Drug Monograph

Drug/Drug Class: **Tecfidera® (dimethyl fumarate) Capsule / Immunomodulator**

Prepared for: MO HealthNet
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☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms & Manufacturer:	Tecfidera® is available as 120mg and 240mg delayed-release capsules containing dimethyl fumarate. It is also supplied as a 30-day starter pack containing 14 of the 120mg capsules and 46 of the 240mg capsules. Biogen Idec, Inc. Cambridge, MA 02142
Summary of Findings:	Techfidera is an oral delayed-release capsule approved for treating adults with relapsing forms of MS. It is dosed twice daily and the capsules should be swallowed whole.
Status Recommendation:	☐ Prior Authorization (PA) Required ☐ Open Access ☐ Fiscal Edit ☒ PDL Product
Type of PA Criteria:	☐ Increased Risk of ADE ☒ Non-Preferred Agent ☐ Appropriate Indications ☐ 15 Day First Fill Fiscal Edit

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payors are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction

Multiple sclerosis (MS) is an inflammatory disease in which the covers of nerve cells in the brain and spinal cord are damaged. This damage disrupts the ability of parts of the nervous system to communicate, resulting in a wide range of symptoms including physical, mental and sometimes psychiatric problems. The Relapsing form of MS is characterized by symptoms occurring in isolated attacks and then decreasing, sometimes disappearing all together between attacks.

Dosage Form(s)[1]

Tecfidera® is available as 120mg and 240mg delayed-release capsules containing dimethyl fumarate. It is also supplied as a 30-day starter pack containing 14 of the 120mg capsules and 46 of the 240mg capsules.

Manufacturer

Biogen Idec, Inc. Cambridge, MA 02142

Indication(s)[1]

Tecfidera® is an oral delayed-release capsule approved for treating adults with relapsing forms of MS.

Clinical Efficacy[1-3] (mechanism of action/pharmacology, comparative efficacy)

PHARMACOLOGY (1)

Although the exact mechanism is unknown, both Tecfidera and the monomethyl fumarate metabolite are in vitro and in vivo activators of the Nuclear factor (erythroid-derived 2)-like 2(Nrf2) pathway, which plays a role in the cellular response to oxidative stress.

PHARMACOKINETICS (1)

Tecfidera is 27% to 45% protein bound with a volume of distribution of 53 to 73L. It is hydrolyzed by esterases to monomethyl fumarate, excreated via respiration (60%), feces (1%) and urine (16%) with a half-life of 1 hour.

EFFICACY (2,3)

SUMMARY

The approval of Tecfidera was based on 2 international, randomized, double-blind, 2-year, phase 3 trials (DEFINE; CONFIRM) in patients with relapsing-remitting multiple sclerosis (RRMS). Results from both trials showed that oral Tecfidera at twice daily or 3 times daily

dosages significantly reduced relapse rates at 2 years compared with placebo. Although the CONFIRM trial also included an open-label glatiramer arm, it was not designed to compare outcomes with Tecfidera. Direct clinical comparisons with other MS agents are not available at this time.

DEFINE TRIAL

CONCLUSION (2)
Oral Tecfidera significantly lowered rates of relapse and disability progression compared with placebo in patients with RRMS.

STUDY DESIGN	Multinational, randomized, double-blind, phase 3 Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting MS (DEFINE) trial.
INCLUSION CRITERIA	Patients aged 18 to 55 years, with RRMS, a score of 0 to 5 on the Expanded Disability Status Scale (EDSS; range, 0 to 10; higher scores indicate greater disability), and at least one clinically documented relapse in the prior 12 months or at least one gadolinium-enhancing lesion within 6 weeks before randomization.
EXCLUSION CRITERIA	Patients with progressive forms of MS, other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to glatiramer or contraindicated medications.
TREATMENT REGIMEN	Patients were randomized to receive oral doses of either Tecfidera 240 mg twice daily (n=410), Tecfidera 240 mg 3 times daily (n=416), or placebo (n=408). Patients were allowed to switch to an alternative MS therapy if they had completed 48 weeks of therapy and had one or more confirmed relapses after 24 weeks; patients with confirmed progression of disability could switch at any time. The primary efficacy endpoint was the number of patients experiencing a relapse by 2 years. At baseline, the mean number of relapses in the prior 12 months was 1.3 and the mean EDSS scores were 2.4, 2.36, and 2.48 in the Tecfidera 240 mg twice daily, 3 times daily, and placebo groups, respectively. Efficacy was analyzed in the modified intent-to-treat population, which included all randomized patients who received at least 1 dose of the study drug.
RESULTS	Both dosages of Tecfidera were superior to placebo in reducing the number of relapses. At 2 years, 27% and 26% of patients in the Tecfidera twice daily and 3 times daily groups, respectively, had a relapse compared with 46% of patients in the placebo group ($p < 0.001$ for both), reflecting a 49% (hazard ratio (HR), 0.51; 95% CI, 0.4 to 0.66) and 50% (HR, 0.5; 95% CI, 0.39 to 0.65) reduction in the risk of relapse in the twice daily and 3 times daily groups, respectively ($p < 0.001$ for both). The annualized relapse rate at 2 years was 0.17 and 0.19 in the twice daily and 3 times daily groups, respectively, compared with 0.36 in the placebo groups ($p < 0.001$ for both). Among key secondary endpoints, the risk of confirmed progression of disability in the 2-year period was reduced by 38% in the twice daily group (HR, 0.62; 95% CI, 0.44 to 0.87; p=0.005) and by 34% in the 3 times daily group (HR, 0.66; 95% CI, 0.48 to 0.92; p=0.01). Both dosages of Tecfidera also significantly reduced the number of gadolinium-enhancing lesions (0.1 and 0.5 in the twice daily and 3 times daily groups, respectively, vs 1.8

	for placebo) and new or growing T2-weighted hyperintense lesions (adjusted mean number of lesions: 2.6 (95% CI, 2 to 3.5) and 4.4 (95% CI, 3.2 to 5.9) in the twice daily and 3 times daily groups, respectively, vs 17 (95% CI, 12.9 to 22.4) for placebo).
SAFETY	The most commonly reported adverse events in the Tecfidera 240 mg twice daily and 240 mg 3 times daily groups were flushing (38% and 32%, respectively, vs 5% for placebo), diarrhea (15% and 19%, respectively, vs 13% for placebo), nausea (13% for each group vs 9% for placebo), and abdominal pain (11% and 9%, respectively, vs 5% for placebo). Patients receiving Tecfidera also experienced a decrease in lymphocyte counts (28% at 1 year) compared with placebo. Additionally, increased ALT levels (3 or more times the ULN) were seen in 6% of patients in each of the Tecfidera groups compared with 3% of patients in the placebo group.

CONFIRM TRIAL

CONCLUSION (3)

Oral Tecfidera significantly lowered relapses rate compared with placebo in patients with RRMS.

STUDY DESIGN	Multinational, randomized, double-blind, phase 3 Comparator and an Oral Fumarate in Relapsing-Remitting MS (CONFIRM) study.
INCLUSION CRITERIA	Patients aged 18 to 55 years, with RRMS, a score of 0 to 5 on the Expanded Disability Status Scale (EDSS; range, 0 to 10; higher scores indicate greater disability), and at least one clinically documented relapse in the prior 12 months or at least one gadolinium-enhancing lesion within 6 weeks before randomization.
EXCLUSION CRITERIA	Patients with progressive forms of MS, other clinically significant illness, prespecified laboratory abnormalities, and prior exposure to glatiramer or contraindicated medications.
TREATMENT REGIMEN	Patients were randomized to receive oral doses of either Tecfidera 240 mg twice daily (n=359), Tecfidera 240 mg 3 times daily (n=345), or placebo (n=363). A comparator arm was included in which patients received open-label glatiramer acetate 20 mg subQ (n=350)for 96 weeks. Patients were allowed to switch to an alternative MS therapy if they had completed 48 weeks of therapy and had 2 confirmed relapses, or if they had confirmed progression of disability. The primary efficacy endpoint was the annualized rate of relapse at 2 years. At baseline, the mean number of relapses in the prior 12 months ranged from 1.3 to 1.4 across the groups, and the mean EDSS score ranged from 2.5 to 2.6. Efficacy was analyzed in the modified intent-to-treat population, which included all randomized patients who received at least 1 dose of the study drug.
RESULTS	Both dosages of oral Tecfidera were superior to placebo in reducing relapse rates. At 2 years, the annualized relapse rate was 0.22 and 0.2 in the twice daily and 3 times daily groups, respectively, compared with 0.4 in the placebo groups ($p < 0.001$ for both), yielding reductions in relapse rates of 44% and 51% relative to placebo. The annualized relapse rate at 2 years in the glatiramer group was 0.29 (relative reduction of 29% vs placebo; p=0.01). Twice daily and 3 times daily

	therapy reduced the risk of relapse by 34% (p=0.002) and 45% (p < 0.001), respectively, compared with placebo, as did glatiramer (29%; p=0.01). The estimated proportion of patients experiencing a relapse at 2 years was 29%, 24%, and 32% in the twice daily, 3 times daily, and glatiramer groups, respectively, compared with 41% in the placebo group. Among key secondary endpoints, there was no significant difference in confirmed progression of disability in the 2-year period among the Tecfidera or glatiramer groups compared with placebo. Both twice daily and 3 times daily Tecfidera, as well as glatiramer, significantly reduced the number of gadolinium-enhancing lesions (0.5, 0.4, and 0.7, respectively, vs 2 for placebo) and new or growing T2-weighted hyperintense lesions (adjusted mean number of lesions: 5.1 (95% CI, 3.9 to 6.6), 4.7 (95% CI, 3.6 to 6.2), and 8 (95% CI, 6.3 to 10.2), respectively vs 17.4 (95% CI, 13.5 to 22.4) for placebo).
SAFETY	The most commonly reported adverse events in the Tecfidera 240 mg twice daily and 240 mg 3 times daily groups were flushing (35% and 28%, respectively, vs 6% and 3% for placebo and glatiramer, respectively) and gastrointestinal (GI) events (36% and 41%, respectively, vs 26% and 15% for placebo and glatiramer, respectively). Both flushing and GI events were mild to moderate in severity for the majority of patients, with the highest incidence occurring in the first month of the study and declining thereafter. Patients in the Tecfidera twice daily and 3 times daily groups also experienced a decrease in lymphocyte counts (32% and 28%, respectively, at 1 year); grade 3 or higher decreases in lymphocyte counts were seen in 5% and 4% of patients, respectively, compared with < 1% of patients with placebo.

Contraindications[1]

Specific contraindications have not been determined.

Warnings and Precautions[1]

- Lymphopenia has been reported; prior to therapy initiation, obtain a recent CBC (within 6 months), repeat annually while on treatment and as clinically indicated.
- Flushing (warmth, redness, itching and/or burning sensation) has been reported.

Adverse Effects[1]

Most Common, >10%	Tecfidera (n=769)	Placebo (n= 771)
flushing	40%	6%
abdominal pain	18%	10%
diarrhea	14%	11%
nausea	12%	9%

Drug Interactions[1]

No known drug interactions.

Dosage and Administration[1]

The recommended initial dose is 120 mg orally twice daily for 7 days, then increase to the recommended maintenance dose of 240 mg orally twice daily. Administration with food may reduce the incidence of flushing. The capsule should be swallowed whole; do not chew, crush, or sprinkle capsule contents on food.

Cost Comparisons (at commonly used dosages)

GENERIC NAME	BRAND NAME	MANUFACTURER	STRENGTH	DOSE	COST/ MONTH
Dimethyl fumarate	Tecfidera	Biogen Idec	120 mg/240 mg capsules, starter pack	1 capsule twice daily	$ 4500.00
			240 mg capsules	1 capsule twice daily	$ 4500.00

*Wholesale Acquisition Cost (WAC)

Conclusion

Tecfidera is an oral delayed-release capsule approved for treating adults with relapsing forms of MS. It is dosed twice daily and the capsules should be swallowed whole. Common adverse effects include flushing and gastrointestinal events, and administration with food may reduce the incidence of flushing. This drug may also reduce lymphocyte counts and therefore, a baseline and annual CBC is recommended. Direct clinical comparisons with other MS agents are not available at this time.

Recommendation

The Division recommends this product be considered for inclusion in the state specific Preferred Drug List as a non-preferred agent.

References

1. Product Information: Tecfidera™, dimethyl fumarate delayed-release capsules. Biogen Idec Inc, Cambridge, MA, 03/2013.

2. Gold R, Kappos L, Arnold DL et al: Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med 2012; 367(12):1098-1107.

3. Fox RJ, Miller DH, Phillips JT et al: Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med 2012; 367(12):1087-1097.

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