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Medication Policy Manual **Policy No**: dru753

Topic: Medications for Multiple Sclerosis **Date of Origin**: September 1, 2023

- Aubagio, teriflunomide
- Avonex, interferon beta-1a
- Bafiertam, monomethyl fumarate
- Betaseron, interferon beta-1b
- Briumvi, ublituximab-xiiy
- Cladribine (generic, Mavenclad)
- Copaxone, glatiramer acetate
- Extavia, interferon beta-1b
- Gilenya, fingolimod
- Kesimpta, ofatumumab
- Lemtrada, alemtuzumab
- Mayzent, siponimod
- Ocrevus, ocrelizumab
- Ocrevus Zunovo, ocrelizumab and hyaluronidase-ocsq
- Plegridy, peginterferon beta-1a
- Ponvory, ponesimod
- Rebif, interferon beta-1a
- Tascenso ODT, fingolimod
- Tecfidera, dimethyl fumarate
- Tysabri, natalizumab
- Tyruko, natalizumab
- Vumerity, diroximel fumarate
- Zeposia, ozanimod

Committee Approval Date: January 22, 2026 **Next Review Date**: 2027

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IMPORTANT REMINDER

This Medication Policy has been developed through consideration of medical necessity, generally accepted standards of medical practice, and review of medical literature and government approval status.

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control.

The purpose of medication policy is to provide a guide to coverage. Medication Policy is not intended to dictate to providers how to practice medicine. Providers are expected to exercise their medical judgment in providing the most appropriate care.

Description

Medications in this policy are used primarily in the treatment of multiple sclerosis (MS). They help to slow the progression of disability and reduce the number of clinical relapses associated with this condition. Zeposia (ozanimod) can also be used for ulcerative colitis, and natalizumab (Tysabri/Tyruko) for Crohn's disease.

PLEASE NOTE:

This policy does NOT apply to Campath (alemtuzumab), which is used primarily in the treatment of cancer (leukemia).

Policy/Criteria

Most contracts require pre-authorization approval of medications for multiple sclerosis (MS) (as listed in *Table 4*) prior to coverage.

I. Continuation of therapy (COT): Medications for MS may be considered medically necessary for COT when criterion A and B below are met.

A. One of the following (1, 2, or 3) are met:

1. For diagnoses NOT listed in the coverage criteria below, full policy criteria must be met for coverage.

OR

2. For diagnoses listed in the coverage criteria below, criteria a, b, and c must be met:

a. The patient was established on therapy prior to current health plan membership AND attestation that the medication was covered by another health plan.

AND

b. There is documentation of clinical benefit, such as disease stability as detailed in the reauthorization criteria.

AND

c. **For use of branded Aubagio, Copaxone, Gilenya, Tascenso ODT**, **or Tecfidera only**: There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, fingolimod, glatiramer acetate/Glatopa, or dimethyl fumarate).

OR

3. The medication was initiated for acute disease management, as part of an acute unscheduled, inpatient hospital admission. **For use of branded Aubagio**, **Copaxone**, **Gilenya**, **Tascenso ODT**, **or Tecfidera only**: There is clinical documentation (such as chart notes) of an intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, glatiramer acetate/Glatopa, fingolimod or dimethyl fumarate).

AND

B. **For Briumvi (ublituximab-xiiy), natalizumab (Tysabri/Tyruko)**, **Ocrevus (ocrelizumab)**, **and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) only**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408]. PLEASE NOTE: Not all provider-administered medications in this policy are part of the site of care program. Verify with the posted site of care review policy, dru408.

***Please note**: Medications obtained as samples, coupons, or promotions, paying cash for a prescription ("out-of-pocket") as an eligible patient, or any other method of obtaining medications outside of an established health plan benefit (from your insurance) does NOT necessarily establish medical necessity. Medication policy criteria apply for coverage, per the terms of the member contract with the health plan.*

II. New starts (treatment-naïve patients): Medications for MS (as listed in *Table 4*) may be considered medically necessary when the criteria below are met.

A. Relapsing MS

1. **Diagnostic criteria**: Diagnosis of a relapsing form of MS (see *Appendix B*) established by a specialist in neurology or MS.
2. **Low-cost step**: Treatment with at least one low-cost DMT was ineffective [α], not tolerated, or is contraindicated.
3. **Preferred step**: Treatment with at least one preferred DMT has been ineffective [α], not tolerated, or is contraindicated.
4. **Site of care**: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Product Group	Products	Criteria Requirements
Low-cost DMTs	• Dimethyl fumarate (generic for Tecfidera) • Fingolimod (generic for Gilenya) • Glatiramer acetate (generic for Copaxone) or Glatopa • Teriflunomide (generic for Aubagio)	None – Available without prior authorization.
Preferred DMTs	• Briumvi (ublituximab-xiiy) • Interferon beta-1a (Avonex, Rebif) • Kesimpta (ofatumumab) • Natalizumab (Tysabri, Tyruko) • Ocrevus (ocrelizumab) • Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) • Rituximab * • Zeposia (ozanimod)	**1.** Diagnostic criteria **2.** Low-cost step **3.** Site of care – Briumvi ublituximab-xiiy), natalizumab (Tysabri/Tyruko), Ocrevus (ocrelizumab), and Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) only. **Note: These criteria requirements do not apply to rituximab. Refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.*
Non-preferred DMTs	• Bafiertam (monomethyl fumarate) [β] • Betaseron (interferon beta-1b) • Cladribine (generic, Mavenclad) • Extavia (interferon beta-1b) [β] • Lemtrada (alemtuzumab) • Mayzent (siponimod) [β] • Plegridy (peginterferon beta-1a) • Ponvory (ponesimod) [β] • Vumerity (diroximel fumarate) [β]	**1.** Diagnostic criteria **2.** Low-cost step **3.** Preferred step
Brands with generics	• Aubagio (teriflunomide) • Copaxone (glatiramer acetate) • Gilenya (fingolimod) • Tascenso ODT (fingolimod) • Tecfidera (dimethyl fumarate)	**1.** Diagnostic criteria **2.** Low-cost step **3.** Preferred step **4.** Clinical documentation (such as chart notes) of intolerance or contraindication to an inactive ingredient in the generic equivalent medication (teriflunomide, glatiramer acetate/Glatopa, fingolimod, or dimethyl fumarate).

[α] Ineffectiveness is defined as meeting at least one of the following: 1. Patient continues to have clinical relapses (at least one relapse within past 12 months); 2. Patient continues to have CNS lesion progression as measured by MRI; 3. Patient continues to have worsening disabilities (e.g., decreased mobility, decreased ability to perform activities of daily living due to disease progression, EDSS score increase).

[β] Step therapy may be met through adjudicated and paid claims in member's prescription history (see *Appendix C*).

Key: DMT=disease modifying therapy; MS=multiple sclerosis; ODT=orally disintegrating tablet

B. Aggressive Relapsing MS

1. Diagnostic criteria: Diagnosis of a particularly aggressive relapsing form of MS when established by a specialist in neurology or MS when at least one of the following criteria are met.

a. EDSS score ≥ 4 within 5 years of onset.

OR

b. Two or more relapses with incomplete resolution in the past year.

OR

c. Two or more MRI studies showing new or enlarging T2 lesions or Gd-enhancing lesions despite treatment > 6 months.

OR

d. Presence of spinal or brainstem lesions on MRI.

2. Site of care: Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

Product Group	Products	Criteria Requirements
Products for aggressing relapsing forms of MS	• Briumvi (ublituximab) • Kesimpta (ofatumumab) • Natalizumab (Tysabri/Tyruko) • Ocrevus (ocrelizumab) • Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq)	**1.** Diagnostic criteria **2.** Site of care (all products except Kesimpta [ofatumumab])

Key: EDSS=Expanded Disability Status Scale; Gd= gadolinium; MRI=magnetic resonance imaging; MS=multiple sclerosis

C. Primary Progressive Multiple Sclerosis (PPMS)

Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab/hyaluronidase-ocsq) may be considered medically necessary when criteria 1 and 2 below are met.

1. Diagnostic criteria: Diagnosis of PPMS (see *Appendix B*) when established by a specialist in neurology or MS.

AND

2. Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

D. Crohn's Disease (CD)

Natalizumab (Tysabri, Tyruko) may be considered medically necessary when criteria 1 through 4 below are met.

1. Diagnosis of CD established by or in consultation with a specialist in gastroenterology.

AND

2. Adalimumab [α] is ineffective after at least an initial 3-dose induction period, except if documented as not tolerated.

AND

3. Infliximab [β] is ineffective after at least an initial induction period (5 mg/kg on weeks 0, 2 and 6), except if documented as not tolerated.

AND

4. Site of care administration requirements are met [refer to Medication Policy Manual, Site of Care Review, dru408].

[α] For a list of preferred adalimumab product(s), refer to Medication Policy Manual, Drugs for Chronic Inflammatory Diseases, dru444.

[β] For a list of preferred infliximab product(s), refer to Medication Policy Manual, Products with Therapeutically Equivalent Biosimilars/Reference Products, dru620.

E. Ulcerative Colitis (UC)

Zeposia (ozanimod) may be considered medically necessary when criteria 1 through 3 below are met.

1. Diagnosis of UC when established by or in consultation with a specialist in gastroenterology.

AND

2. At least one of the following criterion a, b, or c below are met.

a. Treatment with an adequate course of corticosteroids (e.g., prednisone 40 to 60 mg/day, oral budesonide 9 mg/day, budesonide rectal for 7 to 14 days) was ineffective or is contraindicated.

OR

b. The patient has been unable to taper an adequate course of corticosteroids without experiencing disease worsening.

OR

c. The patient is experiencing breakthrough disease (e.g., active disease flares) while stable on a conventional immunomodulator for at least two months. Conventional immunomodulators for UC include azathioprine, balsalazide, cyclosporine, mercaptopurine, mesalamine, and sulfasalazine.

AND

3. Treatment with at least two of the following preferred products was ineffective after at least a 12-week treatment course unless not tolerated or contraindicated: adalimumab [α], Entyvio (vedolizumab), Skyrizi (risankizumab), Tremfya (guselkumab), ustekinumab [α], Xeljanz/Xeljanz XR (tofacitinib).

[α] For a list of preferred adalimumab and ustekinumab product(s), refer to Medication Policy Manual, Drugs for Chronic Inflammatory Diseases, dru444.

III. Administration, Quantity Limitations, and Authorization Period

A. Regence Pharmacy Services considers oral and subcutaneous (SC) self-injectable medications [as listed in *Table 4*] for multiple sclerosis coverable only under the pharmacy benefit (as self-administered medications).

B. Regence Pharmacy Services considers intravenous (IV) infused medications [as listed in *Table 4*] and **subcutaneous** Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) for multiple sclerosis coverable only under the medical benefit (as a provider-administered medication).

C. When pre-authorization is approved, each drug will be covered in the following quantities and for the following authorization periods outlined in *Table 4* below:

Table 4: Medications for MS Quantity Limits, Authorization Period, and Route of Administration

Product	Quantity Limit and Authorization Period	Route/Benefit
Aubagio (teriflunomide)	- Up to 28 tablets per 28 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that all of the following criteria (a, b, and c) below are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Aubagio (teriflunomide): There is an intolerance or contraindication to an inactive ingredient in generic teriflunomide. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Avonex (interferon beta-1a)	- Up to 4 syringes per 28 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit
Bafiertam (monomethyl fumarate)	- Up to 120 capsules per 30 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Betaseron (interferon beta-1b)	- Up to 15 syringes every 30 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
Briumvi (ublituximab-xiiy)	- Initial authorization: Up to 1500 mg (10 vials) for the first 12 months (one IV infusion of 150 mg on day 1 followed by a second infusion of 450 mg on day 15 with subsequent doses of 450 mg infusions given at 24 weeks intervals from the first infusion). - Maintenance: Up to quantities of 900 mg (6 vials) every 12 months. (450 mg infusions every 24 weeks). - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	IV; medical benefit **(SOC program applies)**
Cladribine (generic, Mavenclad)	- Up to 20 tablets per year for up to a maximum of 2 years only. - Use of cladribine (generic, Mavenclad) beyond the 2-year course is considered investigational. - Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	Oral; pharmacy benefit
Copaxone, (glatiramer acetate)	- Copaxone 20 mg/mL: Up to 30 syringes per 30 days. - Copaxone 40 mg/mL: Up to 12 syringes per 28 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Copaxone: There is an intolerance or contraindication to an inactive ingredient in generic glatiramer acetate. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
Extavia (interferon beta-1b)	- Up to 15 pre-filled syringes per 28 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	SC; pharmacy benefit
Fingolimod (Gilenya or Tascenso ODT)	- Up to 30 capsules or oral disintegrating tablets per 30 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand fingolimod (Gilenya or Tascenso ODT): There is an intolerance or contraindication to an inactive ingredient in generic fingolimod. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Kesimpta (ofatumumab)	- Initial authorization: Up to 15 pen injectors per year. - Maintenance: Up to 13 pen injectors per year. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit
Lemtrada (alemtuzumab)	- Initial authorization (first treatment course; 5 doses): Up to 12 mg/day IV infusion on five consecutive days in a 12-month period. - Second authorization (second treatment course; 3 doses): Following the first treatment course (of five doses), a second treatment course of up to 12 mg/day on three consecutive days in a 12-month period. - Additional Authorizations [additional treatment course(s); 3 doses]: Following the second treatment course (of three doses), subsequent treatment	IV; medical benefit

Product	Quantity Limit and Authorization Period	Route/Benefit
	courses of 12 mg/day on three consecutive days may be administered in a 12-month period. - All subsequent courses must be administered at least 12 months after the last dose of the prior treatment course. - Authorization **shall** be reviewed after each treatment course. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	
Mayzent (siponimod)	- For initial 5-day dose titration: Up to one Starter pack. - Maintenance: Up to 120 of the 0.25 mg tablets, or 30 of the 1mg or 2 mg tablets per 30 days, based on a recommended dose of 1 to 2 mg per day depending on CYP2C9 genotype. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Ocrevus (ocrelizumab)	- Up to 1200 mg (4 vials) per 12 months, based on a recommended initial dose of one 300 mg IV infusion on day 1 and a second 300 mg IV infusion on day 15, followed by a maintenance dose of 600 mg IV infusion every 6 months thereafter. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	IV; medical benefit **(SOC program applies)**
Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)	- Up to two single dose vials (920mg/23,000 units per 23ml single dose vial) per 12 months. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; medical benefit **(SOC program applies)**

Product	Quantity Limit and Authorization Period	Route/Benefit
Plegridy (peginterferon beta-1a)	- Up to 2 syringes per 28 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit
Ponvory (ponesimod)	- For initial 14-day dose titration: Up to one Starter pack. - Maintenance: Up to thirty 20 mg tablets per 30 days, based on a recommended dose of 20 mg once daily. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Rebif (interferon beta-1a)	- Up to 12 syringes per 28 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement	SC; pharmacy benefit
Tecfidera (dimethyl fumarate)	- Up to 60 capsules per 30 days. - Authorization **shall** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that all of the following (a, b, and c) are met: **a.** Current medical necessity criteria are met. **AND** **b.** For brand Tecfidera (dimethyl fumarate): There is an intolerance or contraindication to an inactive ingredient in generic dimethyl fumarate. **AND** **c.** Ongoing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Natalizumab (Tysabri/Tyruko)	- Up to one 300-mg IV infusion every 4 weeks. - **Multiple sclerosis**: Authorization **may** be reviewed at least annually. Clinical documentation	IV; medical benefit **(SOC program**

Product	Quantity Limit and Authorization Period	Route/Benefit
	(such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement. - **Crohn's disease**: Initial authorization **shall** be reviewed at 12 weeks. Continued authorization **shall** be reviewed at least every six months. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	**applies)**
Vumerity (diroximel fumarate)	- Up to 120 capsules per 30 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit
Zeposia (ozanimod)	- Up to 30 capsules per 30 days. - Authorization **may** be reviewed at least annually. Clinical documentation (such as chart notes) must be provided to confirm that current medical necessity criteria are met, and that the medication is providing clinical benefit, such as disease stability or improvement.	Oral; pharmacy benefit

IV. Medications for MS are considered not medically necessary when used in the following settings:

A. **For natalizumab (Tysabri/Tyruko) only** when used in the following settings:

1. For the treatment of Crohn's disease when used concomitantly with any of the following:

a. Adalimumab.

b. Infliximab.

c. Cimzia (certolizumab pegol).

2. For the treatment of ulcerative colitis.

V. Medications for MS are considered investigational when used for all other conditions, including but not limited to:

A. Doses higher than those listed in the Quantity Limits *Table 4,* above.

B. Concomitantly with any other DMTs for MS (see *Appendix A*).

C. For non-relapsing forms of MS, such as SPMS without active relapses OR primary progressive MS (PPMS), unless specifically noted in the coverage criteria above, such as for Ocrevus, ocrelizumab.

D. Any cancer indication, including, but not limited to B-cell chronic lymphocytic leukemia.

E. For Lemtrada (alemtuzumab): Post-transplant antibody induction therapy.

F. For Ocrevus (ocrelizumab), Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq): Neuromyelitis Optica Spectrum Disorders (NMOSD).

G. For Ocrevus (ocrelizumab), Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq), and natalizumab (Tysabri/Tyruko): Rheumatoid arthritis.

Position Statement

Summary

- There are many medications for multiple sclerosis (MS) treatment. Medications for MS have different routes of administration as well as mechanisms of action. These disease modifying therapies (DMTs) help to decrease the number of clinical exacerbations associated with this condition and slow the progression of disability.
- Zeposia (ozanimod) has been proven to be effective in ulcerative colitis (UC), while natalizumab (Tysabri/Tyruko) has proven efficacy in Crohn's disease, with both having FDA approvals in these respective diseases.
- The intent of this policy is to allow for coverage of medications for MS in the settings where they have been proven safe and effective, when lower cost preferred options (as listed in the coverage criteria) are ineffective or not a treatment option (as described in coverage criteria).
- MS consists of two main clinical courses of disease, relapsing or primary progressive (see *Appendix B)* [1 2]:
    - Relapsing forms of MS include clinically isolated syndrome (CIS), relapsing-remitting MS (RRMS), and active secondary progressive MS (SPMS). CIS is the first clinical presentation that shows characteristics of inflammatory demyelination that could be MS, but not a definitive diagnosis of MS. All of the medications for MS are FDA approved for use in relapsing forms of MS. Rituximab may also be used off label for the treatment of relapsing forms of MS.
    - Primary progressive MS (PPMS) is defined as progression of disability without relapses. Only Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) are FDA approved for use in PPMS.
- American Academy of Neurology (AAN) guidelines state[2]:
    - DMTs should be offered to patients with relapsing forms of MS.
    - Guidelines state the choice of initial DMT should be individualized to consider safety, route of administration, lifestyle, cost, efficacy, adverse effects (AEs), and tolerability.
    - Disease activity, adherence, AE profiles, and mechanism of action should be considered when switching DMTs.
    - Natalizumab (Tysabri/Tyruko), fingolimod (generic, Gilenya, and Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease based on improved efficacy in this subgroup.

- For patients with relapsing and remitting MS (RRMS), step therapy is required with a lower-cost option. Among the lower-cost options in Table 1., fingolimod is also used in highly active disease.
- Individual responses and tolerability of DMTs are unpredictable and may vary between patients. If one DMT provides an inadequate response, another DMT may be effective.
- There is limited evidence of increased efficacy or safety between the majority of medications for MS in reducing signs and symptoms of MS or slowing progression of disease due to a lack of head-to-head trials; therefore, the medication with lowest cost often provides the best value for members.
    * Fingolimod (generic, Gilenya, and Tascenso ODT), Zeposia (ozanimod), and Mayzent (siponimod) belong to a class of medications called sphingosine 1-phosphate (S1P) receptor modulators. Of the three, fingolimod (generic) provides the best value.
    * Dimethyl fumarate (generic, Tecfidera), Vumerity (diroximel fumarate), and Bafiertam (monomethyl fumarate) belong to a class of medications called fumarates, of which dimethyl fumarate (generic) provides the best value.
    * Currently, three glatiramer-containing products are available: Copaxone, generic glatiramer, and Glatopa. Generic glatiramer and Glatopa provide the best value to members of this health plan.
- Lemtrada (alemtuzumab) is not recommended as a first- or second-line option due to serious safety concerns[3].
    * Lemtrada (alemtuzumab) has boxed warnings describing an increased risk of autoimmunity, infusion reactions, and malignancies with its use. The FDA labeling states that it should generally be reserved for patients who have had an inadequate response to two or more DMTs for MS.
    * Because of these safety concerns, distribution of Lemtrada (alemtuzumab) is restricted with a REMS program for prescribers, health care facilities, and pharmacies.
- The safety and effectiveness of combination use of disease modifying therapies for MS medications has not been established.
- Medications for MS may be covered at the doses proven to be safe and effective in the clinical trials (as outlined in Table 4 of the coverage criteria above). The safety and effectiveness of higher doses has not been established.
- Use of medications for MS in clinical settings other than described in the coverage criteria is considered investigational.

Clinical Efficacy:

RELAPSING REMITTING MS (RRMS)

Lemtrada (alemtuzumab) for Relapsing Remitting MS (RRMS)[4-6]

- Two, randomized, open-label, rater-blinded, 2-year, studies compared Lemtrada (alemtuzumab) with interferon beta-1a in patients with relapsing-remitting multiple sclerosis (RRMS).
    * The CARE-MS I trial included previously untreated patients while CARE-MS II trial included patients who had at least one relapse while on an interferon beta product or glatiramer acetate.

    - In each trial, there was a statistically significantly lower annualized relapse rate for patients treated with Lemtrada (alemtuzumab) (22%-35%) compared to interferon beta-1a (40%-51%).
    - Treatment-experienced patients treated with Lemtrada (alemtuzumab) experienced a statistically significant reduction in the rate of disease progression compared to those treated with interferon beta 1a (13% vs 20%, p=0.008). The difference in rates of disease progression was not statistically significant among treatment-naïve patients.
- Extension studies for Lemtrada (alemtuzumab) suggest that efficacy is maintained through at least year five but certain patients with disease activity may require additional courses. Among patients who completed CARE-MS II, 58.0% received just no additional courses of alemtuzumab while 30.1% received one additional course at some point in the five-year follow-up period. The most common reason for additional courses was relapse.

Interferon-beta for RRMS

- There are several randomized, controlled trials comparing the efficacy of the different interferon beta products in the treatment of relapsing-remitting multiple sclerosis, with all of them favoring interferon-beta treatment over placebo for reducing relapse rate.

Glatiramer acetate (generic, Copaxone, and Glatopa) for RRMS[7]

- The efficacy of glatiramer acetate was evaluated in five studies in patients with relapsing-remitting MS. The first four studies compared daily glatiramer to placebo and the other studies compared three times weekly glatiramer to placebo.
- Results demonstrated that glatiramer acetate was superior to placebo in reducing the number of relapses.

Teriflunomide (generic, Aubagio) for RRMS[8]

- The efficacy of teriflunomide was evaluated in three studies in patients with relapsing-remitting MS. These studies compared daily teriflunomide (7 mg or 14 mg) to placebo.
- Results demonstrated that teriflunomide was superior to placebo in reduction of annualized relapse rate and relative risk of disease progression at 108 weeks.

Fingolimod (generic, Gilenya, and Tascenso ODT) for RRMS[9 10]

- The efficacy of fingolimod was evaluated in three phase 3 studies in patients with relapsing-remitting MS. The first study compared fingolimod to placebo and the two other studies compared fingolimod to interferon beta-1a.
- Results demonstrated that fingolimod was superior to placebo and interferon beta-1a in reducing annualized relapse rates.

Mayzent (siponimod) for RRMS[11]

- Siponimod was studied in one phase 3 study in patients with SPMS with or without ongoing relapses.
    - Mayzent (siponimod) met its primary endpoint of slowing the time to 3-month confirmed disability progression (CDP). However, the key secondary endpoint of time to 20% worsening in the timed 25-foot walk test (T25FW) was not met.
    - In subgroup analyses, it was observed that efficacy was primarily in patients who were younger, had active relapses, and had active MRI lesions. This population likely had a relapsing form of MS rather than non-active SPMS, thus efficacy in non-active SPMS is unclear and further studies are needed.

Zeposia (ozanimod) for RRMS[12 13]

- Zeposia (ozanimod) was evaluated in two phase 3 studies in patients with relapsing forms of MS. Both studies compared Zeposia (ozanimod) to interferon beta-1a.
- Results showed that Zeposia (ozanimod) was superior to interferon beta-1a in reducing annualized relapse rates. However, pooled results from both studies showed that there was no improvement in disability progression over interferon beta-1a.

Ponvory (ponesimod) for RRMS[14]

- The efficacy of ponesimod was evaluated in one phase 3 study in patients with relapsing-remitting MS. The study compared daily ponesimod (Ponvory) to Aubagio (teriflunomide) for 108 weeks.
- Results demonstrated that ponesimod (Ponvory) was superior to teriflunomide (Aubagio) in reducing annualized relapse rates.

Cladribine (generic, Mavenclad) for RRMS[15]

- The efficacy of cladribine (generic, Mavenclad) was evaluated in one phase 3 study in patients with relapsing-remitting MS. The study compared cladribine (generic, Mavenclad) to placebo for 96 weeks.
- Results demonstrated that cladribine (generic, Mavenclad) was superior to placebo in reducing annualized relapse rates.

Dimethyl fumarate (generic, Tecfidera), diroximel fumarate (Vumerity), and Bafiertam (monomethyl fumarate) for RRMS[16-18]

- The efficacy of dimethyl fumarate was evaluated in two phase 3 studies in patients with relapsing-remitting MS. Both studies compared dimethyl fumarate to placebo.
- Results demonstrated that dimethyl fumarate was superior to placebo in reducing annualized relapse rates.
- The efficacy of Vumerity (diroximel fumarate) was based on bioavailability studies in patients with RRMS and healthy patients comparing oral dimethyl fumarate to oral diroximel fumarate capsules.
- The efficacy of Bafiertam (monomethyl fumarate) was based on bioavailability studies in healthy patients, The studies demonstrated the bioequivalence of Bafiertam (monomethyl fumarate) to oral Tecfidera (dimethyl fumarate).

Kesimpta (ofatumumab) for RRMS[19]

- The efficacy of Kesimpta (ofatumumab) was evaluated in two phase 3 studies in patients with relapsing-remitting MS. The study compared Kesimpta (ofatumumab) to Aubagio (teriflunomide).
- Results demonstrated that Kesimpta (ofatumumab) was superior to teriflunomide (Aubagio) in reducing annualized relapse rates.

Briumvi (ublituximab-xiiy) for RRMS[20-22]

- Briumvi (ublituximab-xiiy) has been shown to significantly reduce annual relapse rate (ARR) and slow worsening of disease based on MRI outcomes in patients with relapsing forms of MS when compared to Aubagio (teriflunomide).
    * Two identical, phase 3, randomized, double-blind, double dummy, active control 96-week studies (ULTIMATE I and ULTIMATE II, total N=1089), evaluated the effects of Briumvi (ublituximab-xiiy) compared to Aubagio (teriflunomide) in patients with relapsing forms of MS. Briumvi (ublituximab-xiiy) was

significantly superior to teriflunomide in reducing annualized relapse (relative risk reduction of 59% in ULTIMATE I and 49% in ULTIMATE II). On MRI outcomes, the patients in the Briumvi (ublituximab-xiiy) groups had significantly fewer new and/or enlarging T2 lesions, and less T1 lesions relative to the Aubagio (teriflunomide) groups.

Ocrevus (ocrelizumab) for RRMS[23-25]

- Ocrevus (ocrelizumab) has been shown to reduce elapse rate, slows disability progression, and slows worsening of disease based on MRI outcomes in patients with relapsing forms of MS.
    * Two identical, 96-week studies (OPERA I and OPERA II) evaluated the effects of Ocrevus (ocrelizumab) compared to Rebif (interferon beta-1a) in patients with relapsing forms of MS. Ocrevus (ocrelizumab) was superior to interferon beta-1a in reducing annualized relapse and in slowing confirmed disability progression. On MRI, the patients in the Ocrevus (ocrelizumab) group had fewer new and/or enlarging T2 lesions, less T1 lesions, and a reduced rate of total brain volume loss relative to the Rebif (interferon beta-1a) group.
- Although there is an ongoing trial investigating higher doses of Ocrevus (ocrelizumab) in the setting of multiple sclerosis, there is currently insufficient published evidence to support the use of higher doses of Ocrevus (ocrelizumab), above those listed in the Quantity Limits *Table 4.*

Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) for RRMS[26 27]

- The efficacy and safety of Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) was established in a phase 3 trial (OCARINA II) that evaluated the pharmacokinetics, safety, and clinical efficacy of the subcutaneous (SC) formulation of Ocrevus (ocrelizumab and hyaluronidase-ocsq) compared with intravenous (IV) Ocrevus (ocrelizumab) infusion, in patients with RRMS and PPMS.
    * The trial met its primary endpoint, demonstrating that the SC formulation was non-inferior to the IV formulation based on ocrelizumab blood levels, and consistent control of clinical relapses through 48 weeks.
    * The safety profile of the SC formulation was consistent with the well-established safety profile of the intravenous formulation, with the exception of injection site reactions.
    * Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) allows for a shorter administration time compared to the intravenous infusion (30 minutes of premedication, 10 minutes of subcutaneous administration, and a 15-minute post-dose observational period). It is administered twice per year.

Natalizumab(Tysabri/Tyruko) for RRMS[2 28 29]

- The efficacy of natalizumab (Tysabri/Tyruko) was evaluated in two phase 3 studies in patients with relapsing-remitting MS. The two studies compared natalizumab to placebo.
- Results demonstrated that natalizumab was superior to placebo in reducing annualized relapse rates and lowering the rate of disability.
- AAN guidelines state that natalizumab (Tysabri/Tyruko), fingolimod (generic, Gilenya, Tascenso ODT), or Lemtrada (alemtuzumab) should be used in patients with highly active disease.

- Although no specific guidelines exist, proposed definitions of aggressive or highly active have been developed. It may be defined as at least one of the following: an EDSS score of 4 within 5 years of onset, multiple (two or more) relapses with incomplete resolution over a one-year period, more than two MRI studies showing new or enlarging T2 lesions or gadolinium-enhancing lesions despite treatment, no response to therapy with one or more disease-modifying therapies for up to 1 year, or the presence of spinal lesions. Monitoring for treatment efficacy via MRI is recommended every 6 months.
- Natalizumab (Tysabri/Tyruko) in combination with any other disease-modifying multiple sclerosis treatment medication has not been shown to be more effective than natalizumab (Tysabri/Tyruko) alone in the treatment of multiple sclerosis and may be contraindicated due to safety concerns.

PRIMARY PROGRESSIVE MS

Ocrevus (ocrelizumab) for Primary Progressive MS (PPMS)[24 30]

- Ocrevus (ocrelizumab) has been shown to slow disability progression and slow the worsening of MRI outcomes in patients with PPMS.
    * One 120-week study (ORATORIO) evaluated the effects of Ocrevus (ocrelizumab) relative to placebo in patients with PPMS. Ocrevus (ocrelizumab) was superior to placebo reducing the proportion of patients who had sustained 12-week confirmed disability progression. The treatment group also showed a significant decrease in T2 volume and showed significantly less brain volume loss on MRI.

Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) for PPMS[26 27]

- The efficacy and safety of Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) was established in a phase 3 trial (OCARINA II) that evaluated the pharmacokinetics, safety, and clinical efficacy of the subcutaneous (SC) formulation of Ocrevus (ocrelizumab and hyaluronidase-ocsq) compared with intravenous (IV) Ocrevus (ocrelizumab) infusion, in patients with RRMS and PPMS.
    * The trial met its primary endpoint, demonstrating that the SC formulation was non-inferior to the IV formulation based on ocrelizumab blood levels, and consistent control of clinical relapses through 48 weeks.
    * The safety profile of the SC formulation was consistent with the well-established safety profile of the intravenous formulation, with the exception of injection site reactions.
    * Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) allows for a shorter administration time compared to the intravenous infusion (30 minutes of premedication, 10 minutes of subcutaneous administration, and a 15-minute post-dose observational period). It is administered twice per year.

CROHN'S DISEASE

Natalizumab (Tysabri/Tyruko) for Crohn's Disease[28 31 32]

- FDA-approval of natalizumab (Tysabri/Tyruko) in Crohn's Disease (CD) was based on three trials: two in induction of clinical response/remission and one in the maintenance of remission.
    * Patients in the induction trials had moderately to severely active CD (Crohn's Disease Activity Index [CDAI] > 220 and < 450).

    * In one of the two induction studies, significant differences in response to natalizumab were only observed in the subgroup of patients with elevated C-reactive protein (CRP) levels. The second induction study used elevated CRP as an entry criterion. However, other medications (e.g. prednisone) may lower CRP levels, making this an insensitive predictor of efficacy.
    * The treatment effect in the induction studies ranged from approximately 13 to 15%.
    * In the trial that looked at maintenance of response of CD over 9 to 15 months, the treatment effect was approximately 33%.
- Concomitant use natalizumab (Tysabri/Tyruko) with immunosuppressives (6-mercaptopurine, azathioprine, cyclosporine, and methotrexate) or inhibitors of TNF-α (e.g., infliximab and adalimumab) is not recommended due to potential safety concerns.
- Natalizumab (Tysabri/Tyruko) is generally considered a last-line agent for Crohn's disease due to lack of comparative efficacy with other therapies and its potential for serious safety risks.
    * Steroids, immunosuppressives, and inhibitors of TNF-alpha are recommended prior to prescribing natalizumab (Tysabri/Tyruko).
    * A study demonstrating the efficacy of Humira (adalimumab) in patients in whom Remicade (infliximab) was not effective is the basis for recommending both Humira (adalimumab) and infliximab prior to natalizumab (Tysabri/Tyruko).
        ▪ A randomized, placebo-controlled study comparing Humira (adalimumab) with placebo in 325 patients with Crohn's disease who had lost response to treatment with, or were intolerant to, previous Remicade (infliximab) therapy demonstrated induction of remission in 21% versus 7% of patients who had received adalimumab and placebo, respectively ($p<0.001$, ABI 14%, NNT=8).
- One small trial (n = 79) studied the concomitant use of natalizumab (Tysabri/Tyruko) and Remicade (infliximab) in patients who did not achieve remission of their CD after 12 weeks of Remicade (infliximab).
    * The trial was not powered to detect differences in efficacy between treatment groups.
    * There were not enough patients in the study to determine whether there were differences in uncommon or rare adverse effects between treatment groups.
    * The natalizumab (Tysabri/Tyruko) prescribing information warns against use of this combination.
- Natalizumab (Tysabri/Tyruko) should be discontinued in patients with CD who:
    * Do not achieve therapeutic benefit after 12 weeks of induction therapy.
    * Cannot discontinue chronic concomitant steroids within six months of starting therapy.

ULCERATIVE COLITIS

Zeposia (ozanimod) for Ulcerative Colitis[33]

- Zeposia (ozanimod) was evaluated in the TRUE NORTH study, a phase 3 study that evaluated Zeposia (ozanimod) for the induction and maintenance of remission for UC versus placebo.

- Results showed that ozanimod improved rates of clinical response and remission compared to placebo. Improvements in histological remission and mucosal healing were also noted.
- Refer to Medication Policy Manual, Drugs for chronic inflammatory diseases, dru444 for treatment guidelines and severity criteria.

INVESTIGATIONAL USES

Lemtrada (alemtuzumab)[34-38]

- The Lemtrada REMS program mitigates off-label use of Lemtrada (alemtuzumab); however, it has been studied in other conditions. Due to a lack of published data, lack of high-quality data, or lack of positive data, these conditions are considered investigational. Details of select investigational uses are reported below.
- B-cell chronic lymphocytic leukemia:
  * A high dose formulation of Campath (alemtuzumab) was approved for the treatment of B-cell chronic lymphocytic leukemia (CLL) but was removed from the market in 2012 to prevent off-label use of Campath (alemtuzumab) in MS. Since 2012, Campath (alemtuzumab) has been available for very limited use in CLL through patient access programs. Lemtrada (alemtuzumab) is given at a lower dose when used for MS, lower doses are considered investigational for any other condition, including CLL and other cancers.
  * There have been no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in B-cell chronic lymphocytic leukemia.
  * High-dose Campath (alemtuzumab) is available for patients with leukemia directly from the manufacturer, free of charge through patient access programs.
- Post-transplant antibody induction therapy:
  * There are no controlled clinical trials evaluating the use of low-dose (12 mg) Lemtrada (alemtuzumab) in the post-transplant setting.

Natalizumab (Tysabri/Tyruko)[28 39]

- A Risk Evaluation and Mitigation Strategy (REMS) Prescribing Program currently prevents off-label use of natalizumab (Tysabri/Tyruko).
- Authors of a small, open-label study in 10 patients with active ulcerative colitis reported clinical benefit at 4 weeks with administration of natalizumab. Larger, well-designed trials are needed before safety and efficacy are established for this indication.
- There are no data available to support the safety and efficacy of natalizumab (Tysabri/Tyruko) in the treatment of rheumatoid arthritis.

Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)[25 40-43]

- Due to a lack of published data, the use of Ocrevus (ocrelizumab) and Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) in conditions other than relapsing forms of MS and PPMS is considered investigational.
- *Higher dosing*: Although there is an ongoing trial investigating higher doses of Ocrevus (ocrelizumab) in the setting of multiple sclerosis, there is currently insufficient published evidence to support the use of higher doses of Ocrevus (ocrelizumab), above those listed in the Quantity Limits Table 4.
- *Neuromyelitis optica spectrum disorders (NMOSD; previously known as Devic disease)*
  * NMSOD are characterized by a combination of bilateral optic neuropathy and cervical myelopathy. While both NMOSD and MS are demyelinating diseases

they are: considered different diseases based on unique immunologic features and differences in imaging features, biomarkers, and neuropathology.

* Rituximab has been shown to the frequency of NMOSD relapses and neurologic disability based on results from one systematic review. However, the optimal treatment regimen and duration have not been determined and additional long-term safety experience is needed to clarify the role of rituximab as a first-line option.
* There is no published evidence to support the use of Ocrevus (ocrelizumab) for NMOSD.
* While Ocrevus (ocrelizumab) has a similar mechanism of action to rituximab, it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Kesimpta (ofatumumab) and Briumvi (ublituximab-xiiy)[19 44]

- Due to a lack of published data, the use of Kesimpta (ofatumumab) or Briumvi (ublituximab-xiiy) in conditions other than relapsing forms of MS is considered investigational.
- While Kesimpta (ofatumumab) and Briumvi (ublituximab-xiiy) have a similar mechanism of action to rituximab, it has not been studied for the same indications. Thus, due to a lack of data, these conditions are considered investigational.

Zeposia (ozanimod)[30]

- The use of combination (more than one) targeted immunomodulator for UC, such as Humira (adalimumab), or tofacitinib (Xeljanz/Xeljanz XR), is considered investigational. Ozanimod has only been studied as monotherapy for UC. There is no evidence supporting the safety or efficacy of combination therapy with another targeted immunomodulator.

Safety

Copaxone (glatiramer acetate)

- Copaxone (glatiramer acetate) has a boxed warning for risk of life-threatening and fatal anaphylaxis.[7]

Lemtrada (alemtuzumab)[3]

- Lemtrada (alemtuzumab) has boxed warnings for the following:
  * Sometimes fatal autoimmune conditions, such as immune thrombocytopenia and anti-glomerular basement membrane diseases.
  * Serious and life-threatening infusion reactions.
  * An increased risk of malignancies including thyroid cancer, melanoma, and lymphoproliferative disorders.
- Due to its significant safety concerns an FDA Risk Evaluation and Mitigation Strategy (REMS) program limits the availability of Lemtrada (alemtuzumab) to certified prescribers, healthcare facilities, and specialty pharmacies.
- Regular monitoring is required due to the potential for long-term adverse events. Complete blood count, serum creatinine levels, urinalysis should be collected prior to treatment and at monthly intervals. Thyroid function tests should be conducted prior to treatment and every three months thereafter. Baseline and annual skin exams should be conducted to monitor for melanoma.

Mayzent (siponimod)[45]

- Mayzent (siponimod) requires an initial 5-day dose titration period due to the risk of first-dose bradycardia. Additionally, first-dose monitoring is required for patients with sinus bradycardia, first- or second-degree atrioventricular block, or a history of myocardial infarction or heart failure.

Natalizumab (Tysabri/Tyruko)[28]

- Several cases of progressive multifocal leukoencephalopathy (PML), a progressive demyelinating disease of the CNS, have been associated with natalizumab (Tysabri/Tyruko) use. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability.
- The natalizumab (Tysabri/Tyruko) prescribing information contains a Boxed Warning describing the increased risk of PML, which may lead to death or severe disability.
- Because of the risk of PML, distribution of natalizumab (Tysabri/Tyruko) is restricted via a REMS Prescribing Program.
    * Providers must register to prescribe, distribute, or infuse natalizumab (Tysabri/Tyruko).
    * Only patients who are registered with and who meet all the conditions of either the MS or CD REMS programs are eligible to receive natalizumab (Tysabri/Tyruko).
- The most common side effects observed in patients receiving natalizumab (Tysabri/Tyruko) include infections, acute hypersensitivity reactions, depression, and cholelithiasis (gall stones).
- There are several case reports of patients who developed melanoma after starting treatment with natalizumab (Tysabri/Tyruko)). Although cause has not been established, clinicians should be aware of this potential risk, especially when considering therapy for patients with a history of melanoma.
- The natalizumab (Tysabri/Tyruko) prescribing information contains a warning regarding the potential for liver injury. In some patients this occurred as early as six days after an initial dose.

Appendix A: Disease-Modifying Agents Used in the Treatment of Multiple Sclerosis (MS)
Bafiertam (monomethyl fumarate)
Briumvi (ublituximab-xiiy)
Cladribine (generic, Mavenclad)
Dimethyl fumarate (generic, Tecfidera)
Fingolimod (generic, Gilenya, and Tascenso ODT)
Glatiramer acetate (generic glatiramer, Glatopa, and Copaxone)
Interferon beta-1a (Avonex, Rebif)
Interferon beta-1b (Betaseron, Extavia)
Kesimpta (ofatumumab)
Lemtrada (alemtuzumab)
Mayzent (siponimod)
Natalizumab (Tysabri/ biosimilar Tyruko)
Novantrone (mitoxantrone)
Ocrevus (ocrelizumab)
Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq)
Plegridy (peginterferon beta-1a)
Ponvory (ponesimod)
Rituximab*
Teriflunomide (generic, Aubagio)
Vumerity (diroximel fumarate)
Zeposia (ozanimod)

*Rituximab is not FDA-approved for use in MS, but has evidence for efficacy[2]

Appendix B: Multiple Sclerosis Forms/Clinical Course Definitions[1 2]	
Clinically isolated syndrome (CIS)	The first clinical presentation that shows characteristics of inflammatory demyelination that could be MS.
Relapsing-remitting MS (RRMS)	Characterized by acute relapses that are followed by some degree of recovery. These attacks develop acutely, evolving over days to weeks. Over the next several weeks to months, most patients experience a recovery of function that is often (but not always) complete. Between attacks the patient is neurologically and symptomatically stable.
Secondary progressive MS (SPMS)	Defined as sustained progression of physical disability occurring separately from relapses, in patients who previously had RRMS. SPMS may be active or not active. Activity is determined by the presence of ongoing relapses or MRI activity. There are no clinical, imaging, immunologic, or pathologic criteria to determine when a patient transition from RRMS to SPMS, it is usually diagnosed retrospectively.
Primary progressive MS (PPMS)	Defined as progression of disability from onset without superimposed relapses. The AAN defines PPMS as the third clinical type characterized by a steady decline in function from the beginning without acute attacks.

Appendix C: Step Therapy Medications

Targeted Agents and GPIs/NDCs (multisource code)	Prior Agents and GPIs/NDCs (multisource code) Prerequisites	Look-Back Time Frame
• Bafiertam 62405550****** (M,N,O,Y) • Extavia 00078-0569-** (NDC) • Mayzent 62407070******(M,N,O,Y) • Ponvory 62407060****** (M,N,O,Y) • Vumerity 62405530****** (M,N,O,Y)	**ONE** of the following: • dimethyl fumarate 62405525**** (Y) • fingolimod 62407025****** (Y) • teriflunomide 62404070****** (Y) • glatiramer 62400030****** (Y) **AND** **ONE** of the following: • Avonex/Rebif 6240306045**** (M,N,O,Y) • Kesimpta 62405065****** (M,N,O,Y) • Zeposia 62407050****** (M,N,O,Y)	180 days

Cross References
Site of Care Review, Medication Policy Manual, Policy No. dru408
Drugs for Chronic Inflammatory Diseases, Medication Policy Manual, Policy No. dru444
Products with Therapeutically Equivalent Biosimilars/Reference Products, Medication Policy Manual, Policy No. dru620

Codes	Number	Description
HCPCS	J0202	Injection, alemtuzumab (Lemtrada) 1mg
HCPCS	J2323	Injection, natalizumab (Tysabri), 1 mg
HCPCS	Q5134	Injection, natalizumab (Tyruko), 1 mg
HCPCS	J2350	Injection, ocrelizumab (Ocrevus), 1 mg
HCPCS	J2351	Injection, ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo), 1 mg
HCPCS	J2329	Injection, ublituximab-xiiy (Briumvi), 1mg
ICD-10	G35	Multiple sclerosis

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Revision History

Revision Date	Revision Summary
1/22/2026	• Added generic Mavenclad (cladribine) at parity with brand. • Removed Rinvoq (upadacitinib) from preferred options for ulcerative colitis. • Added HCPCS for Ocrevus Zunovo. • Updated criteria formatting without any change to intent other than changes listed above.
3/6/2025	Effective 7/1/25: SOC requirement added for natalizumab (Tysabri/Tyruko).
12/12/2024	Added new subcutaneous Ocrevus Zunovo (ocrelizumab and hyaluronidase-ocsq) to policy.
10/10/2024	Effective 12/1/2024: • Updated preferred options to include Skyrizi (risankizumab) and Tremfya (guselkumab) for treatment of ulcerative colitis • No change to intent. Effective 1/1/2025: • Updated preferred options to include Entyvio SC (vedolizumab) for treatment of ulcerative colitis • No change to intent.
12/7/2023	• Added newly approved Tysabri (natalizumab) biosimilar Tyruko (natalizumab) to policy. • Added Briumvi (ublituximab) and Kesimpta (ofatumumab) as options for highly active disease, no change to intent.
9/14/2023	Effective 1/1/2024, Betaseron (interferon beta-1b), Mavenclad (cladribine) and Plegridy (peginterferon beta-1a) have been moved to non-preferred.
6/15/2023	New combination policy (effective 9/1/2023): • Combined the following medication policies: dru111 Tysabri (natalizumab), dru479 Ocrevus (ocrelizumab), dru511 Non-preferred MS treatments, dru570 Non-preferred Glatiramer Products, dru674 Zeposia (ozanimod), dru739 Briumvi (ublituximab-xiiy). • Prior authorization (PA) not required for the following DMTs for MS: - Generic dimethyl fumarate, generic fingolimod, generic teriflunomide, generic glatiramer (no change to coverage).

Revision Date	Revision Summary
	- Glatiramer (Glatopa) (changed to "no PA required"). • Change in PA requirements for relapsing forms of MS (RRMS, CIS, SPMS) for the following higher-cost DMTs for MS: - Preferred branded products: now require PA and step therapy with a low-cost product. - Non-preferred branded products: modified step therapy to require a low-cost product and a higher-cost preferred brand product. • Clarification that Ocrevus (ocrelizumab) is also coverable under "particularly aggressive relapsing form of MS" criteria. • No changes to criteria or intent of Zeposia (ozanimod) for ulcerative colitis or Tysabri (natalizumab) for Crohn's disease.

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