs tend to have a lower level of risk than high efficacy DMTs. A patient's individual risk to a particular DMT may vary based on individual characteristics (e.g., JCV antibody status, preexisting conditions, childbearing potential, etc.). Thus, DMT decisions should include balancing patient-specific risks and benefits.

Figure 1: Comparative Efficacy and Safety of DMTs

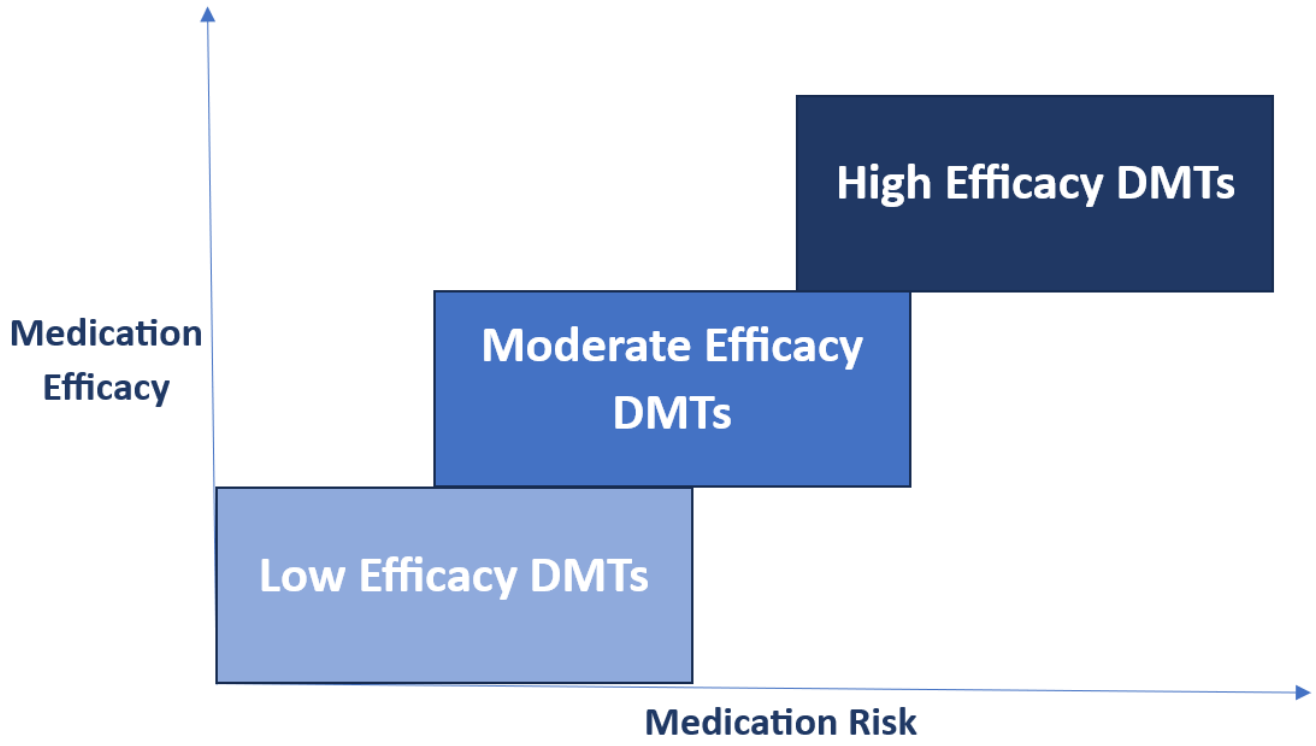

Table 3: DMTs by Efficacy Category

Low Efficacy	**Interferons (e.g., interferon beta-1b)** **Glatiramer** **Teriflunomide**
Moderate Efficacy	**Fumarates (e.g., dimethyl fumarate)** **S1PR modulators (e.g., fingolimod)**
High Efficacy	**Natalizumab** **Anti-CD20 antibodies (e.g., ublituximab)** **Alemtuzumab (for refractory disease)** **Cladribine (for refractory disease)**

De-escalating / Discontinuing a DMT for MS

Considerations for De-escalating or Discontinuing DMT

Although age is not the only factor to determining MS activity, there is evidence to support that as patients with MS age, they are at decreasing risk for MS relapses and increasing risk of drug-related adverse events such as infection and malignancy.[8] Most clinical trials of MS DMT have enrolled relatively young (less than 55 years old) cohorts. Therefore, the efficacy and risks of these medications in patients older than 55 has not been well established. Based on the currently available evidence, it is reasonable to consider de-escalation or discontinuation of DMT for some older veterans with MS. At the same time, there is no consensus regarding the criteria for DMT discontinuation.

DISCO-MS was the largest interventional study of DMT discontinuation in patients with stable disease (no relapses for at least 5 years). In this study, new MRI activity was seen in 5% of those continuing DMT and 12% of those who discontinued DMT. Despite the greater MRI activity in discontinuers, both groups had similar disability worsening, patient-reported outcomes, and total adverse events.[9] The conclusion of the authors was that it may be reasonable to discontinue DMT in patients older than 55 years with stable MS, although there may be a small risk of increased new MRI activity. A retrospective registry study comparing "stoppers" and "stayers" on DMT found no difference in time to first relapse or disability progression, but greater risk of reaching higher disability (EDSS 6 or higher) in stoppers.[10] The authors concluded that it may be reasonable to consider early discontinuation in patients older than 50 years on lower efficacy DMT, such as interferons or glatiramer.

Several factors have been identified to be associated with an increased risk for relapse following discontinuation of DMT. These include age under 55 years, a history of disease activity or disability progression within 3 years prior to stopping DMT, patients with moderate disability (EDSS 4-5.5), and being on a higher potency DMT immediately prior to discontinuation.[11-12] Patients on a DMT that has evidence for relapse risk after discontinuation (e.g., natalizumab and S1PR modulators) should be considered for de-escalation rather than discontinuation (See Table 4).

The decision to discontinue DMT requires a discussion of patient-specific risks and benefits. Priorities of patients may differ from clinicians'. De-escalation of DMT to one with fewer risks for a period to observe for possible renewed disease activity prior to discontinuation of DMT can also be considered.

Care After Discontinuing DMT

Disease activity monitoring should not stop once there is discontinuation of DMT. Clinical examinations and MRI imaging should continue, although the rate and intensity may decrease over time if stability persists. A suggested practice guideline for DMT discontinuation includes obtaining a baseline brain MRI at the time of DMT discontinuation, annual brain MRI for the first two years after stopping DMT, and regular clinic visits during years 1 and 2 for clinical monitoring. If MS activity remains stable, a transition to annual clinical visits could be considered with intermittent MRIs.

Considering discontinuation of MS DMTs is an important consideration for aging veterans with MS in which the risks for ongoing therapy may outweigh its benefits. Importantly, discontinuing DMT in older veterans with MS does not represent a cessation of care, but a shift of focus from relapse control to symptomatic management, risk reduction, and ongoing disease surveillance.

Disease Modifying Therapies for Multiple Sclerosis

Pharmacotherapeutic options for MS are summarized in Table 4. The information in this table is not all-inclusive and should be used in collaboration with current prescribing information (PI), REMS program (if applicable), and other relevant drug information for complete details (e.g., dosing, lab monitoring frequency, etc.).

If possible, patients should receive all eligible live or live-attenuated vaccines at least 4 weeks and non-live vaccines at least 2 weeks before starting DMT. Patients should not receive any live or live-attenuated vaccine while on DMT. Specific requirements may apply for some DMTs; see Table 4.

Washout information in "Potential Adverse Events & Washout" column pertains to considerations in situations other than pregnancy or pregnancy planning. Pregnancy and pregnancy planning washout information is in the "Pregnancy & Lactation" column. Pregnancy and lactation information is compiled from prescribing information, National Institutes of Health (NIH) Drugs and Lactation Database, and additional literature.[15,27, 53] Lactation data is largely from mature (at least two weeks postpartum)

breastmilk. DMT decisions in people planning or who are pregnant or breastfeeding should be in collaboration with their obstetrician.

DMTs are listed by class. See above for clinical considerations to starting, switching, de-escalating, and discontinuing DMT. Table 3 indicates what classes are generally considered low, moderate, and high efficacy DMTs. Refer to the *PBM INTRAnet* or VA Formulary Advisor for current formulary status, additional formulary information, and VA Criteria for Use.

Table 4: Disease Modifying Therapies for Multiple Sclerosis[13-52]

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
Alemtuzumab (LEMTRADA), IV infusion	**IV** infusion daily for 5 days then 1 year later, IV infusion daily for 3 days Repeat 3-day courses can be considered if clinically indicated and if at least 12 months after last dose. Typical pre-medication: high dose corticosteroid such as methylprednisolone 1000mg immediately prior to first alemtuzumab dose and for the first 3 days of each treatment course	Has a REMS program which also provides lab and imaging frequency guidance. Contraindicated if HIV Delay treatment if active infection Give antivirals for herpes prophylaxis starting the first day of treatment until 2 months or CD4+ lymph count is > 200 cells/microliter Instruct patients to avoid potential sources of Listeria monocytegenes Provide antiviral prophylaxis against herpes for at least 2 months after each dose or until CD4>200cells/mm3	**Baseline** HIV, VZV, TB, HBV, HCV, CBC w/ diff, CMP, UA w/ cell counts and protein, thyroid function tests, skin exam **Routine** CBC w/ diff, CMP, TSH, LFT, and UA w/ cell counts and protein, skin exam **Vaccines** Consider giving VZV vaccine if patient has not been vaccinated and is negative for VZV antibodies. Complete vaccinations at least 6 weeks prior to starting alemtuzumab.	**Serious:** Secondary autoimmune diseases (including autoimmune hepatitis, thyroid disorders, hemophagocytic lymphohistiocytosis, adult onset Still's disease, thrombotic thrombocytopenic purpura, autoimmune encephalitis, and acquired hemophilia), serious infusion reactions, stroke or cervicocephallic arterial dissection, malignancy, PML **Common:** rash, headache, pyrexia, nasopharyngitis, nausea/vomiting, minor infections, fatigue, insomnia, urticaria, pruritus, thyroid disorders, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pian, flushing **Washout**: An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. Additive immunosuppression should be considered. If switching from alemtuzumab to another DMT, lymphocyte counts can help assess magnitude of immunosuppression and additive risks.	Avoid if pregnant Use contraception during and for 4 months after treatment course Avoid breastfeeding during treatment and at least 3 months after last dose

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
ANTI-CD20 ANTIBODIES					
Rituximab and biosimilars (RITUXAN, RUXIENCE, etc.) IV infusion	**IV** infusion every 6 months Typical pre-medications: acetaminophen 650mg PO diphenhydramine 50mg PO methylprednisolone 100mg IVP over 3-5 minutes	**Special Indication Information:** - Rituximab and biosimilars: MS is an off-label, though evidence-based, indication - Ocrelizumab: only anti-CD20 antibody FDA approved for PPMS. Contraindicated if active HBV infection Delay infusion/injection if acute infection For IV formulations: to prevent infusion reactions, premedicate. Also, slower infusion rates are recommended for first doses. Then rate can be increase as tolerated. Can consider using CD19 results to guide dose and/or dosing interval	**Baseline** CBC w/ diff, CMP, immunoglobulins (IgG, IgM), Screen for hepatitis B (required), hepatitis C, TB, pregnancy as indicated **Routine** Immunoglobulins, CBC w/ diff, CMP	**Serious**: HBV reactivation, serious infusion/injection-related reactions (most common with initial dose), serious infections, PML Skin reactions, CV events (rituximab) Malignancy, immune-mediated colitis (ocrelizumab) **Common**: minor infusion/injection-related reactions, infections, hypoglobulinemia **Washout**: An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. In considering risks of additive immunosuppression, refer to individual PIs for average B-cell repletion time. Immunoglobulins can also be used to estimate lasting immunosuppressive effect after discontinuing therapy.	PIs still recommend avoiding anti-CD20 during pregnancy and that people of childbearing potential use contraception during and for at least 6 months after stopping therapy. Emerging post-marketing safety data with pregnancy exposures indicate there may be the potential for safe use. For infants born to mothers who were exposed to anti-CD20 antibodies, live vaccines should not be administered until normal B-cell counts are verified. Probably compatible with breastfeeding
Ublituximab (BRIUMVI) IV infusion	**IV** infusion every 24 weeks Typical pre-medications: diphenhydramine 50 mg PO/IV methylprednisolone 100 mg IVP over 3-5 minutes +/- acetaminophen				
Ocrelizumab (OCREVUS), IV infusion	**IV** infusion every 6 months Typical pre-medications: acetaminophen 650mg PO				

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
	diphenhydramine 50mg PO methylprednisolone 100mg IVP over 3-5 minutes				
Ofatumumab (KESIMPTA) prefilled syringe	**SubQ** once monthly First dose should be given under guidance of a healthcare professional Pre-medications showed only limited benefit in trials so are not routinely recommended. Symptomatic treatment is recommended if injection-related reactions occur Can be stored at room temperature for up to 7 days				
Cladribine (MAVENCLAD) oral tablet	**PO** given in 2 yearly treatment courses. Each course is divided into 2 treatment cycles.	Cytotoxic drug Contraindicated if current malignancy, HIV infection, or active chronic infection such as	**<u>Baseline</u>** CBC w/ diff, LFT Screen for latent infections, VZV, pregnancy, HIV,	**Serious**: malignancies, lymphopenia, serious infections, serious skin reactions including SJS and TEN, liver injury, hypersensitivity, cardiac failure, PML	Contraindicated during pregnancy. All patients with reproductive potential (regardless of gender) should use contraception during

As above with all anti-CD20 antibodies

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
	Separate from other oral medications by at least 3 hours.	hepatitis or TB. Delay treatment if active infection. Do not start unless lymphocytes are WNL and >800 cells/microliter before starting second course. Give antivirals for herpes prophylaxis if lymphocytes<200 cells/microliter.	TB, Hepatitis B, Hepatitis C, and any indicated cancer screenings **Routine** CBC w/ diff, LFT **Vaccines** Give VZV vaccine if seronegative prior to starting cladribine. Give recombinant zoster vaccine if VZV positive.	Graft-versus-host disease with blood transfusion **Common**: minor infections, headache, lymphopenia, neutropenia, anemia, thrombocytopenia **Washout**: An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. Additive immunosuppression should be considered. If switching from cladribine to another DMT, lymphocyte counts can help assess magnitude of immunosuppression and additive risks.	and for 6 months after the last dose in each treatment course. Four-month washout, intermediate half-life but prolonged biologic activity, no human evidence of fetotoxicity. Not compatible with breastfeeding.
FUMARATES					
Dimethyl fumarate (DMF, TECFIDERA), oral capsule	**PO** BID	Most common intolerances are GI related (diarrhea, abdominal pain, nausea) and flushing. Strategies that may help: **Administer with food** Can administer meals or a snack to decrease flushing and GI side effects. Healthy-fat or protein containing food such as yogurt or peanut	**Baseline** CBC with differential, LFT Screen for hepatitis and/or TB if high risk. **Routine** LFT, CBC Discontinue if lymphocytes <	**Serious**: lymphopenia, PML (in context of lymphopenia), liver injury **Common**: flushing, abdominal pain, diarrhea, nausea, infection **Washout**: An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. In considering risks of additive immunosuppression,	Should be discontinued before conception, no specified washout required. Evolving evidence on breastfeeding (serum levels have been detected in infants, unknown clinical adverse outcomes, use with caution). DMF: Active metabolite in breastmilk low and not expected to cause any AEs in breastfed infants. Exposed
Diroximel fumarate (DRF, VUMERITY), oral capsule	**PO** BID				
Monomethyl fumarate (MMF, BAFIERTAM), oral capsule	**PO** BID				

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
		butter may help for DMF and MMF. Limit food to 700 calories and 30g fat or less (DRF). **Aspirin** Can premedicate with non-enteric coated aspirin (up to 325 mg) 30 minutes prior to dose to reduce flushing. **Temporary Dose Reduction** May return to initial dose for up to 4 weeks and then resume maintenance dose **Diroximel Fumarate** DRF has been associated with lower GI intolerances, flushing incidence not significantly different from other fumarates Post marketing cases of PML have been reported with DMF, all fumarates should be monitored for PML risk (see Monitoring & Vaccines).	500 for >6 months. Monitor lymphocytes until resolved. UA if proteinuria suspected (DMF).	fumarates may result in prolonged lymphocytopenia after discontinuation which may be an especially relevant consideration if switching to a higher efficacy DMT. Lymphocyte counts can help assess magnitude of immunosuppression and additive risks after fumarate discontinuation.	infants should be monitored for adequate weight gain and development, especially in younger, exclusively breastfed infants. DRF: Acceptable to use during breastfeeding, at least after 1 month of age. Breastfed infants should be monitored, especially in younger, exclusively breastfed infants.

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
Glatiramer acetate (COPAXONE, GLATOPA, other generics), prefilled syringe	**SubQ** daily OR 3 times weekly Doses should be at least 48 hours apart Can inject with or without autoinjector. Can be stored at room temperature for up to one month	Contraindicated if hypersensitivity to mannitol Idiosyncratic post-injection reactions which may include chest pain, flushing, dyspnea, palpitations and/or anxiety that tends to subside within 30 minutes. Can occur at any point during treatment	**Baseline/Routine** No specific lab monitoring indicated, can consider LFT as clinically indicated to monitoring for hepatotoxicity. **Vaccines** Labelling does not contraindicate use of live vaccines. Consider risk vs. benefit.	**Serious:** hepatotoxicity, skin necrosis **Common**: injection site pain or itching, lipoatrophy at injection site **Washout**: An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. In considering risks of additive immunosuppression, glatiramer has a relatively low level of immunosuppression compared to other DMTs.	No washout, may be used up to conception and throughout pregnancy Compatible with breastfeeding
INTERFERONS					
Interferon beta-1b (AVONEX), prefilled syringe, pen	**IM** once weekly. Can be stored at room temperature for up to 7 days.	Contraindicated if hypersensitivity to albumin Some formulations contain latex - refer to agent's PI. Use with caution if history of seizure disorder. Use caution if severe renal impairment (pegylated interferon	**Baseline** CBC w/ differential, LFT, thyroid function Screen for hepatitis and/or TB if high risk. **Routine** CBC w/ differential, LFT, and TSH **Vaccines**	**Serious:** bone marrow suppression, depression, HF **Common:** injection site reaction, flu-like symptoms, fatigue, myalgia, abdominal pain, nausea, UTI, leukopenia, lymphadenopathy, increased LFTs **Washout:** An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. In considering risks of additive immunosuppression,	No washout needed, may be used up to conception. Compatible with breastfeeding.
Interferon beta-1b (BETASERON, EXTAVIA), vial with prefilled syringe	**SubQ** every other day Requires patient to reconstitute vial with a prefilled syringe of diluent. Can inject with or without autoinjector. Can be				

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
	stored at room temperature. Use within 3 hours after reconstitution.	beta-1a). Can pre-medicate with acetaminophen or ibuprofen to decrease flu-like symptoms.	Labelling does not contraindicate use of live vaccines. Consider risk vs. benefit.	interferons have a relatively low level of immunosuppression compared to other DMTs.	
Interferon beta-1a (REBIF), prefilled syringe	**SubQ** 3 times weekly Doses should be at least 48 hours apart. Can inject with or without autoinjector. Can be stored at room temperature for up to 30 days.				
Peginterferon beta-1a (PLEGRIDY), prefilled syringe, pen	**SubQ or IM** every 14 days Can be stored at room temperature for up to 30 days.				
Natalizumab (TYSABRI), IV Infusion	**IV** infusion every 4 weeks	Has a REMS program to help monitor for and assess risk for development of PML. Three baseline risk factors associated with increased risk of PML: 1. Presence of JCV antibodies (higher index value carries higher PML	**Baseline** CBC, LFT, JCV antibody with index value **Routine** JCV antibody with index value, CBC and LFTs	**Serious**: PML, other infections, antibody formation, melanoma, hepatic injury, hypersensitivity **Common**: Infusion reactions, headache, diarrhea, arthralgia, depression, pain in extremity, rash, vaginitis **Washout:** MS rebound after	PI still recommends avoiding during pregnancy and that people of childbearing potential use contraception during and for at least 3 months after stopping therapy. Emerging post-marketing safety data with pregnancy exposures indicate there may be the

As above with all interferons

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
		risk) 2. Longer treatment duration 3. Prior treatment with an immunosuppressant The REMS program also provides lab and imaging frequency guidance.	Risk of PML increases if patient develops JCV antibody during treatment. Hold natalizumab if any sign or symptom of PML until appropriate evaluation and ruling out PML has occurred.	treatment discontinuation has been found with natalizumab. 2018 AAN guidelines recommend switching to an alternative DMT within 8-12 weeks to decrease rebound risk. In considering risks of additive immunosuppression, consider additive risk of PML if switched to another DMT with PML risk.	potential for safe use, however anemia and thrombocytopenia have been reported in neonates exposed to natalizumab during the third trimester. For infants born to mothers who were exposed to natalizumab, live vaccines should be postponed. Probably compatible with breastfeeding. *MS rebound after treatment discontinuation should be considered if discontinuation is decided. This may include careful monitoring and/or switching to a DMT with evidence for safety. 2018 AAN guidelines recommend switching to an alternative DMT within 8-12 weeks to decrease rebound risk.
S1PR MODULATORS					
Fingolimod (GILENYA), oral capsule	**PO** daily Missed doses: Repeat First dose observation (FDO) if treatment interrupted ≥1 day	Many cardiac contraindications. Avoid concurrent therapy with medications that decrease heart rate or prolong QT. Frist Dose Observation	**Baseline** EKG, LFT, CBC with differential, Varicella titer Screen for hepatitis and/or TB if high risk.	**Serious**: AV block, PML, serious infection, liver injury, macular edema (history of diabetes or uveitis increases risk), cutaneous malignancy posterior reversible encephalopathy syndrome (PRES). **Common**: headache, bradycardia,	Human evidence of fetotoxicity. Recommended to use contraception during treatment and after treatment (duration varies for each agent, refer to PI). The latter duration can also be considered as the recommended washout period

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
	during first 2 weeks, >7 days during weeks 3 to 4, or >14 days after 1 month of treatment.	(FDO): required for all patients due to risk of bradycardia and AV block. FDO is monitoring of pulse, BP, and ECG. By a healthcare professional for at least 6 hours. Patients who experience abnormalities or with other preexisting conditions may require longer observation.	Baseline ophthalmologic and skin exam requirements vary between agents - refer to PI. **<u>Routine</u>** BP, CBC with differential, LFT Routine ophthalmologic and skin exam frequencies vary between agents - refer to PI **<u>Vaccines</u>** Consider giving VZV vaccine if no confirmed history of chickenpox and antibody negative.	increased LFTs infection, BP increase, orthostatic hypotension (ozanimod) back pain (fingolimod and ozanimod), nausea (fingolimod), diarrhea (fingolimod), cough (fingolimod), sinusitis (fingolimod), abdominal pain (fingolimod), pain in extremity (fingolimod) **Washout**: MS rebound after treatment discontinuation has been found with fingolimod. Other S1PR modulators carry this warning as well. In considering risks of additive immunosuppression, discontinuation of S1PR Modulators tends to result in increases in lymphocytes within days. Return to normal lymphocyte count varies from ~2 weeks to ~2 months, refer to individual agent's PI. This may be an especially relevant concern if switching to a higher efficacy DMT and/or DMT with PML risk. Also, check LFT 2 months after treatment discontinuation recommended for fingolimod.	prior to planning pregnancy. See MS rebound information below for additional considerations. Not compatible with breastfeeding. MS rebound after treatment discontinuation should be considered if discontinuation is decided. This may include careful monitoring and/or switching to a DMT with evidence for safety.
Ozanimod (ZEPOSIA) oral capsule	**PO** daily Reduce dose in mild or moderate hepatic impairment. Use in severe hepatic impairment not recommended.	Many cardiac contraindications. Additionally contraindicated in severe untreated OSA . Many drug interactions: Active metabolite inhibits MAO-B, so serotonergic medications should be avoided. MAO-Is are contraindicated Avoid concomitant medications that decrease heart rate or prolong QT, CYP2C8 inducers and inhibitors.			

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
		Avoid foods high in tyramine.			
Ponesimod (PONVORY) oral tablet	**PO** daily Missed doses: If ≤3 consecutive doses missed: If during titration, resume with the first missed titration dose, and resume the titration schedule at that dose and titration day. If during maintenance, resume treatment with the maintenance dosage. If ≥ 4 consecutive doses missed: Reinitiate treatment with day 1 of the initial titration regimen, including FDO if applicable.	Many cardiac contraindications. Not recommended in severe OSA. Many drug interactions: Strong CYP3A4 and UGT1A1 inducers, medications that decrease heart rate or prolong QT are not recommended Assess for concomitant meds that might lower HR. FDO: recommended if sinus bradycardia (<55bpm), first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of MI or HF FDO is monitoring of pulse, BP, and ECG. By a healthcare professional for at least 6 hours. Patients who experience abnormalities or with other preexisting CV	As above with all S1PR modulators		

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
		conditions may require longer observation.			
Siponimod (MAYZENT) oral tablet	**PO** daily Dose determined by CYP2C9 genotype. Missed doses: Restart titration if any dose missed more than 24 hours during initial titration or if 4 or more consecutive days after titration including first-dose monitoring when appropriate.	Many cardiac contraindications. Additional contraindications: CYP2C9 *3/*3 genotype, concomitant use with CYP2C9 or CYP3A4 inhibitors or inducers (caution with drug interaction with moderate inhibitors and inducers). FDO: recommended if certain cardiac conditions FDO is monitoring of pulse, BP, and ECG. By a healthcare professional for at least 6 hours. Patients who experience abnormalities or with other preexisting conditions may require longer observation.	As above with all S1PR modulators		

Drug	Maintenance Administration Method and Frequency	Contraindications & Special Considerations	Monitoring & Vaccines	Potential Adverse Events & Washout	Pregnancy & Lactation
Teriflunomide (AUBAGIO), oral tablet	**PO** daily	Contraindicated in pregnancy. All patients with reproductive potential should use contraception (regardless of gender). If liver injury or other serious reaction, pregnancy, or if pregnancy is desired stop teriflunomide and start drug accelerated elimination procedure with cholestyramine or activated charcoal. Especially in pregnancy or planning pregnancy (for either gender), procedure should be repeated until plasma teriflunomide concentration are less than 0.02 mg/L (0.02 mcg/mL).	**Baseline** CBC, LFT, serum phosphorus, BP Screen patients for: pregnancy (if applicable), tuberculosis, hepatitis if high risk **Routine** LFT, CBC, BP, serum phosphorus periodically as clinically indicated	**Serious:** hepatotoxicity, teratogenicity, skin reactions including SJS, infection, interstitial lung disease, hematologic disorders **Common:** alopecia, hypophosphatemia, diarrhea, nausea, lymphocytopenia, headache **Washout:** An appropriate washout time from previous DMT is unknown. The risks of a longer washout period should be weighed against the risks of another relapse. In considering risks of additive immunosuppression, teriflunomide has a relatively low level of immunosuppression compared to other DMTs.	Not compatible with pregnancy. Very long half-life, see Contraindications/Special Considerations for washout and elimination protocol Not compatible with breastfeeding.

References

1. Langer-Gould A, Klocke S, Beaber B, Brara SM, Debacker J, Ayeni O, Nielsen AS. Improving quality, affordability, and equity of multiple sclerosis care. Ann Clin Transl Neurol. 2021 Apr;8(4):980-991. doi: 10.1002/acn3.51326. Epub 2021 Mar 10. PMID: 33751857; PMCID: PMC8045931.
2. Olek MJ & Mowry E. (2023). Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults. In: F. Gonzalez-Scarano and JF Dashe (Eds.), *Up to Date*. Retrieved October 20, 2020, from Initial disease-modifying therapy for relapsing-remitting multiple sclerosis in adults - UpToDate.
3. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis. Neurology. 2018;90:777-788. doi:10.1212/WNL.0000000000005347
4. Corboy JR et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): A multicentre, randomised, single-blind, phase 4, non-inferiority trial. *Lancet Neurol* 2023 Jul; 22:568
5. Wolinsky JS, Narayana PA, O'Connor P, Coyle PK, Ford C, Johnson K, Miller A, Pardo L, Kadosh S, Ladkani D; PROMiSe Trial Study Group. Glatiramer acetate in primary progressive multiple sclerosis: results of a multinational, multicenter, double-blind, placebo-controlled trial. Ann Neurol. 2007 Jan;61(1):14-24. doi: 10.1002/ana.21079. PMID: 17262850.
6. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology. 2016;87(20):2074-2081.
7. Zhovtis Ryerson L, Frohman TC, Foley J, et al. Extended interval dosing of natalizumab in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2016 Aug;87(8):885-9.
8. Graves JS, Krysko KM, Hua LH, Absinta M, Franklin RJM, Segal BM. Ageing and multiple sclerosis. Lancet Neurol. 2023 Jan;22(1):66-77. doi: 10.1016/S1474-4422(22)00184-3. Epub 2022 Oct 7. PMID: 36216015.
9. Corboy JR et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): A multicentre, randomised, single-blind, phase 4, non-inferiority trial. *Lancet Neurol* 2023 Jul; 22:568
10. Kaminsky AL, Omorou AY, Soudant M, Pittion-Vouyovitch S, Michaud M, Anxionnat R, Guillemin F, Debouverie M, Mathey G. Discontinuation of disease-modifying treatments for multiple sclerosis in patients aged over 50 with disease Inactivity. J Neurol. 2020 Dec;267(12):3518-3527. doi: 10.1007/s00415-020-10029-9. Epub 2020 Jul 2. PMID: 32617659.
11. Kister I, Spelman T, Patti F, Duquette P, Trojano M, Izquierdo G, Lugaresi A, Grammond P, Sola P, Ferraro D, Grand'Maison F, Alroughani R, Terzi M, Boz C, Hupperts R, Lechner-Scott J, Kappos L, Pucci E, Hodgkinson S, Solaro C, Butzkueven H. Predictors of relapse and disability progression in MS patients who discontinue disease-modifying therapy. J Neurol Sci. 2018 Aug 15;391:72-76. doi: 10.1016/j.jns.2018.06.001. Epub 2018 Jun 2. PMID: 30103975.
12. Pasca M, Forci B, Mariottini A, Mechi C, Barilaro A, Massacesi L, Repice AM. Sustained disease remission after discontinuation of disease modifying treatments in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2021 Jan;47:102591. doi: 10.1016/j.msard.2020.102591. Epub 2020 Oct 21. PMID: 33142245.
13. Rebif [package insert]. Rockland, MD: EMD Serono, Inc.; 2023.

14. Interferon beta-1a: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
15. Bove RM, Houtchens MK. Pregnancy management in multiple sclerosis and other demyelinating diseases. *Continuum (Minneap Minn)*. 2022;28(1):12-33.
16. Avonex [package insert]. Cambridge, MA: Biogen Inc; 2020.
17. Betaseron [package insert]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc; 2021.
18. Extavia [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
19. Plegridy [package insert]. Cambridge, MA: Biogen Inc.; 2023.
20. Copaxone [package insert]. Parsippany, NJ: Teva Neuroscience, Inc; 2023.
21. Glatopa [package insert]. Princeton, NJ: Sandoz Inc.; 2018.
22. Glatiramer acetate: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
23. Aubagio [package insert]. Cambridge, MA: Genzyme Corporation; 2021.
24. Teriflunomide: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
25. Tecfidera [package insert]. Cambridge, MA: Biogen Inc.; 2023.
26. Dimethyl fumarate: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
27. Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501922/
28. Vumerity [package insert]. Cambridge, MA: Biogen Inc.; 2023.
29. Diroximel fumarate: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
30. Bafiertam [package insert]. High Point, NC: Banner Life Sciences LLC; 2021.
31. Monomethyl fumarate: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
32. Gilyena [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2022.
33. Fingolimod: Drug information. Monitoring Parameters. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
34. Mayzent [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2023.
35. Siponimid: Drug information. Monitoring Parameters. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
36. Zeposia [package insert]. Summit, NJ: Celgene Corporation; 2020.
37. Ozanimod: Drug information. Monitoring Parameters. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
38. Ponvory [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc.; 2022.
39. Ponesimod: Drug information. Monitoring Parameters. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
40. Rituximab (intravenous) including biosimilars: Drug information. Dosing: Adult. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
41. Techa-Angkoon P, Siritho S, Tisayipat N, Suansanae T. Current evidence of rituximab in the treatment of multiple sclerosis. *Mult Scler Relat Disord.* 2023;75:104729.
42. Rituximab (intravenous) including biosimilars: Drug information. Administration: Adult. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
43. Rituxan [package insert]. South San Francisco, CA: Genentech, Inc.; 2021.

44. AbdelRazek MA, Casasola M, Mollashahi R, et al. Extended B-cell depletion beyond 6-months in patients receiving ocrelizumab or rituximab for CNS demyelinating disease. *Mult Scler Relat Disord.* 2022;59:103505.
45. Ocrelizumab: Drug information. Warnings/Precautions. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
46. Ocrevus [package insert]. South San Francisco, CA: Genentech, Inc.; 2023.
47. Kesimpta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2020.
48. Briumvi [package insert]. Morrisville, NC: TG Therapeutics, Inc; 2022.
49. Tysabri [package insert]. Cambridge, MA: Biogen Inc.; 2023.
50. Natalizumab: Drug information. Monitoring Parameter. Hudson, OH: Lexicomp, Copyright 2023. http://online.lexi.com/
51. Mavenclad [package insert]. Rockland, MA: EMD Serono, Inc.; 2022.
52. Lemtrada [package insert]. Cambridge, MA: Genzyme Corporation; 2022.
53. Krysko KM, Dobson R, Alroughani R, et al. Family planning considerations in people with multiple sclerosis. Lancet Neurol. 2023 Apr;22(4):350-366.

Prepared June 2024. Contact person: N. Antonovich, PharmD, BCPS, National PBM Clinical Pharmacy Program Manager, Formulary management, VA Pharmacy Benefits Management Services (12PBM)