PDL NEW DRUG REVIEW

Proprietary Name: Tecfidera®
Common Name: dimethyl fumarate
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Aubagio	Non-Preferred with Conditions
Avonex	Preferred
Copaxone	Preferred
Gilenya	Non-Preferred with Conditions

Summary

Indications and Usage: Treatment of patients with relapsing forms of multiple sclerosis (MS). This is a pregnancy category C medication. The safety and efficacy of use in children under the age of 18 have not been established.

Drug Interactions: There were no drug interactions listed in the prescribing information.

Dosage Forms: Delayed-release capsules: 120mg, 240mg

Recommended Dosage: Take 120mg twice daily. After 7 days, increase to the maintenance dose of 240mg twice daily, with or without food. The capsules should not be crushed, chewed, or opened as the contents of the capsule should not be sprinkled on food. Prior to starting therapy, a complete blood cell count (CBC) is recommended (within 6 months prior to therapy).

While pharmacokinetic studies have not been performed in patients with renal or hepatic impairment, neither condition is expected to affect exposure. Therefore, dosage adjustments are not required in those with renal or hepatic impairment.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions = reported % incidence for drug minus reported % incidence for placebo.* The most common adverse events reported with Tecfidera® include lymphopenia (>1%), abdominal pain (8%), diarrhea (3%), nausea (3%), vomiting (4%), dyspepsia (2%), flushing (34%), pruritus (4%), rash (5%), erythema (4%), albumin urine present (2%), and aspartate aminotransferase increased (2%).

The reported incidence of G.I. adverse events was higher in the early part of treatment (ie primarily in month 1) and usually decreased over time as compared with placebo. 4% discontinued treatment due to GI events in the Tecfidera® group vs <1% of the placebo group.

Lymphocyte counts decreased by about 30% during the first year of treatment with Tecfidera®, and thereafter remained stable. While lymphocyte counts increased after four weeks of stopping treatment, they did not return to baseline. In trials, 6% experienced lymphocyte counts $<0.5X10^9$/L in the Tecfidera® group as compared with <1% of the placebo group. Therefore, it is recommended that a recent CBC be performed prior to starting therapy, and thereafter annually or as clinically indicated. Furthermore, it is recommended to be withheld in those with serious infection until the infection has resolved.

Contraindications: There are no contraindications listed in the prescribing information.

Manufacturer: Biogen Idec Inc.

Analysis: Dimethyl fumarate (DMF), the active ingredient of Tecfidera®, has an active metabolite, monomethyl fumarate (MMF). While the exact mechanism of action of DMF for use as a treatment for MS is not known, both DMF and MMF have been shown to activate nuclear factor-like (Nrf2) pathway, which is involved in the cellular response to oxidative stress.

Two randomized, double-blind, placebo-controlled studies were performed in adults with relapsing-remitting MS to assess the safety and efficacy of Tecfidera®. The primary outcome of study 1 (N=1234) was the number of subjects who relapsed at 2 years, while the number of new or newly enlarging T2 hyperintense lesions, the annualized relapse rate (ARR), and the time to confirmed disability progression were also assessed. Results suggested that a significantly greater number relapsed in the placebo vs the Tecfidera® group (46% vs 27%; p<0.0001). [This calculates to an NNT of 6.] The ARR was 0.364 with placebo vs 0.172 with Tecfidera®, which was also statistically significantly different (p<0.0001). Significantly fewer in the Tecfidera® group had disability progression as compared with placebo (16% vs 27%, p<0.0050, calculating to an NNT of 10). The placebo group had 17 new/newly enlarged T2 lesions over 2 years of treatment vs 2.6 with Tecfidera®, which was statistically significantly different (p<0.0001).

Study 2 (N=1417)[2] also included glatiramer as an open-label comparator, with a placebo-arm and two doses of Tecfidera® being 240mg BID and 240mg TID. The primary outcome of study 2 was the ARR at 2 years. Results suggested that the frequency of relapses was significantly reduced with Tecfidera® (BID and TID) as assessed by an adjusted ARR of 0.22 and 0.20, respectively, as compared with placebo (ARR 0.40; p<0.0001). Glatiramer also reduced the ARR (0.29) and was statistically significantly different from placebo (p=0.01). Significantly fewer subjects in the BID (29%; p≤0.01) and TID (24%; p<0.001) Tecfidera® groups had a relapse at 2 years as compared with placebo (41%). The glatiramer group also had significantly fewer relapses vs placebo (32% vs 41%; p≤0.01). Statistically significant differences between treatment groups were not seen with disability progression at 2 years and this study was not designed to assess the superiority of Tecfidera® to glatiramer but established the non-inferiority between these two treatments. There were 17.4 new/enlarging T2 lesions at 2 years with the placebo group as compared with 5.1 with the BID group (p<0.001), 4.7 with the TID group (p<0.001), and 8 with glatiramer (p<0.001).

There is no evidence at this time to support that Tecfidera® is more efficacious or safer than the currently available, more cost effective medications. While glatiramer was included in study 2, this was an open-label treatment arm and was not a true head-to-head study. Therefore, it is recommended that Tecfidera® remain non-preferred and be available to the few who are unable to tolerate any preferred medications or who have had treatment failures.

PDL Placement: ☐ **Preferred**
☒ **Non-Preferred**

References

[1] Tecfidera [package insert]. Cambridge, MA: Biogen Idec, Inc; 2013.

[2] Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *NEJM*. 2012; 367(12): 1087-97.