1. **REASON FOR ISSUE:** This Multiple Sclerosis Centers of Excellence (MSCoE) Consensus Statement addresses Clinically Isolated Syndrome, Relapses, Pseudo relapses, and Disease management of veterans with multiple sclerosis (MS).

2. **SUMMARY OF MAJOR CHANGES:** This is a new Consensus Statement.

3. **RELATED ISSUES:** VHA Directive1011.06 and MSCoE Program Guide.

4. **RESPONSIBLE OFFICE:** The Directors of the MSCoE are responsible for the contents of this Consensus Statement. Questions may be referred to the MSCoE.

5. **RESCISSIONS:** None.

6. **REVIEW:** This MS COE Consensus Statement is scheduled for review every two years, or earlier in case of major practice or medication changes.

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MULTIPLE SCLEROSIS SYSTEM OF CARE PROCEDURES

1. PURPOSE: This Multiple Sclerosis Centers of Excellence (MSCoE) Consensus Statement provides guidance to VA providers on MS relapse and disease management for Veterans with MS.

2. BACKGROUND: The MSCoE were established in 2003 with a mandate to establish a national network for the care of Veterans with MS. As part of that mandate, the MSCoE have developed consensus statements to assist VA providers caring for Veterans with MS. MS is a unique disease in the VA system due to its onset in young adulthood and common connection with military service. MS can be difficult to diagnose due to its variable presentations. It is also challenging to manage due to its dynamic and unpredictable course, progressive nature, variable symptoms, required monitoring, costly and potentially high risk treatments and its radically changing face over the 4 to 5-decade course of the disease. To adequately care for Veterans with MS requires a multidisciplinary team, including neurologists, physiatrists, internists, primary care providers, nurses, occupational therapists, physical therapists, psychologists, recreation therapists, social workers, urologists, vocational counselors and other providers who are knowledgeable about the care of MS.

3. SCOPE: This Consensus Statement is a document that presents the current MSCoE opinion on treatment approaches which may be used in MS relapse and disease management throughout the Regional and Support Programs of the MSCoE Network. Note that not all approved Food and Drug Administration (FDA) treatments in use in the community are discussed.

4. MANAGEMENT OF CLINICALLY ISOLATED SYNDROME:
   a. Definition of clinically isolated syndrome (CIS): A term that describes symptoms of a typical MS relapse in a person not previously diagnosed with MS.
   b. CIS is diagnosed after a single episode of neurological symptom(s) indicative of demyelinating or inflammatory disease of the brain or spinal cord. Symptoms of CIS may be monofocal (e.g. optic neuritis), or multifocal (e.g. optic neuritis plus unilateral weakness).
   c. Persons with CIS may not go on to develop MS. If lesions seen on MRI brain are similar to MS, there is a high risk of conversion to MS.
   d. Persons with CIS who start on a disease modifying therapy (DMT) may delay or prevent a second neurological episode or minimize future disability. Several DMTs are now FDA-approved for CIS: glatiramer, interferon beta-1a intramuscular (IM) and interferon beta-1b subcutaneous (SC).
5. MANAGEMENT OF MS RELAPSES:

a. **Definition of relapse:** A relapse is the acute appearance of at least one neurological symptom that is present for more than 24 hours in the absence of fever, infection, other significant physiological stress or severe psychological distress.

b. **Pseudo-relapse:** A pseudo-relapse is new or worsening neurological symptoms associated with a trigger such as infection, elevated or low body temperature, pain, fatigue, trauma, menses or other stressors. The symptoms are not related to increased disease activity or progression of disease. Pseudo-relapses should be ruled out in patients with acute neurological symptoms. Symptoms resolve with treatment of the underlying cause.

c. **Determining if a relapse requires treatment:** Relapse treatment has not been shown to alter the long-term course of MS but only to shorten recovery time. Treatment is not indicated for every incident. Potential benefits must be weighed against potential adverse effects. Relapses with significant disability, such as ambulation impairment or loss of vision, usually warrant treatment. Relapses with little or no disability (e.g. sensory loss or myokymia) may not warrant treatment. Factors such as prior adverse reactions to corticosteroids should also influence the decision as to whether treatment should be given.

d. **Relapse treatment:** The standard treatment for relapses associated with significant disability is a short course of intravenous (IV) or oral corticosteroids.

   A. **Intravenous corticosteroid treatment.** Intravenous treatment remains the most widely used route for corticosteroid administration in acute relapses. The most common regimens are:

      • 1,000 mg of intravenous methylprednisolone (IV MP) daily for 3 to 5 days.
      
      • Intravenous dexamethasone (Decadron) may be used in place of IV MP at 160-180 mg/day for 3 to 5 days.

   Intravenous steroids may be administered in several settings, including a VA Medical Center (VAMC), Community Based Outpatient Clinic (CBOC), non-VA infusion center or the Veteran’s home.

   B. **Oral corticosteroid treatment.** A growing body of evidence supports the safety and efficacy of the use of an equivalent dose of oral prednisone. Studies indicate no difference in response between oral and IV routes. The primary limitation in the use of oral treatment at present is that large number of pills is required using current formulations of prednisone.

      • Oral equivalent of 1,000 mg IV methylprednisolone is 1,250 mg prednisone/day in two divided doses (625 mg dose in a.m. and 625 mg dose in p.m.).
      
      • Prednisone 50 mg form: Take 12½ tabs/dose.
      
      • Prednisone 20 mg form: Take 31¼ tabs/dose.
• Omeprazole or similar medication is helpful to increase gastric tolerance.

Insomnia is a common side effect of steroid treatment, and a sedative medication may be indicated. Monitor glucose in diabetics and those at high risk of diabetes. High-dose steroid treatment, whether IV or oral, may be followed by a short oral steroid taper, although there is no clear evidence that this taper is necessary or beneficial.

C. Plasma exchange. For severe MS relapses, plasma exchange may be considered.

Treatment of a relapse does not affect the long-term course of MS. Response may be seen within a few days, but may take longer. There is no significant difference in the degree of remission at 1 year between those who did and did not receive treatment. Depending on degree of residual impairment, rehabilitation may be helpful.

6. MANAGEMENT OF MULTIPLE SCLEROSIS DISEASE PROCESS:
   a. Relapsing forms of MS: The goals of disease modification in relapsing MS are to reduce the frequency of relapses, reduce occurrence of new lesions and slow disease progression.

   A. Disease-modifying therapies (DMTs) for relapsing MS.
   • Reduce rate of relapses.
   • May slow rate of disease progression.
   • Will not restore lost function.
   • Are not recommended for women who are pregnant or plan to become pregnant.
   • Most are not FDA-approved for progressive forms of MS with relapses. Mitoxantrone is FDA-approved for SPMS; however, it has a significant risk profile in addition to requiring lifetime follow-up monitoring. It is rarely used in current practice.

   b. Primary progressive MS (PPMS): The goal of MS disease modification in PPMS is to reduce the rate of disease progression. Currently only one DMT, ocrelizumab, is FDA-approved for PPMS.

7. CONSIDERATIONS FOR DISEASE MODIFYING THERAPY (DMT) USE:
   a. General considerations for DMT use:
   • Appropriate candidates for DMTs should start as early as possible after diagnosis.
   • DMT use for relapsing forms of MS is not limited by age, relapse frequency or disability level.
b. **Considerations for specific DMT selection:**
   - Aggressiveness of disease.
   - DMT risk/benefit profile.
   - Veteran preference for specific dosing route (injection vs. oral) and/or frequency.
   - Likelihood of adherence to dosing frequency and recommended monitoring.
   - Prior DMTs used, if any.
   - Relevant comorbidities.

c. **DMT choices:**
   A. **Injectable (SC or IM) DMTs.**
      - Daclizumab (Zinbryta SC)
      - Glatiramer (Copaxone SC, Glatopa SC)
      - Interferon beta 1-a (Avonex IM, Rebif SC, Plegridy SC)
      - Interferon beta 1-b (Betaseron SC, Extavia SC)
   B. **Oral DMTs.**
      - Dimethyl fumarate (Tecfidera)
      - Fingolimod (Gilenya)
      - Teriflunomide (Aubagio)
   C. **Infusion DMTs.**
      - Alemtuzumab (Lemtrada)
      - Natalizumab (Tysabri)
      - Novantrone (Mitoxantrone)
      - Ocrelizumab (Ocrevus)

d. **VHA Pharmacy Benefits Management guidance:**
INJECTABLE DMTS

a. **Daclizumab (Zinbryta):**

**Mechanism of Action (MoA):** Unknown. Daclizumab is an interleukin-2 receptor blocking antibody. It modulates IL-2 mediated activation of lymphocytes through binding to CD25, a subunit of the high-affinity IL-2 receptor (IL-2R). Daclizumab is theorized to bind to the alpha subunit (DC25) of the IL-2R expressed on activated T lymphocytes, thereby preventing interaction of IL-2 with its high-affinity receptor. This inhibits activation of CNS antigen-experienced proinflammatory activated T lymphocytes.

**Indications:** Relapsing forms of MS. Because of its safety profile, daclizumab should generally be reserved for patients who have had an inadequate response to two or more other DMTs.

**Dosing and Administration:** 150 mg/mL SC once monthly.

**Contraindications:** Pre-existing hepatic disease or hepatic impairment, including alanine aminotransferase (ALT) or aspartate transaminase (AST) at least twice the upper limit of normal (ULN). History of autoimmune hepatitis or other autoimmune condition involving the liver. History of hypersensitivity to daclizumab or any other component of the formulation.

“**Black Box**” **Warning:** Severe liver injury including liver failure and autoimmune hepatitis. Immune-mediated disorders including skin reactions and lymphadenopathy. These conditions may require treatment with systemic corticosteroids or immunosuppressive medication. Has a Risk Evaluation and Mitigation Strategy (REMS) program.

**Warnings and Precautions:**

**Vaccines:** Patients without a documented history of varicella zoster virus infection or vaccination against it should be evaluated for vaccination against varicella prior to daclizumab initiation. Zostavax should not be used in these individuals. Patients should be vaccinated with the live varicella virus product (Varivax). Daclizumab therapy should not be initiated for 6 weeks after the two doses of Varivax are completed.

**Hypersensitivity reactions:** Risk of anaphylaxis and angioedema. Discontinue and do not re-start if anaphylaxis or other allergic reactions occur.

**Infections:** Increased risk of infections. If serious infection develops, consider withholding until infection resolves.

**Depression and suicide:** Advise patients to immediately report symptoms of depression or suicidal ideation to their health care provider. Consider discontinuation if severe depression or suicidal ideation occur.

**Adverse Reactions:** Nasopharyngitis (upper respiratory tract infection); rash; influenza; dermatitis; oropharyngeal pain; bronchitis; eczema; lymphadenopathy; depression; pharyngitis; ALT.
Monitoring:
Baseline: ALT, AST and total bilirubin levels; screening Hepatitis B and C panels; PPD or Quantiferon TB gold test. Patients testing positive for TB should be treated prior to initiating daclizumab. Because vaccination with live vaccines is not recommended during treatment and up to 4 months after discontinuation of treatment, consider and initiate immunization with live vaccines prior to treatment.
Ongoing: ALT, AST; total bilirubin monthly prior to next dose. Ongoing evaluation for depression and suicidal ideation during therapy.
After Discharge: ALT, AST; total bilirubin monthly for 6 months.

Pregnancy: No data on risk in humans. Primate exposure resulted in embryo/fetal death and reduced fetal growth when exposed to dose 30x that expected clinically. Exposure during organogenesis produced highest risk.

Lactation: No data on risk in humans; not recommended.

Drug Interactions: Caution when using hepatotoxic drugs including over-the-counter (OTC), herbal and supplements when used concomitantly.

VHA Criteria for Use (CFU): Yes.
VHA Drug Monograph: Yes.

b. Glatiramer (Copaxone, Glatopa):
MoA: Unknown. Glatiramer is theorized to inhibit antigen-presenting cells which promotes shift to anti-inflammatory Th2 T cells in peripheral circulation.

Indications: CIS, RRMS.

Dosing and Administration: 20 mg SC daily or 40 mg SC 3x week.

Titration: None.

Contraindications: Known hypersensitivity to glatiramer acetate or mannitol.

Warnings and Precautions: Immediate post-injection reaction: flushing; chest pain; palpitations; anxiety; dyspnea; throat constriction; urticaria (generally transient and self-limiting). Chest pain (usually transient). Lipoatrophy and skin necrosis may occur. Instruct patients on proper injection technique and to rotate injection sites.

Adverse Reactions:
20 mg/mL: Injection site reactions; vasodilatation; rash; dyspnea; chest pain.
40 mg/mL: Injection site reactions.

Monitoring:
Baseline: MRI brain (within 6 months); Labs: None.
Ongoing: Labs: None.

Pregnancy: Category B.
c. **Interferon Beta-1a, IM (Avonex):**

**MOA:** Unknown. Interferon beta-1a is theorized to down-regulate proinflammatory cytokines, decrease major histocompatibility antigens and reduce T-lymphocyte passage across the blood-brain-barrier (BBB).

**Indications:** CIS, relapsing forms of MS.

**Dosing and Administration:** 30 mcg IM weekly.

**Titration:** Start 7.5 mcg IM weekly for one week, then increase by 7.5 mcg/week every week until 30 mcg.

**Contraindications:** History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation.

**Warnings and Precautions:**

**Depression, suicide and psychotic disorders:** Advise patients to immediately report any symptoms of depression, suicidal ideation and/or psychosis. Consider discontinuation if depression occurs.

**Hepatic injury:** Monitor liver function tests, monitor patients for signs and symptoms of hepatic injury and consider discontinuation if hepatic injury occurs.

**Anaphylaxis and other allergic reactions:** Discontinue use.

Monitor patients with preexisting significant cardiac disease for worsening of cardiac symptoms.

**Decreased peripheral blood counts:** Monitor complete blood count (CBC).

**Autoimmune disorders:** Consider discontinuation if new autoimmune disorder occurs.

**Adverse Reactions:** Flu-like symptoms including chills; fever; myalgia; asthenia. Prophylactic use of analgesics and/or antipyretics may reduce flu-like symptoms.

**Monitoring:**

**Baseline:** MRI brain (within 6 months); CBC with differential; LFTs; TSH.

**Ongoing:** CBC with differential; liver function test (LFT) at every 1, 2, 3, 6 months; then every 6 months. Thyroid stimulating hormone (TSH) 3 to 6 months; 12 months; then yearly.

If insufficient disease control, check for neutralizing interferon antibodies (NAbs) at 12 and 24 months.

**Pregnancy:** Category C.
**Lactation:** Unknown.

**Drug Interactions:** None known.

**VHA CFU:** No.

**VHA Drug Monograph:** No.

d. **Interferon Beta-1a, Pegylated, SC (Plegridy):**

**MoA:** Unknown. Interferon beta-1a pegylated is theorized to work by the same MoA as the non-pegylated form. Pegylation results in longer effective half-life and, thus, extended dosing intervals. Also, reduces formation of NAbs.

**Indications:** Relapsing forms of MS.

**Dosing and Administration:** 125 mcg SC every 2 weeks.

**Titration:** Start ½ dose on day 1; ¾ dose on day 15; 125 mcg SC (i.e. full dose) on day 29; and every 2 weeks thereafter.

**Contraindications:** History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation.

**Warnings and Precautions:**

- **Depression, suicide and psychotic disorders:** Advise patients to immediately report any symptoms of depression, suicidal ideation and/or psychosis; consider discontinuation if depression occurs.

- **Hepatic injury:** Monitor liver function tests, monitor patients for signs and symptoms of hepatic injury and consider discontinuation if hepatic injury occurs.

- **Anaphylaxis and other allergic reactions:** Discontinue use. Monitor patients with preexisting significant cardiac disease for worsening of cardiac symptoms.

- **Decreased peripheral blood counts:** Monitor CBC.

- **Autoimmune disorders:** Consider discontinuation if new autoimmune disorder occurs.

- **Injection site reactions including necrosis:** Do not administer into affected area until fully healed. If multiple lesions occur, discontinue until skin lesions heal.

**Adverse Reactions:** Flu-like symptoms including chills; fever; myalgia; asthenia. Prophylactic use of analgesics and/or antipyretics may reduce flu-like symptoms.

**Monitoring:**

- **Baseline:** MRI brain (within 6 months); CBC with differentials; LFTs; TSH.

- **Ongoing:** CBC with differentials; LFT at every 1, 2, 3, 6 months; then every 6 months. TSH 3-6 months; 12 months; then yearly.

If insufficient disease control, check for NAbs at 12 and 24 months.

**Pregnancy:** Category C.

**Lactation:** Unknown.
Drug Interactions: None known.

VHA CFU: No.

VHA Drug Monograph: Yes.

e. **Interferon Beta-1a, SC (Rebif):**

- **MoA:** Unknown. Interferon beta-1a is theorized to down-regulate proinflammatory cytokines, decrease major histocompatibility antigens and reduce T-lymphocyte passage across the BBB.

- **Indications:** Relapsing forms of MS.

- **Dosing and Administration:** 44 mcg SC 3x week.

- **Titration:** Start 8.8 mcg SC 3x/week for 2 weeks; then 22 mcg SC 3x/week for 2 weeks; then 44 mcg SC 3x/week thereafter. Alternatively: Start 4.4 mcg SC 3x/week for 2 weeks; then 11 mcg SC 3x/week for 2 weeks; then 22 mcg SC 3x/week thereafter.

- **Contraindications:** History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation.

- **Warnings and Precautions:**
  - **Depression, suicide and psychotic disorders:** Advise patients to immediately report any symptoms of depression, suicidal ideation and/or psychosis. Consider discontinuation if depression occurs.
  - **Hepatic injury:** Monitor liver function tests, monitor patients for signs and symptoms of hepatic injury and consider discontinuation if hepatic injury occurs.
  - **Anaphylaxis and other allergic reactions:** Discontinue use. Monitor patients with preexisting significant cardiac disease for worsening of cardiac symptoms.
  - **Decreased peripheral blood counts:** Monitor CBC.
  - **Autoimmune disorders:** Consider discontinuation if new autoimmune disorder occurs.
  - **Injection site reactions including necrosis:** Do not administer into affected area until fully healed. If multiple lesions occur, discontinue until skin lesions heal.

- **Adverse Reactions:** Injection site disorders; influenza-like symptoms; abdominal pain; depression; elevation of liver enzymes; hematologic abnormalities. Prophylactic use of analgesics and/or antipyretics may reduce flu-like symptoms.

- **Monitoring:**
  - **Baseline:** MRI brain (within 6 months); CBC with differential; LFT; TSH.
  - **Ongoing:** CBC with differential; LFT 1, 2, 3, 6 months; then every 6 months. TSH 3 to 6 months; 12 months; then yearly.

  If insufficient disease control, check for NAbs at 12 and 24 months.
Pregnancy: Category C.
Lactation: Unknown.
Drug Interactions: None known.
VHA CFU: No.
VHA Drug Monograph: No.

f. Interferon Beta-1b, SC (Betaseron, Extavia):
MoA: Unknown. Interferon beta-1b is theorized to down-regulate proinflammatory cytokines, decrease major histocompatibility antigens and reduce T-lymphocyte passage across the BBB.

Indications: CIS; relapsing forms of MS.

Dosing and Administration: 0.25 mg SC every other day.

Titration: Start 0.0625 mg SC every other day for 2 weeks; then 0.125 mg SC every other day for 2 weeks; then 0.1875 mg SC every other day for 2 weeks; then 0.25 mg SC every other day thereafter.

Contraindications: History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation.

Warnings and Precautions:

Depression, suicide and psychotic disorders: Advise patients to immediately report any symptoms of depression, suicidal ideation and/or psychosis. Consider discontinuation if depression occurs.

Hepatic injury: Monitor liver function tests, monitor patients for signs and symptoms of hepatic injury and consider discontinuation if hepatic injury occurs.

Anaphylaxis and other allergic reactions: Discontinue use. Monitor patients with preexisting significant cardiac disease for worsening of cardiac symptoms.

Decreased peripheral blood counts: Monitor CBC.

Autoimmune disorders: Consider discontinuation if new autoimmune disorder occurs.

Injection site reactions including necrosis: Do not administer into affected area until fully healed. If multiple lesions occur, discontinue until skin lesions heal.

Adverse Reactions: Injection site reaction; lymphopenia; flu-like symptoms; myalgia; leukopenia; neutropenia; increased liver enzymes; headache; hypertonia; pain; rash; insomnia; abdominal pain; asthenia. Prophylactic use of analgesics and/or antipyretics may reduce flu-like symptoms.

Monitoring:

Baseline: MRI brain (within 6 months); CBC with differential; LFT; TSH

Ongoing: CBC with differential; LFT 1, 2, 3, 6 months; then every 6 months. TSH every 3 to 6 months; 12 months; then yearly.
If this does not provide sufficient disease control, check for NAbs at 12 and 24 months.

**Pregnancy**: Category C.

**Lactation**: Unknown.

**Drug Interactions**: None known.

**VHA CFU**: No.

**VHA Drug Monograph**: No.

**ORAL DMTS:**

a. **Dimethyl Fumarate (Tecfidera):**

   **MOA**: Unknown. Dimethyl fumarate and its metabolites have been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. Monomethyl fumarate has been identified as a nicotinic acid receptor agonist in vitro.

   **Indications**: Relapsing forms of MS.

   **Dosing and Administration**: 240 mg orally every 12 hours.

   **Titration**: 120 mg every 12 hours for one week; 240 mg every 12 hours thereafter. Toleration improved if taken with food and with extended titration.

   **Contraindications**: Known hypersensitivity to dimethyl fumarate or any of its excipients.

   **Warnings and Precautions:**

   - **Anaphylaxis and angioedema**: Discontinue and do not restart if these occur.
   - **Progressive multifocal leukoencephalopathy (PML)**: Withhold at the first sign or symptom suggestive of PML.
   - **Lymphopenia**: Obtain a CBC including lymphocyte count before initiation, after 6 months and every 6 to 12 months thereafter. Consider interruption if lymphocyte counts <0.5 x 10^9/L persist for more than 6 months.

   **Adverse Reactions**: Flushing; abdominal pain; diarrhea; nausea. Flushing may be reduced with concomitant administration of ASA 81 mg.

   **Monitoring:**

   - **Baseline**: MRI brain (within 6 months); CBC with differential; LFT; pregnancy test. Consider JCV Ab status with index.
   - **Ongoing**: CBC with differential; LFT at 1 month, 3 months, every 3 months thereafter. Consider monitoring CD4 counts. CD4: CD8 ration may increase without significant lymphocytopenia. If JCV Ab negative, repeat testing at intervals.
Hold drug if WBC< 2,000 mm$^3$/mL or lymphocytes do not increase to >500 mm$^3$/ul after 4 weeks.

**Pregnancy:** Category C.

**Lactation:** Not recommended.

**Drug Interactions:** Unknown.

**VHA CFU:** Yes.

**VHA Drug Monograph:** Yes.

b. **Fingolimod (Gilenya):**

**MoA:** Unknown. Fingolimod is metabolized by sphingosine kinase to the active metabolite, fingolimod-phosphate. Fingolimod-phosphate is a sphingosine 1-phosphate receptor modulator that binds with high affinity to sphingosine 1-phosphate receptors 1, 3, 4 and 5. Fingolimod-phosphate blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which fingolimod exerts therapeutic effects in MS is unknown, but may involve reduction of lymphocyte migration into the CNS.

**Indications:** Relapsing forms of MS.

**Dosing and Administration:** 0.5 mg orally daily.

**Contraindications:** Recent (within the last 6 months) myocardial infarction; unstable angina; stroke; transient ischemic attack; decompensated heart failure requiring hospitalization; Class III/IV heart failure; history of Mobitz Type II 2$^{nd}$ degree or 3$^{nd}$ degree AV block or sick sinus syndrome, unless patient has a pacemaker; baseline QTc interval >500 msec; treatment with Class Ia or Class III anti-arrhythmic drugs; hypersensitivity to fingolimod or its excipients.

**Warnings and Precautions:**

**Infections:** May increase the risk of infections. A recent CBC should be available before initiating treatment. Monitor for infection during treatment and for 2 months after discontinuation. Do not start in patients with active infections.

**PML:** Withhold at first sign or symptom suggestive of PML.

**Bradycardia and/or AV conduction after first dose:** Monitor patients.

**Macular edema:** Perform an ophthalmologic fundus evaluation before and 3 to 4 months after treatment initiation. Diabetes mellitus or a history of uveitis adds increased risk.

**Posterior reversible encephalopathy syndrome (PRES):** If suspected, discontinue.

**Respiratory:** Obtain PFT when clinically indicated.

**Liver injury:** Liver enzyme results should be available before initiation. Closely monitor if severe hepatic impairment. Discontinue if significant liver injury occurs.

Women of childbearing potential should use effective contraception during and for 2 months after discontinuation.

Basal cell carcinoma: Suspected skin lesions should be evaluated.

**Adverse Reactions:** Headache; diarrhea; cough; influenza; sinusitis; back pain; liver transaminase elevations; abdominal pain; and pain in extremity.

**Monitoring:**

Baseline: MRI brain (within 6 months); CBC with differential; screening HIV antibody; pregnancy test; HgbA1c; varicella titer (if titer negative, give vaccination; check titer in 1 month; if positive, okay to start fingolimod). Spirometry, if asthmatic. Ophthalmological exam with baseline optical coherence tomography (OCT); electrocardiogram (ECG).

First-Dose Monitoring: Observe all patients for bradycardia for at least 6 hours after first dose with hourly pulse and BP measurement. Obtain an ECG prior to dosing and at end of observation period.

Patients who develop heart rate <45 bpm, 2\textsuperscript{nd} degree or higher AV block or in whom lowest post-dose heart rate is at the end of the observation period should be monitored until resolution.

If symptomatic bradycardia occurs, begin continuous ECG monitoring until resolved. If pharmacological intervention is required, continue this monitoring overnight and repeat first-dose monitoring for the second dose.

Patients at higher risk of symptomatic bradycardia or heart block, or prolonged QTc interval or taking drugs with known risk of torsades de pointes should be observed with cardiac telemetry overnight.

Ongoing: BP; CBC with differential; LFT monthly for first 6 months, then every 6 months. Hold if absolute lymphocyte <200 mm\textsuperscript{3}/ul. Ophthalmologic exam (follow-up OCT) at 3 to 4 months; then yearly.

**Pregnancy:** Category C.

**Lactation:** Not recommended.

**Drug Interactions:** Cardiac arrhythmias with drugs that affect heart rate. Ketoconazole may increase fingolimod blood concentration x 1.7. Avoid live attenuated vaccines during and for 2 months after stopping treatment.

**VHA CFU:** Yes.

**VHA Drug Monograph:** Yes.

c. **Teriflunomide (Aubagio):**

**MoA:** Unknown. Teriflunomide, an immunomodulatory agent with anti-inflammatory properties, inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. It may produce a reduction in the number of activated lymphocytes in the CNS.

**Indications:** Relapsing forms of MS. Restricted distribution under the REMS program limited to registered prescribers and pharmacies.
**Dosing and Administration:** 7 mg or 14 mg orally daily. **Note:** Lower efficacy found with 7 mg dose.

**Contraindications:** Severe hepatic impairment; pregnancy; use in women of childbearing potential who are not using reliable contraception; current leflunomide treatment; hypersensitivity.

**“Black Box” Warning:** Hepatotoxicity and risk of teratogenicity.

**Warnings and Precautions:**
Elimination of teriflunomide can be accelerated by administration of cholestyramine or activated charcoal for 11 days.

May decrease WBC. A recent CBC should be available before starting. Monitor for signs and symptoms of infection. Do not start in patients with active infections. Consider suspending in case of serious infection.

If patient develops symptoms consistent with peripheral neuropathy, evaluate patient and consider discontinuing.

Stop if patient develops anaphylaxis, angioedema, Stevens-Johnson syndrome or toxic epidermal necrolysis; initiate rapid elimination protocol.

May increase BP. Measure BP at treatment initiation and monitor BP during treatment.

**Adverse Reactions:** Headache; diarrhea; nausea; alopecia; increase in ALT.

**Monitoring:**
**Baseline:** MRI brain (within 6 months); bilirubin; screening PPD or Quantiferon TB gold; pregnancy test.

**Ongoing:** CBC with differential; LFT monthly for first 6 months; then every 6 months. Monitor BP regularly.

**Rapid Elimination Protocol:** Cholestyramine 8 gm orally every 8 hours for 11 days.

Or: Activated charcoal 50 gm orally every 12 hours for 11 days.

May need to repeat washout treatment course x 2.

**Goal:** Plasma level <0.02 mcg/mL or <20 ng/mL.

**Pregnancy:** Category X.

**Lactation:** Not recommended.

**Drug Interactions:**
Drugs metabolized by CYP2C8 and OAT3 transporters: May increase exposure of these drugs.

Ethinyl estradiol and levonorgestrel: May increase exposure of these drugs. Choose an appropriate contraceptive.

Drugs metabolized by CYP1A2: May decrease exposure of these drugs.
**Warfarin**: May decrease INR.

**Drugs metabolized by BCRP and OATPB1B1/B3 transporters**: May increase exposure of these drugs.

**Rosuvastatin**: When used with teriflunomide, rosuvastatin dose should not exceed 10 mg once daily.

**VHA CFU**: Yes.

**VHA Drug Monograph**: Yes.

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**INFUSION DMTS**

a. **Alemtuzumab (Lemtrada):**

**MoA**: Unknown. Alemtuzumab binds to CD52, a cell surface antigen present on T and B lymphocytes, and on natural killer cells, monocytes and macrophages. Following cell surface binding to T and B lymphocytes, alemtuzumab results in antibody-dependent cellular cytolysis and complement-mediated lysis.

**Indications**: Relapsing forms of MS. Because of its safety profile, it should generally be reserved for patients who have had an inadequate response to two or more DMTs. Restricted distribution under the REMS program is limited to registered prescribers, pharmacies, and infusion centers.

**Dosing and Administration**: Administered in two IV infusions separated by one year.

**First course**: 12 mg/day IV over 4 hours for 5 consecutive days (60 mg total dose).

**Second course**: 12 mg/day IV over 4 hours for 3 consecutive days (36 mg total dose); 12 months after first course.

Premedicate with 1 gm methylprednisolone or equivalent immediately prior to infusion for first 3 days of each treatment course.

Administer antiviral agents for herpes prophylaxis on first day of treatment course and continue for a minimum of 2 months after completion of dose, or until CD4 count is >200/mL, whichever is later.

Consider pre-infusion treatment with antihistamines and antipyretics.

Required 2-hour post-infusion observation period.

**Contraindications**: Infection with HIV.

**“Black Box” Warning**: Autoimmune conditions such as immune thrombocytopenia and anti-glomerular basement membrane disease. Must be administered in setting with appropriate equipment and personnel to manage anaphylaxis or serious infusion reactions. Monitor patients for 2 hours after each
infusion. Educate patients that serious infusion reactions can occur after the 2-hour monitoring period. May cause increased risk of malignancies, including thyroid cancer, melanoma and lymphoproliferative disorders.

**Warnings and Precautions:**

**Thyroid disorders:** Obtain thyroid function tests prior to initiation of treatment and every 3 months until 48 months after the last infusion.

**Other autoimmune cytopenias:** Monitor CBC monthly until 48 months after the last infusion.

Consider delaying initiation in patients with active infections until the infection is fully controlled.

Do not administer live viral vaccines following a course of alemtuzumab. Complete any necessary immunizations at least 6 weeks prior to treatment.

**Infections:** There have been 21 reported cases of *Listeria monocytogenes* with alemtuzumab. Symptoms of infection can be difficult to distinguish from infusion reactions. Patients should be counseled not to consume foods associated with *Listeria* prior to alemtuzumab infusion.

**Adverse Reactions:** Rash; headache; pyrexia; nasopharyngitis; nausea; UTI; fatigue; insomnia; upper respiratory tract infection; herpes viral infection; urticaria; pruritus; thyroid gland disorders; fungal infection; arthralgia; pain in extremity; back pain; diarrhea; sinusitis; oropharyngeal pain; paresthesia; dizziness; abdominal pain; flushing; vomiting.

**Monitoring:**

**Baseline:** MRI brain within 6 months; screening HIV; CBC with differential; serum creatinine; urinalysis with cell counts; TSH; skin exam.

Determine if patient has history of varicella or has been vaccinated for VZV. If not, test for antibodies to VZV and consider vaccination if antibody-negative.

Postpone treatment until 6 weeks after VZV vaccination.

**Ongoing:**

**Monthly:** CBC with differential; serum creatinine; urinalysis with cell counts.

**Quarterly:** TSH.

**Yearly:** Skin exams.

**After discontinuation:** Monthly CBC with differential and quarterly TSH for 4 years.

Monitor serum creatinine levels and urinalysis with urine counts at periodic intervals for 48 months after last dose.

**Pregnancy:** Category C.

**Lactation:** Not recommended.

**Drug Interactions:** Unknown.
VHA CFU: Yes.
VHA Drug Monograph: Yes.

b. **Mitoxantrone (Novantrone):**

Note: Rarely used in MS due to significant risk profile.

**MoA:** Unknown. Mitoxantrone is a topoisomerase II inhibitor and has been shown to inhibit B cell, T cell and macrophage proliferation in vitro. It also produces an impairment of antigen presentation and secretion of interferon gamma, TNFα and IL-2.

**Indications:** SPMS; worsening RRMS; relapsing forms of MS.

**Dosing and Administration:** 12 mg/m2 given as a short (approximately 5 to 15 minutes) IV infusion every 3 months. Recommended maximum cumulative dose: <140mg/m2 (usually a 30 to 36 month duration).

**Contraindications:** History of hypersensitivity to mitoxantrone.

**“Black Box” Warning:** Potentially fatal CHF; risk of secondary acute myeloid leukemia.

**Warnings and Precautions:**

**Cardiotoxicity:** May cause heart failure.

Myelosuppression may occur at any dose.

Local/regional neuropathy, some irreversible, following intra-arterial injection reported.

Avoid in patients with hepatic impairment.

May cause fetal harm; confirm negative pregnancy status in women prior to each administration.

Systemic infections should be treated concomitantly with or just prior to therapy.

Caution in elderly.

**Adverse Reactions:** CHF; cardiotoxicity; nausea; alopecia; menstrual disorder; upper respiratory infection; UTI; stomatitis; arrhythmia; diarrhea; constipation; back pain; abnormal ECG; headache; sinusitis.

**Monitoring:**

- **Baseline:** ECG; LVEF; LFT; CBC with platelets.
- **Ongoing:** ECG; LVEF; LFT; CBC with platelets prior to each dose.
- **After discharge:** CBC every 6 months for 5 years; LVEF yearly.

**Pregnancy:** Category D.

**Lactation:** Not recommended.

**Drug Interactions:** Increased risk of myeloid leukemia if given with other cytotoxic agents and radiotherapy.
c. Natalizumab (Tysabri):

MoA: Unknown. Natalizumab is theorized to block molecular interaction of alpha-4-beta-integrin expressed by inflammatory cells with VCAM-1 on vascular endothelial cells. Humanized monoclonal antibody binds to alpha 4/beta 1 integrin on activated lymphocytes and monocytes, and blocks leukocyte passage across BBB.

Indications: Monotherapy for relapsing forms of MS.

Dosing and Administration: 300 mg IV infused over 1 hour every 4 weeks. Required 1-hour post-infusion observation.

Contraindications: Patients who have or had PML and patients who have had hypersensitivity reactions to natalizumab.

“Black Box” Warning: PML.

Warnings and Precautions:

Herpes encephalitis and meningitis: Life-threatening and fatal cases have occurred. Discontinue if this occurs and treat appropriately.

PML: Significant liver injury, including liver failure requiring transplant, has occurred. Discontinue if evidence of liver injury.

Hypersensitivity reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred. Permanently discontinue if this occurs.

Immunosuppression/Infections: May increase the risk for certain infections. Monitor for development of infections.

Adverse Reactions: Headache; fatigue; arthralgia; UTI; upper and lower respiratory tract infection; gastroenteritis; vaginitis; depression; pain in extremity; abdominal discomfort; diarrhea; rash; nausea.

Monitoring:

Has a REMS program called “TOUCH”: The TOUCH program will train prescribers, pharmacies and infusion centers in the use and monitoring of natalizumab. Natalizumab is administered only to patients enrolled in the TOUCH program.

Baseline: MRI brain (within 6 months); CBC with differential; LFT; JCV Ab with index; HIV; pregnancy.

Ongoing:

1 month: CBC with differential; LFTs.
3 months: CBC with differential; LFTs.
Every 3 months: JCV Ab with index.
Every 6 months: CBC with differential; LFTs.

Consider monitoring CD4 and CD8 counts.
Pregnancy: Category C.
Lactation: Not recommended.
Drug Interactions: Unknown.
VHA CFU: Yes.
VHA Drug Monograph: Yes.

d. **Ocrelizumab (Ocrevus):**

MoA: OCREVUS is a CD20-directed cytolytic antibody indicated for the treatment of patients with relapsing or primary progressive forms of MS

Indications: Relapsing or primary progressive forms of MS.

Dosing and Administration:

Premedications:
Methylprednisolone 100 mg IV, ½ hour prior to infusion.
Diphenhydramine 50 mg IV ½ hour to 1 hour prior to infusion.
Acetaminophen 650 mg p.o. prior to infusion.

Ocrelizumab:
1\textsuperscript{st} dose: 300 mg IV; then 2 weeks later another 300 mg IV; infused over at least 2½ hours.
2\textsuperscript{nd} and all future doses: 600 mg IV, infused over at least 3½ hours.

Required 1-hour post-infusion observation period.

Contraindications: Active Hepatitis B virus infection, history of life-threatening infusion reaction to ocrelizumab or rituximab.

Warnings and Precautions:

Infusion reactions: Management recommendations for infusion reactions depend on the type and severity of the reaction. Permanently discontinue OCREVUS if a life-threatening or disabling infusion reaction occurs.

Infections: Delay OCREVUS administration in patients with an active infection until the infection is resolved. Vaccination with live-attenuated or live vaccines is not recommended during treatment with OCREVUS and after discontinuation, until B-cell repletion.

Malignancies: An increased risk of malignancy, including breast cancer.

Adverse Reactions: In RMS patients (incidence ≥10% and > REBIF): upper respiratory tract infections and infusion reactions. In PPMS patients (incidence ≥10% and > placebo): upper respiratory tract infections; infusion reactions; skin infections; lower respiratory tract infections.

Monitoring:
Baseline: MRI brain (within 6 months); Hep B surface Ag; Hep B surface antibody; Hep B core antibody; Zoster titer; CBC with differential; LFTs; kidney function; pregnancy. Consider JCV Ab index.

Pregnancy: Not recommended. Use contraception during and for 6 months after last infusion.

Lactation: Not recommended.

Drug Interactions: Unknown.

VHA CFU: Yes.

VHA Drug Monograph: Yes.