Multiple Sclerosis Centers of Excellence
Pocket Reference for MS Disease Modifying Therapies

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Veteran Affairs Multiple Sclerosis Centers of Excellence Pocket Reference for MS Disease Modifying Therapies

The proposed recommendations made in this document are based on available medical evidence and suggestions made by the Multiple Sclerosis Centers of Excellence (MSCoE) and the Pharmacy Benefits Management (PBM) Services (https://www.pbm.va.gov/apps/VANationalFormulary) , including input from subject matter experts, recommendations and guidelines from the Multiple Sclerosis Coalition, the National Multiple Sclerosis Society and the American Academy of Neurology (AAN) Clinical Practice Guidelines. The content of this document is dynamic and revised as new information becomes available. The purpose of the document is to assist clinicians in clinical decision-making and improve the quality of patient care. The clinician will be expected to use and interpret the final version of this guidance in the clinical context of the individual patient using principles of shared decision-making. *(Prepared October 2020)*

VA

U.S. Department of Veterans Affairs

Veterans Health Administration
Multiple Sclerosis Centers of Excellence

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Multiple Sclerosis Disease Modifying Therapies (DMTs)

Injectable Medications

- glatiramer acetate (Copaxone®, Glatopa™)
- interferon beta-1a (Avonex®, Rebif®)
- peginterferon beta-1a (Plegridy®)
- interferon beta-1b (Betaseron®, Extavia®)
- ofatumumab (Kesimpta®)

Oral Medications

- cladribine (Mavenclad®)
- dimethyl fumarate (Tecfidera®)
- diroximel fumarate (Vumerity™)
- fingolimod (Gilenya®)
- monomethyl fumarate (Bafiertam™)
- teriflunomide (Aubagio®)
- ozanimod (Zeposia®)
- siponimod (Mayzent®)

Infused Medications

- alemtuzumab (Lemtrada™)
- natalizumab (Tysabri®)
- ocrelizumab (Ocrevus™)
- mitoxantrone (Novantrone®)

Injectable Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
glatiramer acetate *Copaxone®*, *Glatopa™* FDA approved for relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults Does not cross placenta; compatible with breast feeding. Used during pregnancy in women with active disease No washout recommended	20mg SC daily in prefilled syringe 40mg SC three times a week in prefilled syringe Autoinjector available (*Copaxone®* and *Glatopa™*) Storage: refrigerate- may be stored at room temperature for up to one month.	None Contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol	Immediate Post-Injection Reaction (flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, throat constriction, and/or urticaria), may occur within seconds to minutes after injection and are generally transient and self-limiting Lipoatrophy and skin necrosis Concerns: Cosmetic skin reactions	Immediate Post-Injection Reaction (flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, throat constriction, and/or urticaria), may occur within seconds to minutes after injection and are generally transient & self-limiting Chest pain Lipoatrophy and skin necrosis **Mitigation** Education r/t post injection reaction injection technique Use of autoinjector Rotation of injection sites	No long-term toxicity Injection technique and site rotation Monitor injection site reactions Lipoatrophy and skin necrosis

Injectable Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Interferons are FDA approved for relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease and active forms of secondary progressive disease. **Interferon beta-1a** *Avonex®* *Rebif®* **Peginterferon beta-1a** *Plegridy® SC*	IM 30mcg weekly (*Avonex®*) Prefilled pen Starter pack available with titrating first month dose SC 22mcg & 44mcg 3x/week (*Rebif®*) *Plegridy®* 125 mcg SC every two weeks Prefilled PEN injector or prefilled syring Starter pack available titrating dose For all INFb1a: Storage: Refrigerate; Do not freeze Protect from light May be at room temperature 7 days	Labs: CBC with diff, Chemistry with LFT at baseline and every 3 months for six months and then annually Monitor for liver dysfunction, anemia, leukopenia, thyroid dysfunction Injection site reactions for *Plegridy®*	Lyophilized contraindicated in hypersensitivity to albumin Hepatic Injury, Hematologic abnormalities (*Rebif®*) Concern for significant spasticity, hepatic disease, depression, injection site reactions, leukopenia Autoimmune thyroiditis/ hepatitis Contraindicated if allergy to interferon or human albumin or mannitol	Flu-like symptoms (muscle aches, headache, joint ache, fever, chills, fatigue) Depression Headache Muscle aches Elevated hepatic transaminases AST/ALT Decreased WBC Injection site reactions; skin necrosis Hematologic abnormalities Abdominal pain Risk > spasticity resulting in weakness	Depression, suicide, psychosis Hepatic injury Anaphylaxis and other allergic reaction CHF Seizure Decreased peripheral blood counts Other autoimmune disorders (autoimmune thyroiditis, autoimmune hepatitis)

Interferon beta continued next page

Injectable Medications

Interferon beta continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Interferon beta-1b *Betaseron®* *Extavia®* Crosses placenta in minimal quantities; unknown excretion in breast milk No washout recommended Should be used during pregnancy only if potential benefit justifies potential risk to the fetus	Interferon beta 1b: 0.25mg SC every other day Autoinjector and prefilled syringe Storage: No refrigeration necessary may be stored at room temperature	INFbeta1b Monitor for liver dysfunction, anemia, leukopenia, thyroid dysfunction, injection site reactions, depression Labs similar for all interferons	Lyophilized contraindicated in hypersensitivity to albumin Hepatic Injury Hematologic abnormalities (Rebif®) Concern for significant spasticity, hepatic disease, depression, injection site reactions, leukopenia Autoimmune thyroiditis/ hepatitis Contraindicated if allergy to interferon or human albumin or mannitol	**Mitigation:** NSAIDs; Hydration; Baseline headache; Screen and monitor for depression Pretreatment with NSAIDS and dose titration recommended Give at HS Rotate injection sites	Labs: Monitor for liver dysfunction, anemia, leukopenia, thyroid dysfunction at baseline, 3 months, 6 months, 12 months and then every12 months NABs (assess if disease breakthrough or infusion reaction

Injectable Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Ofatumumab *(Kesimpta®)* CD20-directed cytolytic antibody indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Pregnancy May cross placenta; No data on excretion in breast milk	Refrigerated subcutaneous injection- allow to come to room temperature 30 minutes before injection 20mg/0.4mL single dose Sensoready® pen or pre-filled syringe Loading dose: 20mg subcutaneous Week 0, 1, 2 Skip week 3 and then 20mg subcutaneous every month starting at week 4	Prior to first dose: Labs: Hepatitis B surface antigen; Hepatitis B core antibody ; hep B surface antibody; HIV; QuantiFERON- TB Gold; Hep C CBC & Diff; Chem with LFT JCVAB w/index VZV AB: Varicella zoster titers confirmed & if neg vaccinate w/ Varivax (2 doses, 4 weeks apart) Live and live attenuated vaccines given 4weeks prior to dose and inactivated vaccines given two weeks before ofatumumab injection	Contraindicated in active HBV infection –infections, including respiratory tract infections, UTI and potentially PML –hepatitis B reactivation Avoid live and live attenuated vaccines. Concern for HBV Infection Delay treatment in those with active infection Injection site reactions; systemic injection related reactions usually within 24h after the first injection	Most common adverse reactions (incidence greater than 10%) are upper respiratory tract infection, UTI, headache, back pain Systemic injection-related reactions, (fever, chills, headache, myalgias, fatigue) and local injection site reactions (redness, swelling, itching, pain)	Injection site reactions Injection related reactions PML Surveillance brain MRI at 6mo-12mo and prn Discontinue if low immunoglobulins, serious opportunistic infection or recurrent infections, or if prolonged hypogamma-globulinemia requires treatment with intravenous immunoglobulins.

Ofatumumab continued next page

Injectable Medications

Ofatumumab continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
May cause fetal harm based on animal studies Six-month washout advised before pregnancy Infants may have lymphopenia at birth	Missed doses: give injection as soon as possible and a following injection in one month First dose administered under healthcare supervision (possible mitigation of injection reaction)	Quantitative immunoglobulins G-M-A Monitor injection related reactions: fever, headache, myalgia, chills, fatigue up to 24h after initial injection.	Consider discontinuing in serious opportunistic infection or recurrent infections if immunoglobulin levels indicate immune compromise No carcinogenic studies	**Mitigation** First dose supervision; –injection site rotation; bring drug to room temperature –HBV testing –Ongoing monitoring for infection Little evidence for antihistamine, steroid or acetaminophen preinjection	Hepatitis monitoring Quantitative immunoglobulins a G-M-A at start, periodically and at conclusion of therapy May interfere with effectiveness of inactivated vaccines

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
cladribine *Mavenclad®* FDA approved for adults with relapsing forms of multiple sclerosis, to include relapsing-remitting disease and active secondary progressive disease. Because of its safety profile, use is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Avoid use in >65yrs	3.5mg/kg tablet divided into two yearly treatment courses. Each treatment course is divided into 2 treatment cycles. **Treatment course Year 1:** 1.75mg/kg; treatment course divided into two treatment cycles with second cycle separated by 23-27 days.	Pregnancy testing before each dose Cancer screen (cancer screening guidelines) **Contraindicated in HIV, current or prior malignancy, active infection (hepatitis, TB); hypersensitivity to cladribine** **Contraindicated in pregnancy and breastfeeding** Labs: CBC with diff. LFT (aminotransferase, alkaline phosphatase, bilirubin levels; QuantiFERON-TB Gold, Hepatitis B (Core Ag, Surface Ab, Surface Ag): Hep C; IgG VZV	**Black box** Risk of **malignancy** (pancreatic, melanoma, ovarian) **Teratogenicity:** birth defects Lymphopenia No live vaccinations Caution with blood transfusions: graft vs host dz. Hypersensitivity Infections: herpes zoster, pyelonephritis, hepatitis, TB, PML, hematologic toxicity **Separate administration from other oral drugs by at least 3 hours.**	Teratogenicity Malignancy Upper respiratory infection Headache Nausea Back pain Lymphopenia Neutropenia Anemia Herpes zoster infection Hypersensitivity Myocarditis (heart failure	Monitor for two years following last dose Lymphocyte count at least 800 cells/uL prior to receiving second dose CBC with diff. at 2mo and 6 mo. after starting treatment in each treatment course and for 24 months after final dose If lymphocyte count is<200cells/uL at two months monitor monthly for 6 months. Hold drug for lymphocyte count below 200 cells/uL

cladribine continued next page

Oral Medications

cladribine continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Pregnancy contraindicated in pregnancy and males and females of reproductive potential not using birth control; risk to fetal harm; may cause birth defects Should not be used during pregnancy and breastfeeding. May breastfeed 10 days after last dose. Males and females should use hormonal + barrier birth control during dosing and 4 weeks post dosing. Avoid pregnancy (males and females) for 6 months after each yearly treatment Washout: 6 months	**Treatment course Year 2:** Administered at least 43 weeks after last dose. Dosage form: 10mg tablet (round Kg weight to nearest 10.) If missed dose- do not double dose but resume and extend dosing day for missed day Take with or without food Separate dose from other drugs by 3 hours	Skin evaluation Evaluate for acute infection and hold drug until controlled Vaccinate for negative varicella zoster and hold first dosing for 4- 6 weeks. Brain MRI within 3 months of initial dose to r/o PML Pre brain MRI	Liver injury Cardiac failure Hold second dose cycle if lymphocyte count is below 800 cells/uL. If recovery takes > 6 months, drug should not continue Do not administer more than two treatment courses Delay dose for acute infection	**Mitigation** MRI to monitor PML Herpes prophylaxis for lymphocyte counts below 200 cell/uL Cytotoxic drug: Limit skin contact with pills- wash hands and surfaces exposed to medication.	Discontinue for elevated LFT five times upper limits of normal. CBC, LFT, Chem 7, Hepatitis B & C, TB at two months following treatment cycle and periodically or when clinically indicated Skin check annually PML Herpes zoster MRI q6m-year and then PRN

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
dimethyl fumarate *Tecfidera®* FDA approved for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing remitting disease and active secondary progressive disease, in adults Pregnancy: Unknown effects No washout before pregnancy Should be used during pregnancy only if the potential benefit justifies the potential	Forms: delayed release oral capsule Dose initiation 120 mg capsule bid 7 days then 240 mg cap bid as maintenance Manage SE by taking with high fat, high protein food; (although delays absorption)	CBC LFT (ALK, ASP, Tbili) JCV Ab Index Brain MRI	Contraindicated in known sensitivity Anaphylaxis and angioedema Lymphopenia Liver injury PML in presence of lymphopenia <9.0X109/L persisting > 6 months Herpes zoster Serious opportunistic infections Consider switch Tx. If JCV+ and Abs Lymph <0.7X108/L x 2 lab draws or if JCV- and Abs Lymphs <0.5X108/L x 2 labs Lymphocyte reconstitution may lag for many months after cessation	Flushing: with Pruritis, rash, erythema, Burning, warmth GI symptoms (abdominal pain, diarrhea, nausea) Lymphopenia PML **Mitigation** Flushing managed with non-enteric coated 325 mg ASA 30 min. prior to dosing or diphenhydramine elixir 12.5 mg PO at the time of the flush Take with high fat, high protein food Consider withholding treatment in cases of zoster Clinical and MRI for suspected PML	CBC including lymphocyte count (obtained prior to initiation of therapy and every 6 months to one year and then every 12 months LFT and serum creatinine Discontinued if WBC fall below 200/mm3 or lymph count < 500/uL persist >4weeks Monitor for signs/ symptoms of hypersensitivity, infections, PML MRI 6mo-12mo and then PRN

Similar class to diroximel fumerate and monomethyl fumerate

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
diroximel fumarate *Vumerity™* FDA approved for use in relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease and active secondary progressive disease in adults Pregnancy: Unknown effects No washout before pregnancy Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	Form: Delayed release capsule Dose initiation: 231mg capsule twice daily for 7 days then 462mg (administered as two 231mg capsules) twice daily Do not open, cut, crush or chew Avoid administration with high fat, high caloric meal (44% reduction in Cmax); decreases peak plasma concentration not absorption. Take with meal/food <700calorie Avoid administration with alcohol	CBC prior to start and 6 months from start and then every 6-12 months. JC Ab with Index Metabolic panel to include LFT (ALT, ALP, Tbili) 30% decrease in lymphocyte count in year one with dimethyl fumerate (DMF) MRI	Anaphylaxis, angioedema, lymphopenia PML (seen with lymph counts <0.8X109/L persisting >6 months in DMF Herpes zoster and other opportunistic infection Concern for lymphopenia and delayed recovery after dose cessation Liver injury Not recommended in moderate to severe kidney impairment	Flushing – 40% experience itching, burning, warmth, redness, rash GI symptoms (abdominal pain, diarrhea, nausea) Decrease in WBC PML **Mitigation** Flushing: non-enteric coated aspirin 30 min. prior to dose. At time of flush may use diphenhydramine elixir, 12.5mg/tsp. Administer with food	CBC including lymphocyte count (obtained prior to initiation of therapy and every 6 months for one year and then every 12 months LFT and serum creatinine Discontinued if WBC fall below 200/mm3 or lymph count < 500/uL persist >4weeks Monitor for signs/ symptoms of hypersensitivity, infections, PML MRI q6-12 mo and then PRN

Similar class to dimethyl fumerate and monomethyl fumerate

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
fingolimod *Gilenya®* Approved by FDA for treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in patients 10 years of age and older. Pregnancy: Risk for fetal harm Crosses placenta; excreted in breast milk Two-month washout before pregnancy due to prolonged drug elimination of 2 months	Form and dose: 0.5mg capsule daily If missed dose >14 days must repeat 6h observation with pre- post observation ECG	Varicella zoster titers confirmed and if negative vaccinate with Varivax (two doses, 4 weeks apart); hold fingolimod 6 weeks post vaccination CBC, Chemistry with LFT; JCV Ab VZV titers skin evaluation for those at increased risk for melanoma; Ophthalmology exam of macula r/t risk for macular edema (occurred 0.5% in clinical trial; incr. risk in diagnosis of DM and uveitis)	First dose bradycardia/ and or AV block; Caution in those taking beta blockers or calcium channel blockers Risk for infection fatal herpes simplex encephalitis and zoster and PML Risk of fatal cryptococcal meningitis Macular edema PFT (FEV1) Posterior reversible encephalopathy syndrome (PRES) Hepatic effects Elevated BP Concomitant use of ketoconazole may increase serum conc. by 1.7 fold	Headache Influenza Diarrhea Back pain Cough Hepatic enzymes Macular edema Bronchitis/ pneumonia Caution in asthma Hypertension **Mitigation** Cardiac events on first dose: ECG, FDO, cardiology consult for abnormal ECG Vaccination VZV negative serology	If discontinued >14d, first dose monitoring required due to effects on heart rate and AV conduction CBC with differential, chemistry with LFT every 3-6 month intervals DC if LFT >5X ULN Brain MRI q6-12mo and then PRN Ophthalmology exam of macula three to four months after dose initiation Contraception for 2 months after discontinuation

fingolimod *Gilenya®* continued next page
Similar class to siponimod and ozanimod

Oral Medications

fingolimod *Gilenya®* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus gilenyapregnancyregistry.com		First dose observation FDO w/ hourly pulse & BP for 6 hours w/ EKG prior and post monitoring; increase monitoring if prolonged QTc Pts. with bradycardia risk: Cardiology eval w/EKG monitoring for 24h HPV vaccine Brain MRI	Elimination can take up to 2 months post discontinuation – counsel contraception Discourage live vaccines Caution in asthma Increased risk of basal cell carcinoma Concern for: leukopenia, hepatic disease, macular edema, (incr. risk in diagnosis of DM and uveitis) VZV seronegativity; AV block, basal cell carcinoma, medications affecting cardiac conduction PML Severe incr. in clinical and radiological disability 12-24 wks. after stopping Risk for tumefactive MS lesion fatal		Dermatology monitoring of suspicious skin lesions Monitor signs of hepatic injury Risk of immune reconstitution syndrome following drug cessation

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
monomethyl fumarate *Bafiertam™* Dimethyl fumerate Biosimilar FDA approved for the treatment of relapsing forms of MS, to include clinically isolated syndrome. Relapsing-remitting disease, and active secondary progressive disease in adults Pregnancy: Unknown effects No washout before pregnancy Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	Delayed release capsules for oral use Dose initiation 95 mg capsule bid 7 days then 190mg capsule (administered as two 95mg) capsules twice a day extended-release- do not cut, crush or chew Take with or without food Delayed absorption with high fat meal	CBC prior to start and 6 months from start and then every 6-12 months. JC Ab with Index Metabolic panel to include LFT (ALT, ALP, Tbili) 30% decrease in lymphocyte count in year one with dimethyl fumerate (DMF) MRI	Allergic reaction Anaphylaxis and angioedema Lymphopenia If lymph counts <0.5X109/L And persist for 6 months, consider stopping drug. PML- mostly occurring with lymph counts <0.8X109/L Liver injury Herpes zoster and other opportunistic infection Contraindicated with other fumerate medications	Flushing GI symptoms (abdominal pain, diarrhea, nausea) flushing with itching, redness, rash Decrease in WBC PML **Mitigation** Flushing: non-enteric coated 325 mg ASA 30 min. prior to dose; diphenhydramine elixir 12.5mg/tsp PO at time of flush Take with high fat, high protein food Manage SE by taking with high fat, high protein food (will delay absorption); use of H1 & H2 blockers Administer with food	CBC including lymphocyte count (obtained prior to initiation of therapy and every 6 months LFT and serum creatinine Discontinued if WBC fall below 200/mm3 or lymph count < 500/uL persist >4weeks Monitor for signs/ symptoms of hypersensitivity, infections, PML

Similar class to dimethyl fumerate and diroximel fumerate

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
teriflunomide *Aubagio®* FDA approved for the treatment of patients with relapsing forms of multiple sclerosis to include clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, in adults. Pregnancy: known teratogenicity; Pregnancy is contraindicated; Crosses the placenta; unknown excretion in breast milk; rapid elimination before pregnancy to teriflunomide levels: 0.02ug/mL Men should stop teriflunomide (carried in seminal fluid- scant amounts found in blood of partner)	7mg or 14 mg tablet daily	No live virus vaccines **Risk for reactivation of TB** Screen TB T-spot ; QuantiFERON- TB Gold; CMP LFT (transaminase, bilirubin) CBC Pregnancy testing Assess for effective birth control for males and females Blood pressure Do not initiate if acute or chronic infection	**Black box** **Severe liver injury/ failure** **Hepatotoxicity** **Risk of teratogenicity** decrease neutrophils, lymphocyte, platelets risk of infection, including TB risk malignancy acute renal failure HTN Stevens-Johnson Syndrome renal uric acid clearance incr. K+ peripheral neuropathy Concern for hepatic disease, leukopenia, hypertension, history of TB, short-term plans for pregnancy	ALT elevation Alopecia Diarrhea Influenza Nausea Paresthesia Headache Hypertension **Mitigation** Ensure contraception Accelerated elimination: cholestyramine 8mg TID x 11 days Check leflunomide levels (0.02mcg/mL)	LFT at baseline and every month for six months DC if LFT 2X ULN or pregnancy Pregnancy monitoring for 2 years after discontinuation Ensure reliable birth control Pregnancy registry 1-800-745-4447 Accelerated drug elimination with cholestyramine 8G q8h for 11 days No requirement for accelerated elimination when switching DMT Skin rash Blood pressure

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
ozanimod *Zeposia®* FDA approved for relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses) in adults. Pregnancy: may cause fetal harm; crosses placenta; excreted in breast milk Avoid pregnancy during tx and for three months after stopping tx. 3 month washout after stopping drug	Form: oral capsule Initial titration: Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily Day 8 and thereafter: 0.92 mg once daily (Titration mitigates bradycardia and negates need for first dose monitoring) Maintenance dose: 0.92mg capsule once daily	CBC LFT (ALT, AST, Tbili); VZV titer; JCV Ab Cardiac evaluation and blood pressure **Contraindicated** in AV block; Hx MI, CVA, heart failure; severe OSA; use of MAOI Ophthalmologic evaluation of the fundus and macula Vaccination varicella zoster Wait one month before dosing after VZV vaccination and live attenuated vaccines	Macular edema Bradyarrhythmia AV conduction delays Risk for infection- decrease in peripheral lymphocytes (45% from baseline) Herpes viral infection Cryptococcal infection PML PRES Discontinuation may take up to 3 months Avoid use of attenuated vaccines for 3 months post discontinuation	URI; increase in LFT; orthostatic hypotension; UTI; low back pain; HTN Zoster reactivation Increased transaminase Respiratory effects: dyspnea; decrease in FEV1 **Mitigation** Peripheral blood lymph return to normal in 30 days- adding immune suppressant within 30 day time may have additive effect on immune sx Neuro exam and MRI if suspect PRES or PML-DC drug	CBC. LFT every 3-6 month intervals Discontinue if LFT 5X upper limits of normal Brain MRI annually Continue monitoring for infection up to 3 months from discontinuation of drug Ophthalmic exam for any change in vision- Incr risk visual changes in diabetic and uveitis pts Dyspnea Use of effective contraception for 3 months after stopping drug

ozanimod *Zeposia®* continued next page
Similar class to fingolimod and siponimod

Oral Medications

ozanimod *Zeposia®* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	Treatment interruption: If within first two week- begin with titration schedule If missed doses after two-week initiation, continue with treatment as planned	Assess Pulmonary function (PFT) Delay dose in those with active infection Baseline skin exam	Increased sensitivity to tyramine Severe HTN with foods containing high amounts of tyramine Severe disability after stopping tx.; disease rebound Decline in FEV1 Not recommended after ts with alemtuzumab	Evaluate labs (CBC; LFT) at baseline and Q 3 months	Annual melanoma check Increased risk of disability with stopping

Oral Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
siponimod *Mayzent®* FDA approved for relapsing forms of multiple sclerosis, which include clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses). Pregnancy:may cause fetal harm; crosses placenta; excreted in breast milk 10-day washout after stopping drug	Before tx: Assess CYCP2C9 genotype Oral daily tablet Five-day treatment titration with Starter Pack (Day 1: 0.25 mg; Day 2: 0.25 mg; Day 3: 0.5 mg; Day 4: 0.75 mg; Day 5: 1.25 mg) If one dose is missed, restart the titration to Day 1. Day 6: 2mg tablet po daily = maintenance dose	Test for CYP2C9 genotype **Contraindicated:** CYP2C9*3/3* genotype. **Contraindicated** in AV block; Hx MI, CVA, heart failure; betablocker use Ophthalmologic evaluation of the fundus and macula Cardiac evaluation (ECG) and blood pressure; BP Dose titration First dose observation (e.g. Fingolimod) only for preexisting CVD after consult to cardiology	Contraindications: CYP2C9*3/3* genotype; If in past 6 months experienced MI, stroke, TIA, unstable angina, decompensated heart failure requiring hospitalization or Class III/ IV heart failure Rare posterior reversible encephalopathy syndrome (PRES) Macular edema Bradyarrhythmia AV conduction delays	URI; zoster reactivation Headache GI: nausea, diarrhea Dizziness Hypertension Initial dosing bradycardia Macular edema (within first 4 months post dose) Elevated LFT: transaminase Evaluate labs (CBC; LFT) at baseline and q 3 months Increased infection Convulsions	No need for continued ophthalmologic monitoring CBC, LFT every 3-6 month intervals and then annual Discontinue if LFT 5X upper limits of normal Brain MRI annually Annual melanoma ck HTN Risk for incr disability with stopping Annual JCV Ab

siponimod *Mayzent®* continued next page

Similar class to ozonimod and fingolimod

Oral Medications

siponimod *Mayzent®* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus	If >4 days are missed during maintenance, restart dose titration and monitoring precautions	Zoster vaccine: wait one month before dosing after VZV vaccination. Assess Pulmonary function (PFT) Labs: CBC; LFT (transaminases and bilirubin levels); VZV Titer; JCV Ab Baseline skin exam	Infection- decrease in peripheral lymphocytes (cryptococcal, herpes virus, PML) Risk for disease rebound after stopping	**Mitigation** Peripheral blood lymph return to normal in 30 days–adding immune suppressant within 30 day time may have additive effect on immune sx Neuro exam and MRI if suspect PRES or PML-DC drug	Annual melanoma ck Increased risk of disability with stopping

Similar class to ozonimod and fingolimod

Infused Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
alemtuzumab *Lemtrada™* FDA approved for treatment of relapsing forms of multiple sclerosis, to include relapsing remitting disease and active secondary progressive disease, in adults. Because of safety profile, the FDA recommends that this medication generally be reserved for people who have had an inadequate response to two or more MS therapies. Pregnancy: Crosses the placenta; unknown excretion in breast milk Washout 6 months prior to pregnancy	Cycle 1: 12mg/day IV for 5 consecutive days 12 month later- Cycle 2: 12mg/day IV for 3 consecutive days. As needed: 12mg/d for 3 days at least 12 mo from last dose Pre-medicate: 1000 mg IV Methylprednisolone; 50mg tablet or IV diphenhydramine	REMS program enrollment Screen for infection: Hepatitis B & C; TB; VZV prior to treatment CBC w/ diff, serum creatinine, LFT; urinalysis (measure urine protein to creatinine ratio); TSH; QuantiFERON-TB Gold; Hep B (Core Ab, Sur-face Ab, Surface Ag); Hep C Ab; Pap for HPV Skin exam-melanoma; Brain MRI; Varicella zoster titers confirmed & if neg vaccinate w/ Varivax (2 doses, 4 wks apart); hold alemtuzumab until 6 wks post vaccine	**May cause serious, sometimes fatal, autoimmunity, infusion reactions, stroke and malignancies** Black box warning: risk for autoimmunity, (immune thrombocytopenia, antiglomerular basement membrane disease) life-threatening infusion reactions, malignancy, (melanoma, thyroid cancer, lymphoproliferative diseases) Life-threatening stroke reported within 3 days of dose	Infusion reaction and anaphylaxis: (skin rash, fever, headache, muscle aches, reoccurrence of previous neurological symptoms) **monitor for 2 hours post infusion** (warn patients infusion reaction can occur after monitoring period up to 24h) Risk for malignancy: thyroid cancer, melanoma, lympho-proliferative disorders Stroke and cervicocephalic arterial dissection up to 3 days after infusion	Monitor CBC with differential, serum creatinine, LFT (ALT, AST, Tbili), urine analysis monthly for **48 months** after last infusion; TSH every 3 months until 48 months post infusion; Annual skin exam; Annual MRI brain Serious infections include: appendicitis, gastroenteritis, pneumonia. CNS herpetic infections, dental infections, listeria meningitis; HPV PML

alemtuzumab *Lemtrada™* continued next page

Infused Medications

alemtuzumab *Lemtrada™* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Should be used in pregnancy only if potential benefit justifies risk to the fetus	Three to five days; herpes antiviral prophylaxis on day one and for two months or until CD4+ lymph count is >200 cells/mL Three days prior to dosing give 150mg ranitidine PO bid; 10mg cetirizine PO daily; 650mg acetaminophen tablet daily Ibuprofen 800mg headache Brain MRI Observation 2h post dose	Educate on stroke and cervicocephalic symptoms and to seek immediate medical attention	Available through REMS No live vaccines Listeria precautions–CDC.gov\listeria\prevention Concern for thyroid disease	**Mitigation:** Prophylaxis before infusion; viral prophylaxis until CD4 count >200/ cubic mm Listeria precautions prior to dosing (infections occurred 3days to 8months post infusion) -no established criteria post dose	Autoimmune hepatitis (sx.: N&V, abdominal pain, fatigue, anorexia, jaundice) MRI q 6mo-year and then PRN Annual screen: skin exam; HPV;TB

Infused Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
natalizumab *Tysabri ®* FDA approved as monotherapy for the treatment of relapsing forms of multiple sclerosis, which include clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses) Pregnancy: Crosses the placenta; is excreted in breast milk No washout recommended prior to pregnancy due to risk of first trimester relapse	Intravenous infusion of 300mg in 100mL NaCl over 1 hour, followed by 1 hour monitoring every 4 weeks. New evidence for efficacy of extended dosing to 6-8 weeks between infusions Drug must be given within one hour of reconstitution or may be refrigerated up to 8 hrs.	REMS Program enrollment: TYSABRI TOUCH prescribing program for pt., provider and pharmacist JCV Ab testing Brain MRI CBC with diff Chemistry to include LFT Brain MRI Skin check – melanoma	PML (cognitive and personality change; hemiparesis; change in vision) Other infections -Antibody formation -Melanoma -Hepatic injury -Herpes encephalitis meningitis -Hypersensitivities Black Box warning (PML risk) Concern hepatotoxicity history of immunosuppression, JCV positivity, prolonged use longer than 2 years	-Headache -Fatigue -UTI -arthralgia -Lower respiratory infection -Urticaria -Vaginitis -Gastroenteritis -Depression -Diarrhea **Mitigation** Monitor infusion JCV AB testing every 6 months with prior immunosuppression or index >1.5, limit infusions to 24 mo. unless overwhelming evidence to continue	Assess risk for developing PML: tx duration >2yr; JCV AB+; prior chemotherapy use JCV AB every 3-6 months and at 6 months post dosing Brain MRI w/o GD every 3-6 months in JCV AB + patients and annually in JCV AB-, Hypersensitivity reactions during dosing and 1 hr. following Suspected cases of PML- GD enhanced brain MRI and when indicated CSF for JC viral DNA CBC; Chemistry; LFT prior to each dose for one year

natalizumab *Tysabri®* continued next page

Infused Medications

natalizumab *Tysabri®* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus			Risk for clinical and radiological worsening following stop of drug (IRIS risk)		– Hypersensitivity; antibody 60% develop NABS Baseline and monthly hepatic function Skin check annually

Infused Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Ocrelizumab *Ocrevus™* FDA approved for the treatment of relapsing forms of multiple sclerosis in adults, which include clinically isolated syndrome, relapsing-remitting disease (RRMS) and active secondary progressive disease (SPMS with relapses). Ocrevus is also approved by the FDA to treat primary progressive MS in adults. Pregnancy Crosses placenta; likely excretion in breast milk *ofatumumab Kesmita®*	Initial dose 300mg IV on day one and day 15. Maintenance dose: 600mg IV every 6 months Premedication: 30-60 min prior to infusion 100 mg IV methylprednisilone 50 mg PO or IV push diphenhydramine 1000 mg Acetaminophen	Labs: -Hepatitis B surface antigen -Hepatitis B core -Hep B surface antibody -HIV -QuantiFERON-TB Gold -CBC & Diff -Chem with LFT -JCVAB w/index VZV AB: Varicella zoster titers confirmed & if neg vaccinate w/ Varivax (2 doses, 4 weeks apart); hold ocrelizumab until 6 weeks post vaccine Quantitative immunoglobulins G-M-A	-Infections, including respiratory tract infections, herpes and potentially PML -Hepatitis B reactivation -Possible increased immunosuppressive effect if immunosuppressant used prior to or after ocrelizumab -Administer all vaccinations at least 6 weeks prior to administration of ocrelizumab; no live-attenuated or live vaccines during treatment and until B-cell repletion	Infusion reactions (potentially life-threatening) -Infections : URI, herpes, PML, Hep B reactivation Depression back pain extremity pain Possible increased risk of malignancies elevated LFT **Mitigation** Premedication monitoring HBV testing Ongoing monitoring for infection	Prior to next dosing: repeat hepatitis and QuantiFERON- TB; LFT; CBC with diff PML Hold dose for infection Tell patients that infusion reactions can occur up to 24 hours after infusion Hepatitis monitoring Reactivation HepB Surveillance brain MRI at 6mo-12mo and prn Herpes infection Standard malignancy screen

Ocrelizumab *Ocrevus™* continued next page

Similar class to rituximab and ofatumumab

Infused Medications

natalizumab *Tysabri®* continued

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Six-month washout advised before pregnancy No adequate data on fetal developmental risks in pregnant women	Ofatumumab: 20mg subcutaneous injection monthly. Start 20mg at week 0, week 1, week 2 and week 4 and then monthly	Premedication and observation period **Infusion reaction;** (pruritis, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, tachycardia Cancer screen Infusion reaction can occur up to 24h post dose –	B cell suppression 96 weeks; 9% have early reconstitution before 6 months Risk for herpes infection Acute retinal necrosis malignancies Concern for HBV Infection Delay treatment in those with active infection Contraindicated in those with active Hepatitis B virus and history of life-threatening infusion reactions risk for hypogammaglobulinemia	Ofatumumab: injection site reactions; injection reaction; URI, headache	Quantitative immunoglobulins annually G-M-A

Infused Medications

Drug, indication & pregnancy statement	Administration & dosage forms/ storage	Drug Start Requirements	Warnings & precautions	Common side effects & mitigation strategies	Ongoing monitoring
Mitoxantrone *Novantrone®* FDA Approved for treatment in secondary progressive MS, progressive-relapsing MS and worsening relapsing-remitting MS Pregnancy: Teratogenicity Should not be used in pregnancy Pregnancy should be avoided Crosses the placenta in limited amounts; is excreted in breast milk; Six-month washout before pregnancy	12mg/m2 IV every three months; Cumulative dose no >140mg/m2	CBC, Metabolic panel with LFTs; urinalysis Baseline LVEF by MUGA and prior to each dose	Cardiac toxicity Decrease in LVEF CHF Acute myelogenous leukemia Myelosuppression **Black box warning for cardiotoxity and secondary leukemias** Concern for cardiac disease neutropenia less than 1,500cell/mm^3 Contraindicated in LVEF<50%; hepatic impairment Immunosuppression Pulmonary fibrosis	Alopecia Rash Cardiac toxicity Abnormal EKG CHF Temporary blue discoloration of urine and sclera Nausea, alopecia, amenorrhea and infertility Infection (URI, UTI, stomatitis) **Mitigation** Hydration Close monitoring of labs and clinical LVEF follow-up to monitor CHF	CBC with diff; LFT; monitor injection site for extravasation LVEF by MUGA prior to each dose Life-long annual LVEF to monitor for CHF following discontinuation of therapy

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