Therapeutic Class Overview
Multiple Sclerosis Agents

Therapeutic Class

- **Overview/Summary:** Several biologic response modifiers are Food and Drug Administration (FDA)-approved for the treatment of relapsing-remitting multiple sclerosis (RRMS) and include alemtuzumab (Lemtrada®), daclizumab (Zinbryta®), glatiramer acetate (Copaxone®, Glatopa®), interferon β (IFNβ)-1b (Betaseron®, Extavia®), intramuscular (IM) IFNβ-1a (Avonex®), subcutaneous (SC) IFNβ-1a (Rebif®), SC peginterferon β-1a (Plegridy®) along with the oral products dimethyl fumarate (Tecfidera®), fingolimod (Gilenya®) and teriflunomide (Aubagio®).[1-14] Both IFNβ-1b and IM IFNβ-1a are also FDA-approved for the treatment of patients experiencing a first clinical episode with magnetic resonance imaging (MRI) evidence of multiple sclerosis (MS), which is often referred to as a clinically isolated syndrome.[7,8,10] The exact mechanisms of action of daclizumab, dimethyl fumarate, teriflunomide, the INFs and glatiramer acetate are unknown or not completely understood but are likely due to their antiproliferative and immuno-modulatory effects.[2,3,5-12]

  MS is a chronic and potentially disabling neurological disease characterized by repeated episodes of inflammation within the nervous tissue of the brain and spinal cord, resulting in injury to the myelin sheaths and subsequently the nerve cell axons.[16-17] There are four clinical subtypes of MS: RRMS, primary progressive (PPMS), progressive relapsing (PRMS), and secondary progressive (SPMS).[16-19] The most common form is RRMS, characterized by acute relapses followed by partial or full recovery.[17,19] Patients with PPMS have a continuous and gradual decline in function without evidence of acute attacks. Patients with PRMS also have a continuous decline in function while experiencing occasional attacks. Finally, SPMS begins as RRMS, but as time progresses the attack rate declines and patients experience a gradual deterioration.[19]

Table 1. Current Medications Available in the Therapeutic Class[1-12]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Alemtuzumab (Lemtrada)	Relapsing-remitting multiple sclerosis*		-
Daclizumab (Zinbryta®)	Relapsing-remitting multiple sclerosis#		-
Dimethyl fumarate (Tecfidera®)	Relapsing-remitting multiple sclerosis*	Delayed-release capsule: 120 mg 240 mg	-
Fingolimod (Gilenya®)	Relapsing-remitting multiple sclerosis†	Capsule: 0.5 mg	-
Glatiramer acetate (Copaxone®**, Glatopa®††)	Relapsing-remitting multiple sclerosis‡, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Prefilled syringe: 20 mg	✔
Interferon β-1b (Betaseron®, Extavia®)	Relapsing-remitting multiple sclerosis§, treatment of first clinical episode with magnetic resonance imaging features consistent with multiple sclerosis	Single use vial: 0.3 mg lyophilized powder	-
Interferon β-1a (Rebif®)	Relapsing-remitting multiple sclerosis‖	Prefilled syringe: 8.8 µg 22 µg 44 µg	-
Interferon β-1a (Avonex®, Avonex	Relapsing-remitting multiple sclerosis¶, treatment of first clinical episode with	Prefilled syringe: 30 µg	-

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Administration Pack®)	magnetic resonance imaging features consistent with multiple sclerosis	Single use vial: 30 µg lyophilized powder	
Peginterferon β-1a (Plegridy®)	Relapsing-remitting multiple sclerosis*		
Teriflunomide (Aubagio®)	Relapsing-remitting multiple sclerosis*	Tablet: 7 mg 14 mg	-

*Treatment of patients with relapsing forms of multiple sclerosis.
†Treatment of patients with relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability.
‡Reduction of the frequency of relapses in patients with relapsing-remitting multiple sclerosis.
§Treatment of relapsing forms of multiple sclerosis to reduce the frequency of clinical exacerbations.
‖Treatment of patients with relapsing forms of multiple sclerosis to decrease the frequency of clinical exacerbations and delay the accumulation of physical disability.
¶ Treatment of patients with relapsing forms of multiple sclerosis to slow the accumulation of physical disability and decrease the frequency of clinical exacerbations.
#Treatment of patients with relapsing forms of multiple sclerosis in patients who have an inadequate response to two or more drugs indicated for the treatment of multiple sclerosis.
**Generic available in at least one dosage form or strength.
††Glatopa® is considered a biosimilar to reference product Copaxone®

Evidence-based Medicine

- The safety and efficacy of glatiramer acetate and interferon (IFNβ) products are well established. Recent clinical trials have not produced clinically different results compared to trials published previously.
- The FDA-approval of daclizumab was based on the results of two randomized double-blind studies in adults with a diagnosis of relapsing MS (RMS). Both utilized the primary endpoint of annualized relapse rate (ARR). The first study evaluated 1,841 patients over 96 to 144 weeks who were randomized to either daclizumab 150 mg every four weeks or to IFN β-1a 30 µg weekly. Both groups received a placebo matching the other treatment arm. The ARR was significantly reduced in the daclizumab arm (0.216) compared with the IFN β-1a group (0.393) representing a relative reduction of 45% (P<0.0001).[2,33] The second study, SELECT, evaluated a total of 621 patients over 52 weeks who were randomized to daclizumab 150 mg every four weeks, daclizumab 300 mg every four weeks or placebo. The ARR was significantly lower in both the daclizumab 150 mg group (0.21) and the daclizumab 300 mg group (0.23) compared to the placebo group (0.46; P<0.001 for both).[2,34]
- In two large, randomized trials with dimethyl fumarate 240 mg twice-daily or three times daily compared to placebo, there were statistically significant reductions in the annualized relapse rate (ARR) with both dimethyl fumarate regimens compared to placebo (P≤0.001 for both).[37,61] Fox et al also included an open-label glatiramer acetate comparator group. In a post-hoc analysis, there were significant improvements favoring dimethyl fumarate over glatiramer acetate with regard to ARR (three times daily group only), new or enlarging T2 hyperintense lesions and new T1 hypointense lesions (three times daily group only).[61]
- In the 24-month, placebo-controlled FREEDOMS trial, treatment with fingolimod 0.5 or 1.25 mg once daily significantly reduced ARR compared to placebo (54 and 60%, respectively; P<0.001 for both).[38]
- The FREEDOMS II trial had similar results, with fingolimod providing a lower ARR over 24 months compared to placebo.[87]
- In the 12-month TRANSFORMS trial, fingolimod 0.5 or 1.25 mg once-daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 µg intramuscularly (IM) once-weekly (P<0.001 for both).[43] In a 12-month extension of TRANSFORMS, patients initially randomized to IM IFNβ-1a were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IM IFNβ-1a.[44]

- In the TEMSO trial, treatment with teriflunomide 7 or 14 mg was associated with significantly greater relative reductions in ARR compared to placebo (31.2 and 31.5%. respectively; *P*<0.001).[56] In an unpublished extension study, ARR remained low after five years and the adverse event rates were similar to those reported in previous trials.[57,58]
- The TOWER study showed that over one year teriflunomide had a lower ARR than placebo.[88]
- The ComiRX trial, evaluated the combination of IFNβ-1a and glatiramer acetate versus IFNβ-1a alone versus glatiramer acetate alone. After three years, the ARR of the combination was not statistically significantly improved to the better of the two single-agent arms when adjusting for baseline age. Glatiramer acetate provided statistically significant greater reduction in risk of exacerbation compared to interferon by 31%, and the combination group provided statistically significant greater reduction in risk of exacerbation compared to interferon by 25% (P=0.027, P=0.022 respectively).[89]
- Two phase III clinical trials evaluated treatment outcomes with IFNβ-1a 44 µg SC three times weekly and alemtuzumab 12 mg. One trial evaluated a study population of treatment-experienced MS patients and the second study evaluated treatment outcomes in treatment-naive patients. In both trials, treatment with alemtuzumab resulted in a statistically significant reduction in the annualized relapse rate compared to treatment with IFNβ-1a. Time to onset of six-month disability progression was only significantly delayed in treatment-experience patients.[103,104]
- The safety and efficacy of peginterferon β-1a, was established in a single, randomized, double-blind, placebo controlled study. Annualized relapse rate was 0.26 in the peginterferon β-1a group compared to 0.40 with placebo (P=0.007). This represented a hazard ratio of 0.61 (95% CI, 0.47 to 0.80; P=0.0003). The proportion of patients with a relapse was also significantly lower with the peginterferon β-1a group compared to placebo (0.19 vs 0.29; P=0.003). [105]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - The approach to treating MS includes: the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies to reduce the frequency and severity of relapses, and delay disease and disability progression.[14,16,19,22]
    - IFNβ products or glatiramer acetate are recommended as first-line therapy in patients with RRMS.[18,19]
    - The Association of British Neurologists also recommend either of the oral agents as potential first-line options.[18]
    - Due to its adverse effect profile, fingolimod is sometimes recommended as a second-line option.[19,20] NICE recommends use of fingolimod only if patients have an unchanged or increased relapse rate, or ongoing severe relapses compared to the previous year despite treatment with IFNβ.[20]
    - Consensus guidelines do not recommend a change of therapy in patients positive for neutralizing antibodies who are responding to IFN therapy, noting that neutralizing antibodies disappear with continued treatment in the majority of patients.[18,23-25]
    - A change of therapy may be considered in patients experiencing a suboptimal response or intolerable adverse effects.[26,28,29]
    - Data suggests a significant reduction in relapse rate and a delay in disease and disability progression in patients switching from IFNβ to glatiramer acetate therapy or vice versa due to poor response.[26,28,29]
- Other Key Facts:
    - A biosimilar version of Copaxone® (glatiramer acetate 20 mg/mL) was recently approved by the FDA and is marked under the trade name Glatopa®. There are no other generic MS products available, including other strengths of glatiramer acetate.[1-14]
    - The safety and efficacy of retreatment with alemtuzumab after the initial standard treatment cycles remains uncertain. There is no information regarding retreatment in alemtuzumab's FDA-approved label.[1]
    - There are no head-to-head trials comparing IFNβ-1b products (Betaseron® and Extavia®) and the drugs are not interchangeable despite Extavia® being approved with the same active ingredient and registration trials as Betaseron®.[5,6]

- Alemtuzumab must be administered by a healthcare professional.
- Alemtuzumab and daclizumab are available only through restricted access programs. Both are associated with causing serious autoimmune disorders. In addition, alemtuzumab has been associated with life threatening infusion reactions as well as increased risk of malignancy.[1,2]

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