Original Effective Date: 10/1/2013
Current Effective Date: 06/21/2023
Last P&T Approval/Version: 04/26/2023
Next Review Due By: 04/2024
Policy Number: C10267-A

Multiple Sclerosis Agents- Interferons

PRODUCTS AFFECTED

Avonex (interferon beta 1a), Extavia (interferon beta 1b), Betaseron (interferon beta 1b), Rebif (interferon beta 1a), Plegridy (peginterferon beta 1a)

COVERAGE POLICY

Coverage for services, procedures, medical devices and drugs are dependent upon benefit eligibility as outlined in the member's specific benefit plan. This Coverage Guideline must be read in its entirety to determine coverage eligibility, if any.
This Coverage Guideline provides information related to coverage determinations only and does not imply that a service or treatment is clinically appropriate or inappropriate. The provider and the member are responsible for all decisions regarding the appropriateness of care. Providers should provide Molina Healthcare complete medical rationale when requesting any exceptions to these guidelines.

Documentation Requirements:
Molina Healthcare reserves the right to require that additional documentation be made available as part of its coverage determination; quality improvement; and fraud; waste and abuse prevention processes. Documentation required may include, but is not limited to, patient records, test results and credentials of the provider ordering or performing a drug or service. Molina Healthcare may deny reimbursement or take additional appropriate action if the documentation provided does not support the initial determination that the drugs or services were medically necessary, not investigational or experimental, and otherwise within the scope of benefits afforded to the member, and/or the documentation demonstrates a pattern of billing or other practice that is inappropriate or excessive.

DIAGNOSIS:
Multiple Sclerosis (MS)

REQUIRED MEDICAL INFORMATION:
This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. If a drug within this policy receives an updated FDA label within the last 180 days, medical necessity for the member will be reviewed using the updated FDA label information along with state and federal requirements, benefit being administered and formulary preferencing. Coverage will be determined on a case-by case basis until the criteria can be updated through Molina Healthcare, Inc. clinical governance. Additional information may be required on a case-by-case basis to allow for adequate review. When the requested drug product for coverage is dosed by weight, body surface area or other member specific measurement, this data element is required as part of the medical necessity review.

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:
1. Documentation of a definitive diagnosis of a relapsing form of multiple sclerosis including: Relapsing- remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, and progressive- relapsing multiple sclerosis [PRMS] or First clinical episode with MRI features consistent with multiple sclerosis

AND

2. Prescriber attests that member is not currently being treated with a disease modifying agent (DMA) other than the requested agent
   AND
3. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [Contraindications to AVONEX (interferon beta-1a) include: History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation. Contraindications to EXTAVIA (interferon beta-1b) include: History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol. Contraindications to REBIF (interferon beta-1a) include: History of hypersensitivity to natural or recombinant interferon beta, human albumin, or any other component of the formulation. Contraindications to PLEGRIDY (peginterferon beta-1a) include: History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of the formulation.]
   AND
4. IF REQUEST IS FOR A NON-FORMULARY/NON-PREFERRED PRODUCT: Documentation of trial/failure of or intolerance to a majority (not more than 3) of the preferred formulary/PDL alternatives for the given diagnosis. Submit documentation including medication(s) tried, dates of trial(s) and reason for treatment failure(s).

CONTINUATION OF THERAPY:

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Documentation of positive clinical response or stable disease based on ONE of the following:
   (a) Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months
   OR
   (b) Documentation of lack of progression or sustained disability
   OR
   (c) Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions
   AND
2. Adherence to therapy at least 85% of the time as verified by Prescriber and member's medication fill history
   AND
3. Prescriber attests to or clinical reviewer has found no evidence of intolerable adverse effects or drug toxicity

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of therapy: 12 months

PRESCRIBER REQUIREMENTS:

Prescribed by or in consultation with a board-certified neurologist or a multiple sclerosis specialist. [If prescribed in consultation, consultation notes must be submitted with initial request and reauthorization requests]

AGE RESTRICTIONS:

18 years of age or older

QUANTITY:

Avonex (interferon beta 1a): maximum of 30 mcg IM once weekly
Extavia (interferon beta 1b) & Betaseron (interferon beta 1b): maximum 0.25mg SC once every other day
Rebif (interferon beta 1a): maximum 44mcg SC three times a week
Plegridy (peginterferon beta-1a): 63 micrograms on day 1, 94 micrograms on day 15, and 125 micrograms (full dose) on day 29 then 125 micrograms every 14 days

PLACE OF ADMINISTRATION:
The recommendation is that injectable medications in this policy will be for pharmacy benefit coverage and patient self-administered.

The recommendation is that injectable medications in this policy will be for pharmacy or medical benefit coverage and the intramuscular injectable products be administered in a place of service that is a non-hospital facility-based location.

DRUG INFORMATION

ROUTE OF ADMINISTRATION:
Intramuscular, Subcutaneous

DRUG CLASS:
Multiple Sclerosis Agents - Interferons

FDA-APPROVED USES:
Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

COMPENDIAL APPROVED OFF-LABELED USES:
None

APPENDIX

APPENDIX:
Summary of 2017 McDonald Criteria for the Diagnosis of MS

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
• 2 or more attacks and clinical evidence of 2 or more lesions; OR • 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location	None. DIS and DIT have been met.
• 2 or more attacks and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
• 1 attack and clinical evidence of 2 or more lesions	DIT shown by <u>one</u> of these criteria: - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
• 1 attack and clinical evidence of 1 lesion	DIS shown by <u>one</u> of these criteria: - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord **AND** DIT shown by <u>one</u> of these criteria: - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time **CNS** = central nervous system **CSF** = cerebrospinal fluid
DIS = Dissemination in space **T2 lesion** = hyperintense lesion on T2-weighted MRI

BACKGROUND AND OTHER CONSIDERATIONS

BACKGROUND:
Multiple sclerosis (MS) is an immune mediated disease that affects the central nervous system (CNS). It is characterized by demyelization and inflammation of the CNS. Diagnosis of MS is primarily based on clinical presentation. The core requirement for the diagnosis is demonstration of CNS lesion dissemination and presence of symptoms such as visual loss, motor function loss, difficulty with balancing, and vertigo. There are currently four major types of MS: Relapsing MS (RRMS), Primary Progressive MS (PPMS), Secondary Progressive MS, and Progressive-Relapsing MS (PRMS). MS is primarily treated with corticosteroids and disease modifying agents (DMAs).
Most of the currently FDA approved DMAs are indicated for treatment of RRMS.

The goal of treatment with DMAs is to reduce the number and severity of relapses, reduce the number of new lesions appearing on magnetic resonance imaging, and reduce long-term progression of MS. There are several agents currently FDA approved for the treatment of relapsing remitting MS (RRMS). These include Avonex and Rebif (both interferon beta-1a), Plegridy (peginterferon beta-1a), Betaseron and Extavia (both interferon beta-1b), Copaxone (glatiramer acetate), Lemtrada (alemtuzumab), Tysabri (natalizumab), mitoxantrone, Gilenya (fingolimod), Aubagio (teriflunomide), Tecfidera (dimethyl fumarate) and Ocrevus. Guidelines from the United States and Europe consider glatiramer and interferon beta (INF) as appropriate first line therapies for treatment of RRMS. 8,9,29 The INF agents are considered appropriate for patients at high risk of developing clinically definite MS, or those who already have RRMS or secondary progressive MS and are experiencing relapses. Currently there are three interferon beta-1a agents (Rebif, Avonex, and Plegridy). The three products differ in dose and frequency of dosing (three times a week, once weekly, and once every other week respectively). There is a probable dose or frequency of dosing response curve associated with use of INF agents. Interferon beta-1a has been associated with less neutralizing antibody formation than interferon beta- 1b (Betaseron, Extavia). The clinical effects of these neutralizing antibodies are uncertain. Their presence has been associated with a possible decrease in interferon efficacy. The route of administration of the INF agents does not have apparent effects on efficacy but side effect profiles differ between routes of administration.

Beta interferons are approved to be used for relapsing forms of Multiple Sclerosis (MS). The exact mechanism of action is unknown. Beta interferons are proteins and therefore injectable products. Beta interferons addressed in this policy include Avonex, Betaseron, Extavia, Plegridy, and Rebif. Dosing frequency varies between beta interferon products.

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:
All other uses of beta interferon products are considered experimental/investigational and therefore, will follow Molina's Off-Label policy. Contraindications to AVONEX (interferon beta-1a) and REBIF (interferon beta-1a) include: History of hypersensitivity to natural or recombinant interferon beta, albumin or any other component of the formulation. Contraindications to BETASERON (interferon beta-1b) and EXTAVIA (interferon beta-1b) include: History of hypersensitivity to natural or recombinant interferon beta, albumin or mannitol. Contraindications to PLEGRIDY (peginterferon beta-1a) include: History of hypersensitivity to natural or recombinant interferon beta or peginterferon, or any other component of Plegridy.

OTHER SPECIAL CONSIDERATIONS:
None

CODING/BILLING INFORMATION

Note: 1) This list of codes may not be all-inclusive. 2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement

HCPCS CODE	DESCRIPTION
Q3027	Injection, interferonbeta-1a, 1 mcg for intramuscular use
Q3028	Injection, interferon beta-1a, 1 mcg for subcutaneous use
J1826	Injection, interferon beta-1a, 30 mcg
J1830	Injection, interferon beta-1b, 0.25 mg (code maybe used for Medicare when drug administered under the direct supervision of a physician, not for use when drug is self-administered)
J3590	(Plegridy for intramuscular use) Unclassified biologics

AVAILABLE DOSAGE FORMS:
Avonex Pen AJKT 30MCG/0.5ML
Avonex Prefilled PSKT 30MCG/0.5ML
Betaseron KIT 0.3MG
Extavia KIT 0.3MG
Plegridy SOPN 125MCG/0.5ML
Plegridy SOSY 125MCG/0.5ML
Plegridy SOSY 125MCG/0.5ML
Plegridy Starter Pack SOPN 63 & 94MCG/0.5ML
Plegridy Starter Pack SOSY 63 & 94MCG/0.5ML
Rebif Rebidose SOAJ 22MCG/0.5ML
Rebif Rebidose SOAJ 44MCG/0.5ML
Rebif Rebidose Titration Pack SOAJ 6X8.8 & 6X22MCG
Rebif SOSY 22MCG/0.5ML
Rebif SOSY 44MCG/0.5ML
Rebif Titration Pack SOSY 6X8.8 & 6X22MCG

REFERENCES

1. Avonex prescribing information. Biogen Idec, Inc. November 2021
2. Betaseron prescribing information. Bayer HealthCare Pharmaceuticals Inc. November 2021.
3. Extavia prescribing information. Novartis. November 2021.
4. Rebif prescribing information. Serono, Inc./Pfizer Inc. November 2021.
5. Plegridy (peginterferon beta-1a) [prescribing information]. Cambridge, MA: Biogen Idec Inc; March 2022.
6. Montalban X, Gold R, Thompson AJ, et al. ECTRIMS/EAN Guideline on the pharmacological treatment of people with multiple sclerosis. Mult Scler 2018; 24:96.
7. 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; 90:777.
8. Thompson, A., Banwell, B. et al. (2018). Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. The Lancet Neurology, 17(2), pp.162-173.

SUMMARY OF REVIEW/REVISIONS	DATE
REVISION- Notable revisions: Required Medical Information Continuation of Therapy Prescriber Requirements FDA-Approved Uses Contraindications/Exclusions/Discontinuation HCPCS Code and Description Available Dosage Forms	Q2 2023
REVISION- Notable revisions: Coding/Billing Information References	Q2 2022
Q2 2022 Established tracking in new format	Historical changes on file