Clinical Policy Title:	natalizumab
Policy Number:	RxA.532
Drug(s) Applied:	Tysabri®
Original Policy Date:	01/2020
Last Review Date:	09/14/2021
Line of Business Policy Applies to:	All lines of business

Background

Natalizumab (Tysabri®) is an integrin receptor antagonist. It is indicated for the treatment of:

- Multiple Sclerosis (MS):
  Natalizumab is indicated as monotherapy for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

- Crohn's Disease (CD):
  Natalizumab is indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and TNF-α inhibitors.

Limitation(s) of use:

- Natalizumab increases the risk of progressive multifocal leukoencephalopathy. When initiating and continuing treatment with natalizumab, providers should consider whether the expected benefit of natalizumab is sufficient to offset this risk.
- In CD, natalizumab should not be used in combination with immunosuppressants or TNF-α inhibitors.

Dosing Information

Drug Name	Indication	Dosing Regimen	Maximum Dose
natalizumab (Tysabri®)	Relapsing Multiple Sclerosis Crohn's Disease	300 mg intravenously every 4 weeks. In CD, discontinue in patients who have not experienced therapeutic benefit by 12 weeks of induction therapy and in patients that cannot discontinue chronic concomitant steroids within six months of starting therapy	300 mg/4 weeks

Dosage Forms

- Single-use vial: 300 mg/15 mL

Clinical Policy

Provider must submit documentation (such as office chart notes, lab results or other clinical information) supporting that member has met all approval criteria. The provision of provider samples does not guarantee coverage under the terms of the pharmacy benefit administered by RxAdvance. All criteria for initial approval must be met in order to obtain coverage.

I. Initial Approval Criteria

A. Multiple Sclerosis (must meet all):

1. Diagnosis of one of the following (a, b, or c):
   a. Clinically isolated syndrome;
   b. Relapsing-remitting multiple sclerosis;
   c. Secondary progressive multiple sclerosis;
2. Prescribed by or in consultation with a neurologist;
   Note: Only prescribers registered in the MS TOUCH® Prescribing Program may prescribe Tysabri® for multiple sclerosis.
3. Age 18 ≥ years of age;
4. Trial and failure of at least one (1) preferred disease modifying therapy (Avonex®, Betaseron®, Copaxone®, Vumerity®, Bafiertam®, or Kesimpta®), at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced.*
   *Prior authorization may be required for disease modifying therapies for MS
5. Natalizumab is not prescribed concurrently with other disease modifying therapies for multiple sclerosis (see Appendix B);
6. Dose does not exceed 300 mg (1 vial) every 4 weeks.

Approval Duration
Commercial: 6 months
Medicaid: 6 months

B. Crohn's Disease

1. Refer to RxA.592.Biologic_DMARDs.

II. Continued Therapy Approval

A. Multiple Sclerosis (must meet all):

1. Member is currently receiving medication that has been authorized by RxAdvance or member has previously met initial approval criteria listed in this policy;
2. Member is responding positively to therapy (i.e. reduction in the number of acute attacks, no new brain lesions, disease stabilization);
3. Natalizumab is not prescribed concurrently with other disease modifying therapies for multiple sclerosis (see Appendix B);
4. If request is for a dose increase, new dose does not exceed 300 mg every 4 weeks.

Approval Duration
Commercial: 12 months
Medicaid: 12 months

B. Crohn's Disease

1. Refer to RxA.592.Biologic_DMARDs.

III. Appendices

APPENDIX A: Abbreviation/Acronym Key
CD: Crohn's disease
FDA: Food and Drug Administration
MS: Multiple Sclerosis
TNF-α: Tumor Necrosis Factor-α

APPENDIX B: Therapeutic Alternatives
Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Infusion therapies		
mitoxantrone	12 mg/m^2 given as a short (approximately 5 to 15 minutes) intravenous infusion every 3 months	Cumulative lifetime dose of ≥ 140 mg/m^2
ocrelizumab (Ocrevus™)	Initial 300 mg intravenous infusion with a second 300 mg intravenous infusion two weeks later, followed by subsequent doses of 600 mg via intravenous infusion every 6 months	600 mg/6 months
alemtuzumab (Lemtrada®)	Intravenous infusion for 2 or more treatment courses: • First course: 12 mg/day on 5 consecutive days • Second course: 12 mg/day on 3 consecutive days 12 months after first course • Subsequent courses as needed: 12 mg/day on 3 consecutive days 12 months after any prior course	See regimen
Injectable therapies		
glatiramer (Copaxone®, Glatopa®)	20 mg subcutaneously once daily or 40 mg subcutaneously three times weekly	20 mg/day or 40 mg three times per week
interferon beta-1a (Avonex®, Rebif®)	Avonex®: 30 mcg intramuscularly weekly Rebif®: 22 mcg or 44 mcg subcutaneously three times weekly	Avonex®: 30 mcg/week Rebif®: 44 mcg three times per week
interferon beta-1b (Betaseron®, Extavia®)	250 mcg subcutaneously every other day	250 mg every other day
peginterferon beta-1a (Plegridy®)	125 mcg subcutaneously every 2 weeks	125 mcg/2 weeks

Drug Name	Dosing Regimen	Dose Limit/ Maximum Dose
Oral therapies		
dimethyl fumarate (Tecfidera®)	120 mg orally twice daily for 7 days, followed by 240 mg orally twice daily	480 mg/day
monomethyl fumarate (Bafiertam™)	Initial: 95 mg orally twice daily; after 7 days, increase to the maintenance dose: 190 mg orally twice daily.	380mg/day
diroximel fumarate (Vumerity®)	Starting: 231 mg orally twice daily for 7 days Maintenance: 462 mg orally twice daily	924 mg/day
teriflunomide (Aubagio®)	7 mg or 14 mg orally daily	14 mg/day
fingolimod (Gilenya™)	0.5 mg orally daily	0.5 mg/day
siponimod (Mayzent®)	All patients: Day 1 and 2: 0.25 mg orally once daily Day 3: 0.5 mg orally once daily Day 4: 0.75 mg orally once daily For CYP2C9 genotypes *1/*1, *1/*2, or *2/*2: Day 5: 1.25 mg orally once daily Day 6 & onward: 2 mg orally once daily For CYP2C9 genotypes *1/*3 or *2/*3: Day 5 & onward: 1 mg orally once daily	2 mg/day
ozanimod (Zeposia®)	Days 1-4: 0.23 mg orally once daily Days 5-7: 0.46 mg orally once daily Day 8 & onward: 0.92 mg orally once daily	0.92mg/day
cladribine (Mavenclad®)	3.5 mg/kg over 2-year treatment course, administered as 1.75 mg/kg in each year. Divide the 1.75 mg/kg dose over 2 cycles, each cycle lasting 4 to 5 consecutive days	20mg/day
dalfampridine (Ampyra®)	10 mg orally twice daily (approximately 12 hours apart)	20 mg/day

Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only.

APPENDIX C: Contraindications/Boxed Warnings

- Contraindication(s):
  - Patients who have or have had progressive multifocal leukoencephalopathy
  - Patients who have had a hypersensitivity reaction to Tysabri®

- Boxed Warning(s):
  - Progressive multifocal leukoencephalopathy

APPENDIX D: General Information

- Because of the risk of progressive multifocal leukoencephalopathy, natalizumab is only available through a REMS program called the TOUCH® Prescribing Program.
- The American Academy of Neurology 2018 MS guidelines recommend the use of Gilenya™, Tysabri®, and Lemtrada® for patients with highly active MS. Definitions of highly active MS vary and can include measures of relapsing activity and MRI markers of disease activity, such as numbers of gadolinium-enhanced lesions.

References

1. Tysabri Prescribing Information. Cambridge, MA: Biogen Inc; June 2020. Available at: http://www.tysabri.com. Accessed August 20, 2021.
2. Costello K, Halper J, Kalb R, Skutnik L, Rapp R. The use of disease-modifying therapies in multiple sclerosis, principles and current evidence – a consensus paper by the Multiple Sclerosis Coalition. Available at: https://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/DMT_Consensus_MS_Coalition.pdf. March 2017. Accessed August 20, 2021.
3. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018; 90(17): 777-788. Full guideline available at: https://www.aan.com/Guidelines/home/GetGuidelineContent/904. Accessed August 20, 2021.
4. Clinical Pharmacology [database online] powered by ClinicalKey. Tampa, FL: Elsevier, 2020. Accessed with subscription at: http://www.clinicalkey.com. Accessed August 20, 2021.

Review/Revision History	Review/Revision Date	P&T Approval Date
Policy established.	01/01/2020	03/06/2020
Policy updated. 1. Initial approval criteria to include “Trial and failure of at least 2 preferred disease modifying therapies, at up to maximally indicated doses, unless contraindicated or clinically significant adverse effects are experienced.” 2. Approval duration for all lines of business updated. 3. Appendix B list of drugs updated 4. Appendix D updated Approval duration for all lines of business	08/27/2020	09/14/2020
Policy updated. 1. Policy title updated 2. Policy was updated to all lines of business.	09/14/2020	12/07/2020

3. Continued therapy criteria II.A.1 was rephrased to "Currently receiving medication that has been authorized by RxAdvance…". Appendix B updated.		
Policy was reviewed. 1. Statement about provider sample ''The provision of provider samples does not guarantee coverage…" was added to Clinical Policy. 2. Initial Approval Criteria I.A.4, trial and failure criteria, was updated from requiring member to try/fail at least two other therapies to requiring member to try/fail at least one other therapy; possible therapies to try were updated to include "(Avonex®, Betaseron®, Copaxone®, Vumerity®, Bafiertam®, Kesimpta®)". 3. Appendix A was updated to remove abbreviations SC, PO, and IV. 4. Therapeutic Alternatives verbiage was rephrased to "Below are suggested therapeutic alternatives based on clinical guidance. Please check drug formulary for preferred agents and utilization management requirements.". 5. Statement about drug listing format in Appendix B is rephrased to "Therapeutic alternatives are listed as generic (Brand name®) when the drug is available by both generic and brand; Brand name® when the drug is available by brand only and generic name when the drug is available by generic only". 6. References were reviewed and updated.	08/20/2021	09/14/2021