VENTURA COUNTY
HEALTH CARE PLAN

Prior Authorization DRUG Guidelines

AVONEX®; REBIF® (Interferon beta-1a)

Effective Date: 7/28/05

Date Developed: 7/13/05 by C. Wilhelmy MD

Last Approval Date: 1/26/16, 1/24/17, 1/23/28, 1/22/19

(Archived 1/22/19)

Authorization Criteria: relapsing forms of multiple sclerosis (MS), to possibly decrease the frequency of clinical exacerbations and delay the accumulation of physical disability

SPECIAL ALERTS

Interferon Beta-1a: Warnings on Hepatotoxicity Added to Avonex® Labeling - March 16, 2005

Interferon beta-1a (intramuscular) is an agent that is approved by the Food and Drug Administration (FDA) for the treatment of patients with relapsing forms of multiple sclerosis (MS) to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.[1] The safety and efficacy in patients with chronic progressive MS have not been established.[1] The recommended dosing for this condition is 30 mcg intramuscularly (IM) once a week (QW). The precise mechanism of action of interferon beta-1a (intramuscular) in MS is unknown but it is thought that it has effects on interleukin 10. MS is a chronic demyelinating disease of the central nervous system (CNS) characterized by recurrent and progressive neurologic dysfunction. MS lesions occur in many different parts of the CNS and the symptoms and clinical course of the disease are highly variable. Some common signs and symptoms of the disease include nystagmus, gait disturbances, optic neuritis, fatigue, spasticity, depression, ataxia, sensory loss, bladder disturbances, and vertigo. The mean age of onset is around 30 years.[2-4] Approximately 250,000 to 350,000 patients in the United States have MS.[5]

Four different clinical courses of MS have been delineated.[2-4] Relapsing-remitting MS is characterized by acute attacks usually followed by complete recovery to pre-existing levels. Disease progression is minimal between attacks. Secondary progressive MS begins as relapsing-remitting MS but the attack rate reduces at some juncture and is characterized by steady deterioration in function that is not related to acute attacks. Primary progressive MS is noted by a steady decline in function from the beginning without acute attacks, with or without minor temporary improvement. Progressive relapsing MS starts with disease progression at onset with occasional acute relapses and continued disease progression. Around 80-85% of patients have relapsing-remitting MS at onset and around 10-15% have primarily progressive MS. Only a small minority (< 5%) have progressive relapsing MS. About 10% of the MS population have a benign disease course, which is generally determined retrospectively. Among those with relapsing forms of MS, relapse frequencies vary widely among MS patients. The Expanded Disability Scale Score (EDSS) is the scale most often used to assess neurologic disability and evaluates cerebellar, pyramidal, brainstem, sensory, bowel, bladder, visual, and mental functional systems on a scale that ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half point

increments. Magnetic resonance imaging (MRI) has been used as a surrogate measure for MS disease activity.

Two published pivotal trials have demonstrated the efficacy of interferon beta-1a (intramuscular) in MS. In a double-blind, multicenter, phase III trial 301 patients with relapsing MS (EDSS scores of 1.0 to 3.5) were randomized to receive interferon beta-1a 30 mcg IM QW or placebo for up to 2 years.[1,6] Interferon beta-1a 30 mcg IM QW led to a statistically significant delay in sustained disability progression (defined as a 1.0 point increase in the EDSS score) compared with placebo. Also, the annual exacerbation rate was lower among those given interferon beta-1a 30 mcg IM QW (0.67 per year) compared with placebo (0.82 per year) (P = 0.04). In a randomized, double-blind trial[1,7] patients (n = 383) who had experienced an isolated demyelinating event involving the optic nerve, spinal cord, brainstem/cerebellum, and who had brain MRI lesions suggestive of MS received either interferon beta-1a 30 mcg IM QW or placebo for up to three years. The probability of developing clinically definitive MS during the three year period was lower for those receiving interferon beta-1a 30 mcg IM QW compared with placebo (rate ratio, 0.56; P = 0.002). Other studies have also been published which document the efficacy of interferon beta-1a (intramuscular) in MS including a sustained effectiveness for more than 5 years.[12-13,15]

The national clinical advisory board of the National MS Society treatment recommendations for physicians, updated in 2007, states that initiation of treatment with an interferon beta medication or glatiramer acetate is recommended as soon as possible after a definite diagnosis of MS with active, relapsing disease and it may also be considered for selected patients with a first attack who are at high risk for MS.[8] The American Academy of Neurology clinical practice guidelines regarding disease modifying therapies in MS[4], published in 2002, states that interferon beta has been shown to reduce the attack rate (clinically and by MRI) in MS patients or with clinically isolated syndromes who are at high risk for developing MS. Also, interferon beta slows sustained disability progression. Therefore, interferon beta treatment should be considered in any patient who is at high risk for developing MS, or in a patient who has either relapsing remitting MS or secondary progressive MS who is still experiencing relapses.

Pre-Authorization Criteria:

Coverage of interferon beta 1-a (intramuscular) is recommended in those who meet both of the following criteria:

FDA-approved indications - MS

1. Patients with a diagnosis of MS or have experienced an attack and who are at risk of MS. These recommendations are based upon an expert opinion paper published in 2007 by the national clinical advisory board for the National MS Society.[8] Interferon beta-1a IM (Avonex) is FDA approved for the treatment of patients with relapsing forms of MS to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations. The agent has also demonstrated efficacy in patients who have experienced a first clinical episode and have MRI features consistent with MS.[1] The guidelines from the National MS Society also stated that this agent can reduce future disease activity and improve quality of life for many patients with relapsing forms of MS, including those with secondary progressive disease who continue to experience relapses.[8]

AND

2. Prescribed by, or after consultation with, a neurologist or an MS-specialist. MS can be a devastating neurological disease and require extensive follow-up and monitoring of disease activity (e.g., MRI studies to determine axonal damage). Patients are usually followed by a neurologist or MS specialist, or after consultation with such specialist if accesses is limited, to determine the most appropriate care. In the professional opinion of specialized physicians, this criterion has been adopted.

EXCLUSIONS

Coverage of interferon beta-1a (intramuscular) is *not* recommended in the following circumstances:

1. Concurrent use of interferon beta-1a (intramuscular) with interferon beta-1a (subcutaneous) (Rebif®), interferon beta-1b (Betaseron®, Extavia®) or glatiramer acetate (Copaxone®) is not recommended. These agents are not indicated for use in combination and studies that are currently under progress will determine the efficacy of these agents concurrently. Only limited data documents the use of these therapies in combination.[9-10,14] Additional studies are needed to determine if combination therapy is effective and safe.

2. Patient is receiving natalizumab (Tysabri®). Natalizumab is indicated as monotherapy for MS patients with relapsing forms of the disease.[11]

3. Patient is concurrently receiving fingolimod. Use of interferon beta-1a IM QW with fingolimod has not been studied or established.

VCHCP requires that interferon beta 1a be prescribed by a neurologist. MS can be a devastating neurological disease and require extensive follow-up and monitoring of disease activity (e.g., MRI studies to determine axonal damage). Patients are usually followed by a neurologist or MS specialist, or after consultation with such specialist if accesses is limited, to determine the most appropriate care. In the professional opinion of specialized physicians, this criterion has been adopted.

MONITORING PARAMETERS — Monitor for signs and symptoms of thyroid abnormalities, hematologic suppression, liver functions tests, symptoms of autoimmune disorders

Avonex®: Frequency of monitoring for patients receiving Avonex® has not been specifically defined; in clinical trials, monitoring was at 6-month intervals.

Rebif®: CBC and liver function testing at 1-, 3-, and 6 months, then periodically thereafter. Thyroid function every 6 months (in patients with pre-existing abnormalities and/or clinical indications).

DOSING: ADULTS — Multiple sclerosis: Note: Analgesics and/or antipyretics may help decrease flu-like symptoms on treatment days:

I.M. (Avonex®): 30 mcg once weekly

SubQ (Rebif®): Doses should be separated by at least 48 hours:
Target dose 44 mcg 3 times/week: 11
Initial: 8.8 mcg (20 % of final dose) 3 times/week for 8 weeks
Titration: 22 mcg (50% of final dose) 3 times/week for 8 weeks
Final dose: 44 mcg 3 times/week
Target dose 22 mcg 3 times/week:
Initial: 4.4 mcg (20 % of final dose) 3 times/week for 8 weeks
Titration: 11 mcg (50% of final dose) 3 times/week for 8 weeks
Final dose: 22 mcg 3 times/week

DOSING: ELDERLY — Refer to adult dosing.

DOSING: HEPATIC IMPAIRMENT — Rebif®: If liver function tests increase or in case of leukopenia: Decrease dose 20% to 50% until toxicity resolves

ADMINISTRATION
Avonex®: Must be administered by I.M. injection

Rebif®: Administer SubQ at the same time of day on the same 3 days each week (ie, late afternoon/evening Mon, Wed, Fri); rotate injection site

CONTRAINDICATIONS — Hypersensitivity to natural or recombinant interferons, human albumin, or any other component of the formulation

WARNINGS / PRECAUTIONS — Interferons have been associated with severe psychiatric adverse events (psychosis, mania, depression, suicidal behavior/ideation) in patients with and without previous psychiatric symptoms, avoid use in severe psychiatric disorders and use caution in patients with a history of depression; patients exhibiting depressive symptoms should be closely monitored and discontinuation of therapy should be considered.

Allergic reactions, including anaphylaxis, have been reported. Caution should be used in patients with hepatic impairment or in those who abuse alcohol. Rare cases of severe hepatic injury, including hepatic failure, have been reported in patients receiving interferon beta-1a; risk may be increased by ethanol use or concurrent therapy with hepatotoxic drugs. Treatment should be suspended if jaundice or symptoms of hepatic dysfunction occur. Some reports indicate symptoms began after 1-6 months of treatment. Hematologic effects, including pancytopenia (rare) and thrombocytopenia, have been reported. Associated with a high incidence of flu-like adverse effects; use of analgesics and/or antipyretics on treatment days may be helpful. Use caution in patients with pre-existing cardiovascular disease, pulmonary disease, seizure disorders, myelosuppression, or renal impairment. Some formulations contain albumin, which may carry a remote risk

of transmitting Creutzfeldt-Jakob or other viral diseases. Safety and efficacy in patients <18 years of age have not been established.

DRUG INTERACTIONS
ACE inhibitors: Interferons may increase the adverse/toxic effects of ACE inhibitors, specifically the development of granulocytopenia; monitor.

Hepatotoxic drugs: May increase the risk of hepatic injury in patients receiving interferon beta-1a.

Warfarin: Interferons may increase the anticoagulant effects of warfarin; monitor.

Zidovudine: Interferons may decrease the metabolism of zidovudine; monitor.

PREGNANCY RISK FACTOR — C

PREGNANCY IMPLICATIONS — There are no adequate and well-controlled studies in pregnant women. Consideration should be given to discontinue treatment if a woman becomes pregnant, or plans to become pregnant during therapy. A dose-related abortifacient activity was reported in Rhesus monkeys.

Healthcare providers are encouraged to register pregnant women receiving Rebif® during pregnancy online at www.rebifpregnancyregistry.com or by telephone at MS LifeLines 1-877-44-REBIF. A registry has been established for women who become pregnant while receiving Avonex®. Women may be enrolled in the registry by calling 1-800-456-2255.

LACTATION — Excretion in breast milk unknown/not recommended

BREAST-FEEDING CONSIDERATIONS — Potential for serious adverse reactions. Because its use has not been evaluated during lactation, a decision should be made to either discontinue breast-feeding or discontinue the drug.

PATIENT EDUCATION — Flu-like symptoms are not uncommon following initiation of therapy. Acetaminophen may reduce these symptoms. Do not change the dosage or schedule of administration without medical consultation. If self-injecting and you miss a dose, take it as soon as you remember, but 2 injections should not be given within 48 hours of each other. Report depression or suicide ideation to physicians. Avoid prolonged exposure to sunlight or sunlamps. Inform prescriber immediately if you feel depressed or have any thoughts of suicide.

REFERENCES
1. . Jacobs, LD, Beck, RW, Simon, JH, et al. Intramuscular Interferon Beta-1a Therapy Initiated During a First Demyelinating Event in Multiple Sclerosis. CHAMPS Study Group, N Engl J Med, 2000, 343:898.
2. Panitch, H, Goodin, DS, Francis, G, et al. Randomized, Comparative Study of Interferon Beta-1a Treatment Regimens in MS: The EVIDENCE Trial. EVIDENCE Study Group. Evidence of Interferon

Dose-Response: European North American Comparative Efficacy; University of British Columbia MS/MRI Research Group. Neurology 2002; 59:1496.
3. Avonex® [package insert]. Cambridge, MA: Biogen, Inc.; October 2008

Revision History:

Date Revised: 10/4/11 by A. Reeves, MD
Date Reviewed/No Updates: 4/2/12; 1/16/13 by A. Reeves, MD
Date Approved by P&T Committee: 7/28/05; 10/25/11; 4/24/12; 1/29/13
Date Reviewed/No Updates: 1/28/14 by C. Sanders MD
Date Approved by P&T Committee: 1/28/14
Date Reviewed/No Updates: 1/13/15 by C. Sanders, MD
Date Approved by P&T Committee: 1/27/15
Date Reviewed/Updated: 1/13/15 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/26/16
Date Reviewed/No Updates: 1/24/17 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/24/17
Date Reviewed/No Updates: 1/23/18 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/23/18
Date Reviewed/Archived: 1/22/19 by C. Sanders, MD; R. Sterling, MD
Date Approved by P&T Committee: 1/22/19

Revision Date	Content Revised (Yes/No)	Contributors	Review/Revision Notes
1/24/17	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/23/18	No	Catherine Sanders, MD; Robert Sterling, MD	Annual review
1/22/19	No	Catherine Sanders, MD; Robert Sterling, MD	Archived – check ESI