Class: Multiple Sclerosis Agents

Drugs: interferon beta-1a (Avonex), interferon beta-1a (Rebif), interferon beta-1b (Betaseron), interferon beta-1b (Extavia), peginterferon beta-1a (Plegridy), glatiramer acetate (Copaxone, Glatopa), natalizumab (Tysabri), dalfampridine (Ampyra), teriflunomide (Aubagio), fingolimod (Gilenya), dimethyl fumarate (Tecfidera), alemtuzumab (Lemtrada), daclizumab (Zinbryta)

Line of business: Non-Medicare

Effective Date: August 17, 2016

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This policy has been developed through review of medical literature, consideration of medical necessity, generally accepted medical practice standards, and approved by the IEHP Pharmacy and Therapeutics Subcommittee

Policy/Criteria:

- Preferred Non-formulary Medications:
  - Avonex, Rebif, Betaseron, Extavia, Glatopa
    1. Diagnosis of relapsing-remitting Multiple Sclerosis (RRMS)
    2. Prescribed by a neurologist and managed by MS disease management program

- Non-preferred Non-formulary Medications:
  - Copaxone 20mg, 40mg
    1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
    2. Prescribed by a neurologist and managed by MS disease management program
    3. Documentation of inadequate response, adverse reaction or contraindication to Glatopa
  - Plegridy
    1. Diagnosis of relapsing-remitting Multiple Sclerosis (RRMS)
    2. Prescribed by a neurologist and managed by MS disease management program
    3. Documentation of inadequate response, adverse reaction or contraindication to one of the following: Avonex or Rebif
  - Tysabri
    1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
    2. Prescribed by a neurologist and managed by MS disease management program
3. Documentation of inadequate response, adverse reaction or contraindication to interferon beta or glatiramer acetate AND an oral anti-Multiple Sclerosis drug

- Aubagio
  1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
  2. Prescribed by a neurologist and managed by MS disease management program
  3. Documentation of inadequate response, adverse reaction or contraindication to interferon beta or glatiramer acetate
  4. Documentation of liver transaminase and bilirubin levels
  5. If female, confirmation of negative pregnancy test at initiation of therapy and use of contraceptive throughout treatment duration

- Gilenya
  1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
  2. Prescribed by a neurologist and managed by MS disease management program
  3. Documentation of inadequate response, adverse reaction or contraindication to interferon beta or glatiramer acetate
  4. No history or recent (within last 6 months) indications of the following cardiac conditions. Must have plan for cardiac monitoring at initiation by provider per label.
     - Myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization or Class III/IV heart failure within the last 6 months
     - History or presence of Mobitz Type II second-degree or third-degree atrioventricular (AV) block or sick sinus syndrome, unless patient has a functioning pacemaker
     - Baseline QTc interval ≥500 ms
     - Concurrent use of Class Ia or Class III anti-arrhythmic drug

- Tecfidera
  1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
  2. Prescribed by a neurologist and managed by MS disease management program
  3. Documentation of inadequate response, adverse reaction or contraindication to interferon beta or glatiramer acetate

- Lemtrada
  1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
  2. Prescribed by a neurologist and managed by MS disease management program
  3. Documentation of inadequate response, adverse reaction or contraindication to interferon beta or glatiramer acetate
  4. Documentation of inadequate response, adverse reaction or contraindication to one of the oral MS agents
  5. Contraindicated in member with HIV infection.
  6. Recommend premedication with corticosteroids and herpes prophylaxis

- Ampyra
1. Diagnosis of relapsing- remitting Multiple Sclerosis (RRMS)
2. Prescribed by a neurologist and managed by MS disease management program
3. EDSS scale score between 4.5 to 6.5 OR documentation of baseline timed 25-foot walk test within 8 to 45 seconds
4. No history of seizures or moderate/severe renal impairment (CrCl ≤ 50 mL/min)
5. Does not have disease modifying properties

- Zinbryta
  1. Diagnosis of relapse-remitting Multiple Sclerosis (RRMS)
  2. Prescribed by a neurologist and managed by MS disease management program
  3. Documentation of inadequate response, adverse reaction, or contraindication to interferon beta or glatiramer acetate AND an oral anti-Multiple Sclerosis drug
  4. Contraindicated in pre-existing hepatic disease or hepatic impairment, including ALT or AST at least 2 times the ULN or history of autoimmune hepatitis or other autoimmune condition involving the liver

Clinical Justification:

Interferon Beta

Jacobs et al conducted a multicenter, randomized and placebo-controlled study in relapse remitting multiple sclerosis (RRMS) patients in which participants were treated with either Avonex (interferon beta-1a) 30 µg per week or placebo IM for two years. Compared with placebo, there were fewer Avonex treated patients who progressed on the Expanded Disability Status Scale (EDSS) by one point (-37%; p = 0.02). The clinical exacerbation (-18%; p = 0.04) and MRI (-33%; p = 0.05) attack rate were also reduced in the interferon beta-1a treated patients compared to placebo.

In a similar randomized, multicenter, double-blind, placebo-controlled trial, the PRISMS Study Group found a significant benefit of treating patients with either Rebif (interferon beta-1a) 22 µg or 44 µg compared to placebo subcutaneously three times weekly for two years. In the primary endpoint, the Rebif 44 µg treated group reduced the clinical attack rate (-32%; p < 0.005). Furthermore, the MRI attack rate (-78%; p < 0.0001), measured by the median number of T2 active lesions, and the reduction of Expanded Disability Status Scale (EDSS) progression rate by one point (-30%; p < 0.05) was seen in the interferon beta-1a treated group in comparison with placebo.

The PRISMS Study Group continued the Rebif trial for an additional two years to evaluate a dose-response relationship. The placebo treated group was randomized to receive either interferon beta-1a 22 µg or 44 µg subcutaneously three times weekly. The high dose interferon beta-1a group was more effective (p < 0.05) in reducing the relapse rate during the third and fourth year, prolonging the time to a second relapse, and increasing the percentage of relapse free patients. High dose interferon beta-1a also reduced the MRI disease and T2 lesion activity (p < 0.001) compared to low dose interferon beta-1a.
The IFNB Multiple Sclerosis Study Group conducted a randomized, double-blind, placebo-controlled trial comparing Betaseron (interferon beta-1b) with placebo treated patients. Patients received low dose interferon beta-1b (50 µg), high dose interferon beta-1b (250 µg), or placebo subcutaneously every other day. High dose interferon beta-1b reduced the relapse rate after two years (-34%; p < 0.0001). In addition, the MRI attack rate (-83%; p < 0.009), measured by the median number of T2 active lesion, and the median volume of MRI T2 disease burden (-17.3%; p = 0.001) were reduced in the interferon beta-1b group compared to placebo treated patients. After a five year follow-up, the incidence of disease progression was lower in the high dose interferon beta-1b compared to placebo, 35% and 46%, respectively.

Other Injectable Agents

Johnson et al conducted a large multicenter, randomized, double-blind, placebo controlled trial in which patients received either Copaxone (glatiramer acetate) 20 mg or placebo subcutaneously daily. The trial found that glatiramer acetate significantly reduced the clinical attack rate after two years (-29%, p = 0.007). In two trials comparing interferon beta with glatiramer acetate (BEYOND and REGARD study), interferon beta and glatiramer acetate have shown to have similar clinical efficacy.

In a Cochrane review, the efficacy, tolerability and safety of Tysabri (natalizumab) were assessed in patients with RRMS. There was statistically significant evidence of natalizumab reducing the risk of exacerbation rate as well as experiencing progression after two years. However, safety data was not conclusive among studies. Cases of progressive multifocal leukoencephalopathy (PML) were identified. According to clinical guidelines, natalizumab is not a first line agent because of the potential development of PML. Natalizumab should be reserved for patients with active RRMS who are resistant or contraindicated to beta interferons or glatiramer acetate.

CAMMS223 and CARE-CM studies showed alemtuzumab is an efficacious disease-modifying therapy, with benefits on relapse, disability outcomes, and MRI (magnetic resonance imaging) activities. Infection incidence was elevated with alemtuzumab in clinical studies. Autoimmune adverse events occurred in approximately 1/3 of patients, manifesting mainly as thyroid disorders, and less frequently as immune thrombocytopenia or neuropathy. Infusion associated reactions are common.

In the SELECT trial, 600 adult patients with RRMS were randomly assigned to either receive daclizumab 300 mg, daclizumab 150 mg or placebo every four weeks in a 1:1:1 ratio. At one year, the annualized relapse rate was significantly lower in groups assigned to daclizumab of either strength compared to placebo (0.21 for daclizumab 150mg and 0.23 for daclizumab 300mg, vs. 0.46 for placebo), which translates to a reduction of 54% and 50%, respectively. Additionally, daclizumab groups had significant reduction in the risk of three-month sustained disability progression (hazard ratio 0.43 for daclizumab 150mg and 0.57 for daclizumab 300mg). However, daclizumab groups had a 2% rate of serious infection (1 death) compared to no infection in placebo. Furthermore, patients in daclizumab treated group experienced more cutaneous events and hepatic enzymes elevations >5 times the upper limit of normal. In the DECIDE trial, 1800 adults with RRMS were randomly assigned to receive either subcutaneous daclizumab 150mg every 4 weeks or intramuscular interferon beta-1a 30 mcg once a week for up to 144 weeks. Daclizumab treated patients had a significantly lower annualized relapse rate
than those assigned to interferon beta-1a (0.22 vs. 0.39), which is a 45% reduction. At 96 weeks, daclizumab group also experienced a significantly lower number of new or newly enlarged brain lesions on T2-weighted MRI compared to interferon beta-1a group (4.3 vs. 9.4). However, there was no significant difference in the estimated rate of sustained disability progression (16% vs. 20%). Serious adverse events were more common in the daclizumab group than in interferon treated group (15% vs. 10%), including a higher rate of infection (4% vs. 2%). Daclizumab group also experienced more cutaneous adverse event and higher aminotransferase levels.

**Oral Agents**

Goodman et al conducted a double-blind, placebo-controlled trial in which patients were randomly assigned to receive either Ampyra (dalfampridine; 4-aminopyridine) 10 mg or placebo twice daily. The proportion of patients who responded to consistent improvement on a timed 25-foot walk was greater in the dalfampridine group compared to placebo. Timed walk responders also showed greater improvement in a 12-item multiple sclerosis walking scale score than timed walk non-responders. There is concern that Ampyra has a narrow therapeutic index. Increased seizures were observed and appeared to be dose-related. Doses should not exceed 10 mg twice daily and is not recommended for use in patients with a history of seizure or in those with moderate to severe renal impairment.

In a randomized, placebo-controlled trial conducted by O’Connor et al, patients received Aubagio (teriflunomide), 7 or 14 mg, or placebo daily. Following two years of treatment, there was a significant reduction in relapse rate amongst the teriflunomide treated group compared to placebo. The high dose teriflunomide group significantly reduced disability progression compared with placebo. Additionally, there were improved MRI measures of MS disease activity in the high dose teriflunomide group.

The FREEDOMS trial, conducted by Kappos et al, compared oral Gilenya (fingolimod 0.5 mg and 1.25 mg daily) with placebo. After two years, the annualized relapse rate decreased among both fingolimod groups more significantly than placebo. Furthermore, there were statistically significant reductions in the risk of disability progression and new lesions on brain MRI with fingolimod treatment. The incidence of serious infections and herpes virus infections were similar in all groups. Macular edema developed in seven patients in the high dose fingolimod group. The TRANSFORMS trial randomly assigned patients to either oral fingolimod (0.5 mg or 1.25 mg daily) or interferon beta-1a 30 mcg weekly. Following twelve months, the relapse rate was significantly lower in both high and low dose fingolimod compared to interferon beta-1a. However, there were more adverse events in the both fingolimod groups. Significant adverse reactions seen with fingolimod include bradyarrhythmia, atrioventricular block, macular edema, reduced respiratory function, hepatic effects, tumors, and herpes virus infections. There have been post marketing reports of deaths associated with fingolimod. It is recommended that patients be assessed prior to initiating fingolimod and monitored for six hours following the first dose for bradycardia or atrioventricular block in addition to the treatment duration for signs of adverse reactions.

The DEFINE (Determination of the Efficacy and Safety of Oral Fumarate in RRMS) and CONFIRM (Comparator and an Oral Fumarate in RRMS) trials showed early benefits of dimethyl fumarate (as early as 12 weeks) and sustained benefits over the course of the studies. Oral Fumarate demonstrated significant and clinically meaningful reductions in MS relapses and
brain lesions in patients with relapsing-remitting multiple sclerosis (RRMS) compared to placebo or copaxone, as well as showed benefit in slowing the progression of the disease.

References: