

Indiana Medicaid Therapeutics Committee
Therapeutic Class Review Summary

Therapeutic Class:

Agents to Treat Multiple Sclerosis

Overview:

Multiple sclerosis (MS) is the most common cause of neurological disability in young adults. It affects 250,000 to 350,000 people in the US. MS is an immune-mediated, chronic, recurrent inflammatory disorder involving demyelination and damage to axons in the central nervous system (CNS). Four different disease courses have been identified for MS, relapsing-remitting MS (RRMS), secondary-progressive MS (SPMS), primary-progressive MS (PPMS) and progressive-relapsing MS (PRMS). Approximately 80% of patients present with RRMS, and 50% of untreated RRMS patients eventually progress to the SPMS within 10 years. In the past, the treatments for MS included glucocorticoids, immunoglobulins, and anticholinergic agents. However, these agents failed to demonstrate long-term benefits in the management of MS. Immunomodulators were first approved to treat RRMS in 1993. They became the foundation of effective management for RRMS. It was found that immunomodulators reduce or prevent permanent disability in MS patients. Consequently, the National Multiple Sclerosis Society has advised that immunomodulators be initiated as soon as possible after diagnosis and be continued indefinitely. Natalizumab, an alternative treatment, reduces relapses and the appearance of brain lesions in patients with relapsing forms of MS; however, because it increases the risk of progressive multifocal leukoencephalopathy, natalizumab is generally recommended for patients who either have had an inadequate response or are unable to tolerate other therapies for multiple sclerosis.

There are four immunomodulators currently available in the US to treat MS, Copaxone (glatiramer acetate, 20 mg subcutaneously daily), Avonex (interferon beta-1a/albumin, 30 mcg intramuscularly weekly), Rebif (interferon beta-1a/albumin, 44 mcg subcutaneously 3 times per week) and Betaseron (interferon beta-1b, 0.25 mg subcutaneously every other day). Interferon betas have potent activity at the blood-brain barrier and impair the trafficking of inflammatory cells into the CNS. In contrast, glatiramer allows T- helper 2 lymphocytes (anti-inflammatory cytokines) to enter the CNS to decrease inflammation through bystander suppression. All four agents have demonstrated efficacy to reduce the attack rate in patients with RRMS (whether measured clinically or by MRI). In addition, interferon betas (both 1a and 1b) are beneficial for SPMS and patients at high risk for developing MS. Betaseron was approved to treat SPMS in Europe. The comparative clinical data showed that higher doses or more frequent administration of interferon betas provided more clinical benefits. For example, Rebif 44 mcg 3 times weekly was superior to Avonex 30 mcg once weekly, and Betaseron 250 mcg every other day was superior to Avonex 30 mcg once weekly in reducing relapse rate and new lesions on MRI. There are limited studies comparing interferon betas with glatiramer. Because the mechanisms of action are different, it is difficult to determine the superiority of these agents.

Tysabri (natalizumab, 300 mg IV infusion every four weeks) is a monoclonal antibody that delays the accumulation of physical disability and reduces the frequency of clinical exacerbations in patients with relapsing forms of multiple sclerosis. Tysabri recently received approval for use in the treatment of adults with moderate to severe Crohn's Disease. Its specific mechanism of action has not been fully defined. Tysabri contains a boxed warning regarding the increased risk of Progressive Multifocal Leukoencephalopathy (PML), an opportunistic viral infection of the brain that usually leads to death or severe disability. Cases of PML have been reported in patients taking Tysabri who were recently or concomitantly treated with immunomodulators or immunosuppressants, as well as in patients receiving Tysabri as monotherapy. Tysabri is available only under a special restricted distribution program called the TOUCH Prescribing Program. Only prescribers, infusion centers, and pharmacies associated with infusion centers registered with the program are able to prescribe, distribute, or infuse the product. In addition, Tysabri must be administered only to patients who are enrolled in and meet all of the conditions of the TOUCH prescribing program.

The most common side effects for immunomodulators include flu-like symptoms, injection site reactions, blood cell, liver or thyroid function abnormalities. The interferons have also been associated with depression or suicidal ideation. Copaxone, Betaseron and Rebif can all be given as a subcutaneous injection, which is easier to administer on the patient's part whereas Avonex is only available as an intramuscular injection. The most common side effects of Tysabri are infections, headaches, and depression; it is administered as an intravenous infusion only. Because MS is more prevalent in women than men, pregnancy category is important when considering agents. All of the interferons and natalizumab carry a pregnancy category of C, whereas glatiramer has a pregnancy category of B.

Generic Name	Trade Name	Manufacturer	Generic Available
Glatiramer Acetate	Copaxone [®]	Aventis, Teva	N
Interferon Beta 1a (Interferon Beta-1a/Albumin)	Avonex [®] Rebif [®]	Biogen Serono Labs.	N
Interferon Beta-1b	Betaseron [®]	Berlex	N
Natalizumab	Tysabri [®]	Elan	N

Summary:

Multiple sclerosis is a chronic neurological disorder that affects the central nervous system. Although there is no cure, treatments such as glatiramer acetate, interferon beta-1a/albumin, interferon beta-1b, and natalizumab may slow its progression and alleviate associated symptoms. Natalizumab increases the risk of progressive multifocal leukoencephalopathy, and is generally recommended for patients who either have had an inadequate response or are unable to tolerate other therapies for multiple sclerosis.

Clinical data have shown that higher doses or more frequent administration of interferon betas provides more clinical benefits. However, studies comparing interferon betas with

glatiramer are limited. Selection for the preferred drug list should be based upon efficacy, safety, and cost.