



CIGNA PHARMACY COVERAGE POLICY

The following Coverage Policy applies to all health benefit plans administered by CIGNA Companies including plans formerly administered by Great-West Healthcare, which is now a part of CIGNA.

**Subject Multiple Sclerosis
Interferon Products**

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Hyperlink to Related Coverage Positions:

Glatiramer Acetate (Copaxone®)

INSTRUCTIONS FOR USE

Coverage Policies are intended to provide guidance in interpreting certain **standard** CIGNA HealthCare benefit plans. Please note, the terms of a customer's particular benefit plan document [Group Service Agreement (GSA), Evidence of Coverage, Certificate of Coverage, Summary Plan Description (SPD) or similar plan document] may differ significantly from the standard benefit plans upon which these Coverage Policies are based. For example, a customer's benefit plan document may contain a specific exclusion related to a topic addressed in a Coverage Policy. In the event of a conflict, a customer's benefit plan document **always supercedes** the information in the Coverage Policies. In the absence of a controlling federal or state coverage mandate, benefits are ultimately determined by the terms of the applicable benefit plan document. Coverage determinations in each specific instance require consideration of 1) the terms of the applicable benefit plan document in effect on the date of service; 2) any applicable laws/regulations; 3) any relevant collateral source materials including Coverage Policies and; 4) the specific facts of the particular situation. Coverage Policies relate exclusively to the administration of health benefit plans. Coverage Policies are not recommendations for treatment and should never be used as treatment guidelines. Proprietary information of CIGNA. Copyright ©2011 CIGNA

Coverage Policy

Avonex® and Rebif® are preferred brand interferon beta-1a products.

CIGNA covers interferon beta-1a (Avonex®, Rebif®) as medically necessary for ANY of the following:

- clinically definite multiple sclerosis (CDMS)
- relapsing remitting multiple sclerosis (RRMS)
- secondary progressive multiple sclerosis (SPMS) with relapses
- clinically isolated syndrome (CIS)

Betaseron® and Extavia® are non-preferred brand interferon beta-1b products.

CIGNA covers interferon beta-1b (Betaseron®, Extavia®) as medically necessary for ANY of the following when there is a failure, contraindication or intolerance to Avonex® or Rebif®:

- clinically definite multiple sclerosis (CDMS)
- relapsing remitting multiple sclerosis (RRMS)
- secondary progressive multiple sclerosis (SPMS) with relapses
- clinically isolated syndrome (CIS)

When coverage is available and medically necessary, the dosage, frequency, site of administration, and duration of therapy should be reasonable, clinically appropriate, and supported by evidence-based

literature and adjusted based upon severity, alternative available treatments, and previous response to interferon beta-1a or beta-1b.

FDA Approved Indications

Avonex

Avonex (Interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis. Safety and efficacy in patients with chronic progressive multiple sclerosis have not been established.

Betaseron

Betaseron (Interferon beta-1b) is indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Extavia

Extavia is an interferon beta indicated for the treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations. Patients with multiple sclerosis in whom efficacy has been demonstrated include patients who have experienced a first clinical episode and have MRI features consistent with multiple sclerosis.

Rebif

Rebif (interferon beta-1a) is indicated for the treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability. Efficacy of Rebif in chronic progressive multiple sclerosis has not been established.

FDA Recommended Dosing

Avonex

The recommended dosage of Avonex (Interferon beta-1a) is 30 mcg injected intramuscularly once a week.

Betaseron

The recommended dose of Betaseron is 0.25 mg injected subcutaneously every other day. Generally, patients should be started at 0.0625 mg (0.25 mL) subcutaneously every other day, and increased over a six week period to 0.25 mg (1.0 mL) every other day.

Extavia

The recommended dose of Extavia is 0.25 mg injected subcutaneously every other day. Generally, patients should be started at 0.0625 mg (0.25 mL) subcutaneously every other day, and increased over a six week period to 0.25 mg (1 mL) every other day.

Rebif

Dosages of Rebif shown to be safe and effective are 22 mcg and 44 mcg injected subcutaneously three times per week. Rebif should be administered, if possible, at the same time (preferably in the late afternoon or evening) on the same three days at least 48 hours apart each week. Generally, patients should be started at 20% of the prescribed dose three times per week and increased over a 4-week period to the targeted dose.

Drug Availability

Avonex

A vial of Avonex is supplied as a lyophilized powder in a single-use vial containing 33 mcg (6.6 million IU) of Interferon beta-1a; 16.5 mg Albumin (Human), USP; 6.4 mg Sodium Chloride, USP; 6.3 mg Dibasic Sodium Phosphate, USP; and 1.3 mg Monobasic Sodium Phosphate, USP, and is preservative-free. Avonex lyophilized vials are available in the following package configuration: A package containing four Administration Dose Packs; a prefilled syringe of Avonex is supplied as a sterile liquid albumin-free formulation containing 30 mcg of Interferon beta-1a, 0.79 mg Sodium Acetate Trihydrate, USP; 0.25 mg Glacial Acetic Acid, USP; 15.8 mg

Arginine Hydrochloride, USP; and 0.025 mg Polysorbate 20 in Water for Injection, USP. Avonex prefilled syringes are available in the following package configuration: a package containing four Administration Dose Packs and a recloseable accessory pouch.

Betaseron

Betaseron is supplied as a lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP. Drug is packaged in a clear glass, single-use vial (3 mL capacity). A pre-filled single-use syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution), two alcohol prep pads, and one vial adapter with attached 30 gauge needle are included for each vial of drug.

Extavia

Extavia is supplied as a lyophilized powder containing 0.3 mg of Interferon beta-1b, 15 mg Albumin (Human), USP, and 15 mg Mannitol, USP. Drug is packaged in a clear glass, single-use vial (3 mL capacity). A pre-filled single-use syringe containing 1.2 mL of diluent (Sodium Chloride, 0.54% solution), two alcohol prep pads, and one vial adapter with attached 27 gauge needle are included for each vial of drug.

Rebif

Rebif is supplied as a sterile, preservative-free solution packaged in graduated, ready to use in 0.2 mL or 0.5 mL prefilled syringes. The following package presentations are available: Rebif (interferon beta -1a) Titration Pack (six Rebif 8.8 mcg prefilled syringes and Six Rebif 22 mcg prefilled syringes; Rebif (interferon beta -1a) 22 mcg Prefilled syringe; 12 Rebif 22 mcg prefilled syringes; Rebif (interferon beta-1a) 44 mcg Prefilled syringe; 12 Rebif 44 mcg prefilled syringes.

General Background

Pharmacology

Interferon beta products have the same mechanism of action. The amino acid sequence, specific activity, source, molecular weight, and pharmacokinetic parameters differ slightly, although these differences have not correlated into known differences in clinical efficacy or safety.

Guidelines

Clinical guidelines indicate that interferon beta therapy is indicated for patients with relapsing remitting multiple sclerosis (RRMS), patients with a clinically isolated syndrome who are at high risk for developing clinically definite multiple sclerosis, and patients with secondary progressive multiple sclerosis (SPMS) experiencing significant relapses.

The American Academy of Neurology Clinical Practice Guidelines on the treatment of Multiple Sclerosis and a Cochrane analysis do not clearly indicate that one interferon beta product is superior to another on the basis of clinical trial evidence. The relationship between neutralizing antibody (NAb) formation and subsequent effects on clinical efficacy and safety of the interferon products is not entirely understood and remains controversial. However, studies suggest that the presence of NAb against interferon beta reduce the clinical efficacy of the drug and should therefore play a role in treatment decisions. There is no reliable evidence to support superior clinical outcomes when interferon beta-1b is given in dosages greater than what is recommended in the prescribing information and approved by the Food and Drug Administration (FDA).

Clinical Efficacy

Relapsing Remitting Multiple Sclerosis

In terms of relapse rates, Betaseron and Rebif were superior to Avonex for reducing relapse rates in three experimental trials. When Avonex and Betaferon were directly compared, more patients remained relapse free after 24 months of treatment in the Betaferon group (51%) compared to the Avonex group (36%), $p=0.03$. Also Betaferon treated patients had a lower annual relapse rate (0.5) compared to Avonex treated patients (0.7), $p=0.03$. When Avonex and Rebif were directly compared, more patients remained relapse free after 24 weeks of therapy in the Rebif group (75%) compared to the Avonex group (63%), $p<0.05$. Results presented at 48 weeks were secondary endpoints, and results were similar at week 48 (Rebif 62% vs. Avonex 52%), $p<0.05$. Annual relapse rates were lower for Rebif treated patients (0.29) compared to Avonex treated patients (0.40) $p<0.05$ at week 24, but not at week 48 (Rebif 0.54 vs. Avonex 0.64, $p=0.09$). In a comparative trial of all three interferon products ($n=90$), more patients were relapse free at 24 months in the Rebif group (56.7%) and the Betaseron group (43%) compared to the Avonex group (20%), $p<0.05$. Data from eight observational trials involving 8,897

patients showed no differences between the three interferon products with regard to annual relapse rate or percent of patients who were relapse free. The percent of patients relapse free in these trials for the Avonex group ranged from 18% to 59% (5 studies) after 2 to 3 years of therapy. For the Betaferon groups, the results ranged from 22% to 64% (5 studies) and for the Rebif groups the results ranged from 55% to 59% (2 studies).

Regarding disability progression, one experimental trial and one observational trial found conflicting results between the efficacy of Avonex and Betaferon for disability progression. In the experimental trial, fewer patients in the Betaferon group (13%) had disease progression compared to the Avonex group (30%), $p=0.005$. However, in the observational study fewer patients in the Avonex group (16.6%) had disease progression compared to Betaferon (23.8%, $p=0.001$) and Rebif 44 mcg group (30.6%, $p<0.001$).

In terms of MRI outcomes, Betaseron and Rebif were superior to Avonex for MRI outcomes. In the study comparing Betaferon to Avonex, the number of patients free from any MRI activity for the Betaferon group was 51% compared to the Avonex group at 25%, $p=0.001$. The percent of patients free from new T2 lesions for the Betaferon group was 55% compared to the Avonex group at 26% after 24 months of treatment, $p<0.0003$. The number of patients free from gadolinium enhancing lesions was also higher in the Betaferon group (76%) compared to the Avonex group at 49%, $p=0.001$. In the study comparing Avonex and Rebif, the mean number of active MRI lesions for the Rebif group was 0.8 compared to the Avonex group at 1.2 after 6 months of treatment, $p<0.001$. The mean number of active T2 lesions for the Rebif group was 0.9 compared to the Avonex group at 1.4, $p<0.001$. The number of patients with no active T2 lesions for the Rebif group was 58% compared to Avonex at 38%, $p<0.001$.

There are no experimental trials comparing interferon beta products to glatiramer acetate for RRMS.

Secondary Progressive Multiple Sclerosis

In terms of relapse rates, each interferon beta product reduces annual relapse rates as compared to placebo. There are no comparative trials between the interferon products.

Regarding disability progression, only one out of five placebo controlled trials found that interferon beta (Betaseron) reduced the time to confirmed disease progression using a change in Expanded Disability Status Scale (EDSS) score as the definition of disease progression. The IMPACT trial used the MS Functional Composite (MSFC) score as the primary measure of disease progression instead of the EDSS. Avonex reduced the median MSFC worsening by 40% compared to placebo, $p=0.033$. Rebif has not been shown to reduce disability progression in patients with SPMS.

In terms of MRI outcomes, all the interferon beta products showed a benefit on MRI outcomes as compared to placebo.

Primary Progressive Multiple Sclerosis

Interferon beta therapy has not been shown to reduce disease progression.

Two small experimental trials suggest that interferon beta therapy may reduce the number of MRI lesions compared to placebo.

Juvenile Onset Multiple Sclerosis

None of the interferon beta products are labeled for use in pediatric patients with multiple sclerosis. However, all three interferon beta products have been used in pediatric patients. A decrease in relapse rate in patients treated with interferon beta compared to baseline was observed in these studies.

Treatment with interferon beta or glatiramer is recommended for children and adolescents with active relapsing remitting disease, for patients with more than one exacerbation over a period of 1 to 2 years, and if new T2 or gadolinium enhancing lesions appear on repeat MRI over 1 to 2 years.

Seventeen to 41% of patients discontinue interferon therapy, usually within the first 2 years of treatment. Discontinuation rates due to adverse events reported in pivotal trials ranged from 0.5% to 12.5%. The most common adverse reactions are flu-like symptoms including myalgia, fever, fatigue, headache, chills, nausea, vomiting. Injection site reactions are common for the interferon beta products given subcutaneously. Patients should be monitored for liver dysfunction, myelosuppression, and depression. In comparative trials, adverse

effects were more common with Rebif and Betaseron compared to Avonex (white blood cell reductions, injection site reactions); however, discontinuation rates were similar between groups.

Drug-drug interactions have not been studied with the interferon beta products. Concomitant administration with myelosuppressive agents may cause additive myelosuppression. Concomitant administration of interferon products with medications associated with hepatic injury may increase the potential for hepatotoxicity.

Because treatment of multiple sclerosis is life long and the interferon medications are given parenterally, medication selection and compliance are as important issues as efficacy and safety. The percentage of patients who stop interferon therapy ranges from 17% to 41%. The most frequent time frame for stopping therapy is within the first 2 years of treatment. There are no data to indicate that patients are more compliant with one interferon beta product compared to another. Avonex is administered by a once weekly intramuscular injection. Betaseron is administered every other day subcutaneous and Rebif is administered three times weekly subcutaneous. Betaseron requires reconstitution prior to injection. Avonex and Rebif are available in prefilled syringes. Dose titration is recommended for both Rebif and Betaseron.

The use of interferon beta products [Avonex (interferon beta-1a for intramuscular injection), Betaseron (interferon beta-1b), Rebif (interferon beta-1a for subcutaneous injection)] in patients with multiple sclerosis is well substantiated. No clear evidence supports the superiority of one product over another. Experimental trials in patients with RRMS showed that Betaseron and Rebif were superior to Avonex for reducing relapse rates. However, observational trials have not identified differences in efficacy between the three products. Each of the interferon beta products delay the development of clinically definite multiple sclerosis (CDMS) in patients with their first clinically isolated event as compared to placebo. However, there are not enough data to show effects on long-term disability or disease progression. In patients with SPMS, each of the interferon beta products reduces annual relapse rates and improves MRI related outcomes as compared to placebo. However, no consistent results have shown an effect on disability progression. The interferon beta products are not indicated for patients with PPMS. Limited data support the use of interferon beta products in pediatric patients.

Clinically Isolated Syndrome (CIS)

Four large-scale clinical trials have been conducted to determine whether early treatment following a CIS can delay the second clinical event, and therefore the diagnosis of clinically definite MS:

- The CHAMPS (Controlled High-Risk Subjects Avonex MS Prevention Study) study was designed to determine 1) if using interferon beta-1a (Avonex) early in demyelinating disease could delay the second episode of demyelination (which would signal clinically definite MS) and 2) if treatment would have an impact on MRI-detected brain lesions. The subjects in the study had each experienced a single, isolated neurological event suggesting demyelination and had multiple, clinically "silent" (without symptoms) MRI lesions, making them at high risk for a second neurological event and therefore a diagnosis of clinically definite MS. The results indicated that interferon beta-1a significantly delayed the onset of clinically definite MS, as indicated by a delay in a second clinical attack. In addition, MRI findings showed that the patients receiving interferon beta-1a had a significantly smaller increase in the volume of brain lesions, as well as fewer new lesions.

Based on the results of this study, FDA extended the labeling of Avonex to include individuals who experience their first clinical episode and have MRI-detected brain lesions consistent with multiple sclerosis.

- The ETOMS (Early Treatment of MS) study was designed to determine whether very low dose interferon beta-1a (Rebif) would delay the onset of clinically definite MS in people who had experienced one clinical event and had multiple MRI-detected lesions consistent with MS. Results indicated that fewer people on interferon beta-1a (Rebif) developed clinically definite MS (34%) than in the placebo group (45%) during the study time. In addition, the number of new lesions and the increase in the total accumulation of areas of myelin damage were significantly lower in the treatment group. The dose of Rebif used in the study was 1/6 of that generally used in the United States to treat relapsing-remitting MS. To date, the FDA has not reviewed the data from this study.
- The BENEFIT (Betaseron in Newly Emerging MS For Initial Treatment) study was designed to determine whether interferon beta-1b can delay the onset of clinically definite MS in people with CIS who are at high risk for developing MS. Results indicated that treatment may significantly delay the

development of clinically definite MS: At day 255 of the study, one-quarter of patients in the placebo group had developed CDMS while it took 618 days for a comparable number of patients in the treatment group to develop CDMS. At the end of the two-year study, 28 percent of patients in the treatment group had developed CDMS compared to 45 percent of the placebo group. Based on the results of the BENEFIT trial, the FDA has expanded the indication of Betaseron (interferon beta-1b) to include individuals who have experienced a first clinical episode and have MRI features consistent with MS.

Adverse Reactions

A multicenter, randomized, double-blind, placebo-controlled trial was done to assess efficacy, safety, and tolerability of every-other-day interferon beta-1b treatment in patients with a first clinical event suggestive of multiple sclerosis (MS) (clinically isolated syndrome or CIS). Patients with a first clinical demyelinating event and at least two clinically silent brain MRI lesions were randomized to interferon beta-1b (IFNB-1b) 250 mug subcutaneously (SC) every other day (n = 292) or placebo (n = 176), until clinically definite MS (CDMS) was diagnosed or they had been followed for 24 months. After 2 years, 45% of placebo patients had converted to CDMS and 85% fulfilled the McDonald criteria (co-primary outcome measure). Overall interferon beta-1b delayed the time to diagnosis of CDMS and McDonald MS. Treatment was well tolerated, as indicated by the low rate of patients dropping out of the study before CDMS was reached. Interferon beta-1b 250 mug subcutaneously every other day delayed conversion to clinically definite multiple sclerosis, and should be considered as a therapeutic option in patients presenting with a first clinical event suggestive of multiple sclerosis.

Although results of studies are positive in terms of fewer active MRI lesions for the treatment of CIS with interferon products as compared to placebo, current practice guidelines do not recommend using interferon products in this setting. This is still considered experimental and investigational and is not approved for use at this time.

Coding/Billing Information

Note: This section is not in use.

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