Beta Interferons for the Treatment of Multiple Sclerosis

Policy # 00759
Original Effective Date: 01/01/2022
Current Effective Date: 11/13/2023

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc.(collectively referred to as the "Company"), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage

Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- *Benefits are available in the member's contract/certificate, and*
- *Medical necessity criteria and guidelines are met.*

Based on review of available data, the Company may consider interferon beta-1b (Betaseron®, Extavia®)‡, interferon beta-1a (Avonex®, Rebif®, Rebif® Rebidose®)‡, and peginterferon beta-1a (Plegridy®)‡ for the treatment of relapsing forms of multiple sclerosis to be **eligible for coverage.****

Patient Selection Criteria

Coverage eligibility for interferon beta-1b (Betaseron, Extavia), interferon beta-1a (Avonex, Rebif, Rebif Rebidose), and peginterferon beta-1a (Plegridy) will be considered when the following criterion is met:

- Patient has a relapsing form of multiple sclerosis (including clinically isolated syndrome, relapsing-remitting disease, active secondary progressive disease).

When Services Are Considered Investigational

Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers the use of interferon beta-1b (Betaseron, Extavia), interferon beta-1a (Avonex, Rebif, Rebif Rebidose), and peginterferon beta-1a (Plegridy) when the patient selection criterion is not met to be **investigational.***

Beta Interferons for the Treatment of Multiple Sclerosis

Policy # 00759
Original Effective Date: 01/01/2022
Current Effective Date: 11/13/2023

Background/Overview

Beta interferons are some of the oldest disease modifying treatments for multiple sclerosis and are available in a number of different preparations. All are indicated for the treatment of relapsing forms of multiple sclerosis in adults. They are all associated with flu-like symptoms on administration days and can be given with analgesics and/or antipyretics to ameliorate this side effect. Betaseron and Extavia are both essentially the same formulation of interferon beta-1b and should be administered subcutaneously every other day. The difference between Betaseron and Extavia is that Extavia is supplied with a 27 gauge needle and Betaseron is supplied with a 30 gauge needle. Avonex and Rebif are both formulations of interferon beta-1a, but the route of administration is different. Avonex is administered intramuscularly once weekly and Rebif is administered subcutaneously three times weekly. Plegridy contains pegylated interferon beta-1a and can be administered either subcutaneously or intramuscularly every 14 days. Switching between the subcutaneous and intramuscular routes of administration of Plegridy has not been studied.

Multiple sclerosis (MS) is believed to have an immunologic mechanism that is characterized by demyelination in the brain and spinal cord. This is often expressed by symptoms such as visual and oculomotor abnormalities, weakness, urinary dysfunction, and mild cognitive impairment. In the most common forms of MS, patients experience remissions and exacerbations. Treatment includes corticosteroids for acute exacerbations and immunomodulatory (disease modifying) drugs to prevent exacerbations. Disease modifying drugs include oral products such as fingolimod (Gilenya®)‡, ponesimod (Ponvory™)‡, siponimod (Mayzent®)‡, ozanimod (Zeposia®)‡, dimethyl fumarate (Tecfidera®, generics)‡, diroximel fumarate (Vumerity®)‡, teriflunomide (Aubagio®)‡, and cladribine (Mavenclad®)‡; subcutaneous and intramuscular injectable products such as glatiramer acetate (Copaxone®, generics)‡, interferon beta-1a (Avonex, Rebif), interferon beta-1b (Extavia, Betaseron), peginterferon beta-1a (Plegridy), and ofatumumab (Kesimpta®)‡; and intravenous infusions such as ocrelizumab (Ocrevus®)‡, natalizumab (Tysabri®)‡, and alemtuzumab (Lemtrada®)‡.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)

Betaseron, Extavia, Avonex, Rebif, and Plegridy are each approved for the treatment of relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

Beta Interferons for the Treatment of Multiple Sclerosis

Policy # 00759
Original Effective Date: 01/01/2022
Current Effective Date: 11/13/2023

Rationale/Source

This medical policy was developed through consideration of peer-reviewed medical literature generally recognized by the relevant medical community, U.S. Food and Drug Administration approval status, nationally accepted standards of medical practice and accepted standards of medical practice in this community, technology evaluation centers, reference to federal regulations, other plan medical policies, and accredited national guidelines.

Betaseron and Extavia

The efficacy of subcutaneous interferon beta-1b in relapsing remitting MS (RRMS) was demonstrated in a double-blind, placebo-controlled trial of 372 patients who were randomly assigned to treatment with either interferon beta-1b 50 mcg every other day (n=125), interferon beta-1b 250 mcg every other day (n=124), or placebo (n=123). After two years, the annual exacerbation rate was significantly lower for both interferon beta-1b treatment groups and appeared to be dose related; the frequency of relapses was 1.31/year in the placebo group, compared with 1.14/year and 0.9/year in the low- and high-dose interferon beta-1b groups, respectively.

The efficacy of subcutaneous interferon beta-1b in secondary progressive MS (SPMS) was established in Studies 2 and 3. Study 2 was conducted in Europe and Study 3 was conducted in North America. Both studies enrolled patients clinically definite or laboratory-supported MS in the secondary progressive phase, and who had evidence of disability progression or two relapses (Study 2 only) within the previous two years. Patients in Study 2 were randomized to receive Betaseron 250 mcg (n=360) or placebo (n=358). Patients in Study 3 were randomized to Betaseron 250 mcg (n=317), Betaseron 0.16 mg/m^2 of body surface area (n=314), or placebo. The primary endpoint was the progression of disability, defined as a 1 point increase in the Expanded Disability Status Scale (EDSS) score or a 0.5 point increase for patients with a baseline EDSS $\geq$6. In Study 2, time to progression in EDSS was longer in the Betaseron treatment group (p=0.005), with estimated annualized rates of progression of 16% and 19% in the Betaseron and placebo groups, respectively. In study 3, the rates of progression did not differ significantly between treatment groups, with estimated annualized rates of progression of 12%, 14%, and 12% in the Betaseron fixed dose, surface area-adjusted dose, and placebo groups, respectively.

The efficacy of subcutaneous interferon beta-1b in patients with an isolated demyelinating event with lesions typical of MS on brain MRI was established in Study 4. Patients who had experienced

an isolated demyelinating event with in 60 days (n=468) were randomized to receive either 250 mcg Betaseron (n=292) or placebo (n=176). The primary outcome was time to development of a second exacerbation with involvement of at least two distinct anatomical regions. Time to development of a second exacerbation was significantly delayed in patients treated with Betaseron compared to patients treated with placebo ($p<0.0001$).

Avonex
The efficacy of Avonex in patients with RRMS was established in two randomized, multicenter, double-blind, placebo-controlled studies (Studies 1 and 2).

In Study 1, 301 patients received either 30 mcg of Avonex (n=158) or placebo (n=143) by intramuscular injection once weekly. All patients had a definite diagnosis of multiple sclerosis of at least 1 year duration and had at least 2 exacerbations in the 3 years prior to study entry (or 1 per year if the duration of disease was less than 3 years). The primary outcome assessment was time to progression in disability, measured as an increase in the EDSS score of at least 1 point that was sustained for at least 6 months. This time to progression was found to be significantly lower in the Avonex group than in the placebo group ($p=0.02$). The percentage of patients progressing by the end of year 2 was 35% for placebo-treated patients and 22% for Avonex-treated patients.

In study 2, 383 patients who had recently experienced an isolated demyelinating event involving the optic nerve, spinal cord, or brainstem/cerebellum, and who had lesions typical of multiple sclerosis on brain MRI, received either 30 mcg of Avonex (n=193) or placebo (n=190) by intramuscular injection once weekly. Patients were enrolled into the study over a two-year period and followed for up to three years or until they met the primary outcome measure of time to development of a second clinical exacerbation in an anatomically distinct region of the central nervous system. In patients treated with Avonex, the time to development of a second exacerbation was significantly delayed compared to the placebo-treated patients ($p=0.002$).

Rebif
The efficacy and safety of Rebif in patients with RRMS were established in two multicenter studies.

Study 1 was a randomized, double-blind, placebo-controlled study in patients with MS disease duration of at least one year, EDSS score ranging from 0 to 5, and at least 2 acute exacerbations in the previous 2 years. Patients were randomized to receive subcutaneous injections of either placebo

(n=187), Rebif 22 mcg (n=189), or Rebif 44 mcg (n=184) administered three times per week for two years. The primary efficacy endpoint was the number of clinical exacerbations. Rebif at doses of 22 mcg and 44 mcg was found to significantly reduce the number of exacerbations per patient as compared to placebo ($p<0.001$ for both doses). Patients in the placebo group experienced a mean of 2.56 exacerbations, those in the Rebif 22 mcg group experienced a mean of 1.82 exacerbations, and patients in the Rebif 44 mcg group experienced a mean of 1.73 exacerbations over the two years.

Study 2 was a randomized, open-label, evaluator-blinded, active comparator study. Patients with RRMS with EDSS scores ranging from 0 to 5.5, and at least 2 exacerbations in the previous 2 years were eligible for inclusion. Patients were randomized to treatment with three times per week subcutaneous injections of Rebif 44 mcg (n=339) or once weekly intramuscular injections of 30 mcg Avonex (n=338). The primary efficacy endpoint was the proportion of patients who remained exacerbation-free at 24 weeks. In the Rebif group, 75% of patients remained relapse free at 24 weeks compared to 63% in the Avonex group. This corresponds to a relative risk of 0.68 in favor of Rebif (95% CI: 0.54, 0.86).

Plegridy
The efficacy of Plegridy in RRMS was demonstrated in the randomized, double-blind, and placebo-controlled phase of Study 1. The trial compared clinical and MRI outcomes at 48 weeks in patients who received Plegridy 125 mcg (n=512) or placebo (n=500) subcutaneously every 14 days. Patients enrolled had a baseline EDSS Score from 0 to 5, had experienced at least 2 relapses within the previous 3 years, and had experienced at least 1 relapse in the previous year. The primary outcome was the annualized relapse rate over 1 year. At 48 weeks, the ARR in the Plegridy group was 0.26 compared to 0.40 for the placebo group (p=0.0007).

References

1. Betaseron [package insert]. Bayer HealthCare Pharmaceuticals. Whippany, NJ. Updated March 2021.
2. Extavia [package insert]. Novartis Pharmaceuticals. East Hanover, NJ. Updated September 2021.
3. Avonex [package insert]. Biogen, Inc. Cambridge, MA. Updated December 2020.
4. Plegridy [package insert]. Biogen, Inc. Cambridge, MA. Updated June 2021.
5. Rebif [package insert]. EMD Serono, Inc. Rockland, MA. Updated October 2020.

6. Betaseron/Extavia Prior Authorization Policy. Express Scripts. Updated September 2021.
7. Disease-modifying therapies for multiple sclerosis: Pharmacology, administration, and adverse effects. UpToDate. Updated September 2021.

Policy History

Original Effective Date: 01/01/2022
Current Effective Date: 11/13/2023

10/07/2021	Medical Policy Committee review
10/13/2021	Medical Policy Implementation Committee approval. New policy.
10/06/2022	Medical Policy Committee review
10/11/2022	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
10/05/2023	Medical Policy Committee review
10/11/2023	Medical Policy Implementation Committee approval. Coverage eligibility unchanged.

Next Scheduled Review Date: 10/2024

*Investigational – A medical treatment, procedure, drug, device, or biological product is Investigational if the effectiveness has not been clearly tested and it has not been incorporated into standard medical practice. Any determination we make that a medical treatment, procedure, drug, device, or biological product is Investigational will be based on a consideration of the following:

A. Whether the medical treatment, procedure, drug, device, or biological product can be lawfully marketed without approval of the U.S. Food and Drug Administration (FDA) and whether such approval has been granted at the time the medical treatment, procedure, drug, device, or biological product is sought to be furnished; or
B. Whether the medical treatment, procedure, drug, device, or biological product requires further studies or clinical trials to determine its maximum tolerated dose, toxicity, safety, effectiveness, or effectiveness as compared with the standard means of treatment or diagnosis, must improve health outcomes, according to the consensus of opinion among experts as shown by reliable evidence, including:
    1. Consultation with technology evaluation center(s);
    2. Credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community; or

3. Reference to federal regulations.

**Medically Necessary (or "Medical Necessity") - Health care services, treatment, procedures, equipment, drugs, devices, items or supplies that a Provider, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury, disease or its symptoms, and that are:

A. In accordance with nationally accepted standards of medical practice;
B. Clinically appropriate, in terms of type, frequency, extent, level of care, site and duration, and considered effective for the patient's illness, injury or disease; and
C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.

For these purposes, "nationally accepted standards of medical practice" means standards that are based on credible scientific evidence published in peer-reviewed medical literature generally recognized by the relevant medical community, Physician Specialty Society recommendations and the views of Physicians practicing in relevant clinical areas and any other relevant factors.

‡ Indicated trademarks are the registered trademarks of their respective owners.

NOTICE: If the Patient's health insurance contract contains language that differs from the BCBSLA Medical Policy definition noted above, the definition in the health insurance contract will be relied upon for specific coverage determinations.

NOTICE: Medical Policies are scientific based opinions, provided solely for coverage and informational purposes. Medical Policies should not be construed to suggest that the Company recommends, advocates, requires, encourages, or discourages any particular treatment, procedure, or service, or any particular course of treatment, procedure, or service.