Drug Monograph

Brand Name: Tecfidera

Generic Name: dimethyl fumarate

Manufacturer[1]: Biogen Idec Inc.

Drug Class[2,3,4]: Systemic Immunomodulator, Fumaric Acid Derivative[3,4]

Uses:

Labeled[1,2,3,4,5]: Treatment of patients with relapsing forms of multiple sclerosis
Unlabeled: None known

Mechanism of Action: The nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway is involved in the cellular response to oxidative stress. This pathway is activated by dimethyl fumarate in vitro and in vivo. In vitro specifically, it acts as a nicotinic acid receptor agonist. However, the exact mechanism of the effect in multiple sclerosis is unknown.[1,2,3,4] It is believed to be through the Nrf2 pathway due to its anti-inflammatory and cytoprotective properties.[1,3,4]

Pharmacokinetics: All pharmacokinetic analysis were performed using monomethyl fumarate, the active metabolite of dimethyl fumarate due to the rapid pre-systemic hydrolysis by esterases.[1]

Absorption/Distribution:

Tmax[1,2,3,4,5]	2 – 2.5 hours
Vd[1,2,3,4]	53-71 L
Half-life[1,2,3,4,5]	1 hour
Clearance	Not reported
Protein binding[1,2,3,4,5] (extent to albumin)	27-45% (not reported)
Bioavailability	No quantifiable level found in plasma

Metabolism[1,2,3,4,5]: Dimethyl fumarate is extensively metabolized by esterases via hydrolysis into its active metabolite, monomethyl fumarate (MMF) before it reaches systemic circulation. The main sites of this metabolism include the gastrointestinal tract, blood, and tissues. MMF is further metabolized through the tricarboxylic acid cycle. The major metabolites in the plasma are MMF, fumaric acid, citric acid, and glucose. The cytochrome P450 system is not involved in the metabolism of dimethyl fumarate.

Elimination[1,2,3,4,5]: The primary route of elimination is respiratory (60%) via exhalation of carbon dioxide. Other routes of elimination include renal (16%) and feces (1%). Trace amounts of unchanged MMF are present in the urine.

Efficacy:

Kappos L, Gold R, Miller DH, MacManus DG, Havrdova E, Limmroth V, Polman CH, Schmierer K, Yousry TA, Eraksoy M, Meluzinova E, Dufek M, Yang M, Dawson K, O'Neill GN. Effect on BG-12 on contrast-enhanced lesions in patients with relapsing-remitting multiple sclerosis: subgroup analyses from the phase 2b study. Mult Scler. 2012; 18(3): 314-21.

Study design: Multicenter, randomized, double blind, placebo controlled, parallel group, dose ranging

Description of study: *Methods:* The study is a sub-group analysis of the total population in the BG-12 240 mg three times daily on total Gd+ lesion development from weeks 12 to 24. Sub-groups analyzed include the following compared with their baseline status: Expanded Disability Status Scale (EDSS) score $\leq$ 2.5, EDSS score > 2.5, 0 Gd+ lesions, $\geq$ 1 Gd+ lesions, age < 40 years, age $\geq$ 40 years, female patients, male patients, disease duration $\leq$ 6 years and disease duration > 6 years. The original study included 257 patients, aged 18-55 years old. Patients were required to have a diagnosis of relapsing-remitting multiple sclerosis according to McDonald criteria. Other requirements for study inclusion: baseline EDSS score between 0.0 and 5.0 and at least one relapse within the past 12 months before randomization occurred. A previous brain MRI scan must have been consistent with MS or Gd+ lesions within 6 weeks before randomization. *Results:* The study subgroup analyses included 108 patients receiving either placebo or BG-12 240 mg three times daily. The subgroup analyses performed confirmed the results of the overall study. The results for the BG-12 240 mg three times daily treatment group reduced the total number of new Gd+ lesions by 74% (p=0.006) in patients with baseline EDSS scores of 2.5 or lower, by 63% (p=0.002) in patients with baseline EDSS scores higher than 2.5, by 80% (p=0.005) in patients with no Gd+ lesions at baseline and by 55% (p=0.003) in patients with Gd+ lesions at baseline compared with placebo. A sub-analysis based on demographics was also performed for BG-12 240 mg three times daily on the efficacy of reducing development of new Gd+ lesions. Statistically significant results were found for all but one population, a reduction of 38% in male patients compared to placebo (p=0.063). An 81% reduction (p<0.001) was found in female patients, 49% reduction (p=0.009) in patients < 40 years old, 89% (p=0.002) in patients $\geq$ 40 years old, 81% (p<0.001) in patients with a disease duration $\leq$ 6 years, and by 54% (p=0.015) in patients with a disease duration > 6 years, compared with placebo.

Limitations: The authors did not analyze the effect on annualized relapse rates for the subgroups because it was not found to be statistically significant in the original study. Funding for the study was supported by Biogen Idec, Inc. Potential conflicts of interest exist due to the authors many affiliations with Biogen Idec including grant support, employment, or serving on advisory or steering committees. Another major limitation of this study is analyzing the 240 mg three times daily group, because currently only 240 mg twice daily is FDA approved for multiple sclerosis.

Conclusion: Further studies with a larger population need to be investigated to determine the efficacy of BG-12 in reducing the annual relapse rates because the primary phase of the study did not find a statistically significant difference. This may have been due to the study sample size or effect size. Based on the primary study as well as the sub-group analyses it can be stated that BG-12 was effective at reducing the number of new Gd+ lesions at 24 weeks compared to baseline. The study population only included patients with relapsing-remitting multiple sclerosis and results cannot be extrapolated to patients suffering from other types of multiple sclerosis.

Gold R, Kappos L, Arnold DL, Bar-Or A, Giovannoni G, Selmaj K, Tornatore C, Sweetser MT, Yang M, Sheikh SI, Dawson KT. Placebo-controlled phase 3 study of oral BG-12 for relapsing multiple sclerosis. N Engl J Med. 2012; 367(12): 1098-107.

Study design: Multi-center, randomized, double blind, placebo controlled, 2 year study

Description of study: *Methods:* Patients included in this study were from 198 sites in 28 different countries. Inclusion characteristics include ages 18-55 years old, diagnosis of relapsing-remitting

multiple sclerosis (defined by McDonald criteria), EDSS baseline score from 0 to 5.0, and one documented relapse within the previous 12 months or an MRI scan showing at least one gadolinium enhancing lesions within the past 6 weeks. Treatment groups (BG-12 240 mg twice daily, BG-12 240 mg three times daily, or placebo) were randomly assigned using a 1:1:1 ratio. In order to maintain blinding neurologists were either examining results or treating patients, not both. Patients were evaluated and monitored every 4 weeks for adverse effects, lab values, and compliance. Neurologic assessment occurred every 12 weeks, and MRI scans occurred at weeks 24, 48, and 96. Proportion of patients who had relapsed by 2 years was the primary endpoint. Secondary endpoints at 2 years included the number of gadolinium-enhancing lesions and of new or enlarging hyperintense lesions on T2-weighted images, the annualized relapse rate, and the time to progression of disability. *Results:* A total of 952 patients of 1234 that received at least one dose of the study medication completed the study. The percentage of patients with one or more relapses by 2 years and annualized relapse rate was significantly lower in both BG-12 groups compared to placebo ($p<0.001$). Patients in either BG-12 regimen experienced prolonged time to first relapse, less new or enlarging hyperintense lesions on T2-weighted images at 2 years, and experienced reduced odds of an increase in the number of gadolinium-enhancing lesions at 2 years compared to placebo ($p<0.001$). Risk of progression of disability was reduced in BG-12 twice daily group ($p=0.005$) and BG-12 three times daily ($p=0.01$). Flushing, gastrointestinal events, proteinuria, and pruritus occurred more frequently in patients receiving BG-12 than placebo. Serious adverse events including relapse of multiple sclerosis and infections was similar in all treatment groups. Lab values including decreased white cell and lymphocyte count (still WNL) and elevated liver enzymes (3x normal) were noted in BG-12 treatment groups. White cell and lymphocyte counts stabilized after approximately a year of therapy and elevations in liver enzymes occurred within the first 6 weeks.

Limitations: The study did not compare BG-12 to any approved therapies for relapsing-remitting multiple sclerosis. This limits the ability to conclude BG-12s place in therapy. Data was analyzed by the sponsor which is a potential conflict of interest. The manuscript was also in part prepared by a senior author representing the sponsor. The authors have several affiliations and potential conflicts of interest regarding Biogen Idec, who provided funding and support for the study. Author's affiliations include research grant support, serving on advisory committees, and employment. The final limitation of this study is due to currently approved FDA doses, only the information from the BG-12 240 mg twice daily dosing would be clinically relevant.

Conclusion: BG-12 is an effective agent for relapsing-remitting multiple sclerosis. The medication has a relative safe adverse effect profile. The highest risk is within the first month to year of treatment. Flushing and gastrointestinal effects are most significant during the first month. Declines in white blood cell and lymphocyte count continue throughout the first year of treatment before they begin to plateau. Further investigations need to be done in order to determine when to recommend this drug versus current therapy. Based upon current studies a patient who has exhausted many or all other options for relapsing-remitting multiple sclerosis, or a patient who prefers an oral therapy over injectable therapy is a good candidate for BG-12 therapy based on the evidence provided by this study.

Fox RJ, Miller DH, Phillips JT, Hutchinson M, Havrdova E, Kita M, Yang M, Raghupathi K, Novas M, Sweetser MT, Viglietta V, Dawson KT. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. N Engl J Med. 2012; 367 (12): 1087-97.

Study design: multi-center, randomized, placebo controlled study

Description of study: *Methods:* Patients from 200 sites in 28 countries who met the following criteria (diagnosis of relapsing-remitting multiple sclerosis, age 18-55, EDSS score of 0 to 5, and in the past 12 months one or more clinically documented relapse or in the past 4 weeks one or more gadoliunium enhancing lesion present on MRI) were randomized in a 1:1:1:1 ratio to the following treatment groups (oral placebo, BG-12 240 mg two times daily, BG-12 240 mg three times daily, or glatiramer acetate 20 mg subcutaneous injections) for 96 weeks. Patients in the glatiramer acetate group were not blinded to treatment due to the alternative route of administration. Neurologic assessments occurred every 12 weeks and MRI scans, where capabilities existed, were done at weeks 24, 48, and 96. Annualized relapse rate at 2 years, confirmed by an independent (blinded) neurologist, was the primary efficacy end point. Secondary efficacy end points were the number of new or enlarging hyperintense lesions on T2-weighted images, the number of new hypointense lesions on T1 weighted images, the proportion of patients with a relapse, and the time to disability progression, each at 2 years. Tertiary endpoints were a comparison of the relative benefits and risks of BG-12 or glatiramer acetate versus placebo and the number of gadolinium-enhancing lesions at 2 years. *Results:* 1417 of 1430 patients randomly assigned were included in the ITT population, with an overall study completion rate of 80%. The frequency of relapses of multiple sclerosis and the annualized relapse rate at 2 years was significantly decreased in both BG-12 treatment groups ($p<0.001$). The annualized relapse rate vs. placebo was also significantly reduced with glatiramer acetate ($p=0.01$). The risk of relapse was significantly reduced in BG-12 twice daily, BG-12 three times daily, and glatiramer acetate treatment groups compared with placebo ($p=0.002$, $p<0.001$, $p=0.01$), respectively. Treatment groups did not significantly reduce disability progression compared to placebo ($p=0.25$, $p=0.20$, $p=0.70$). The mean number of new or enlarging hyperintense lesions on T2 weight images at 2 years was significantly reduced in all treatment groups compared to placebo ($p<0.001$). Reduced mean number of new hypointense lesions no T1 weighted images ($p<0.001$, $p<0.001$, $p=0.002$), respectively was reported. The odds of having gadolinium-enhancing lesions at 2 years was significantly reduced in all treatment groups compared to placebo ($p<0.001$). A post hoc direct evaluation of the relative benefit of BG-12 versus glatiramer acetate were as follows: annualized relapse rate ($p=0.10$, $p=0.02$), respectively; new or enlarging hyperintense lesions on T2 weighted images ($p=0.007$, $p=0.002$); new hypointense lesions on T1-weighted images ($p=0.08$, $p=0.003$); proportion of patients with a relapse ($p=0.58$, $p=0.09$); and time to disability progression ($p=0.44$, $p=0.37$). Adverse effects reported more frequently in the BG-12 groups than placebo included flushing, gastrointestinal events, upper respiratory tract infections, and erythema. Flushing and GI events were more frequent during the first month of therapy. Injection site reactions was the most frequently reported adverse event the glatiramer acetate group compared to placebo. Discontinuations occurred most frequently due to multiple sclerosis relapses in placebo group. No other serious adverse events were reported in more than 2 patients in each treatment group. In both BG-12 treatment groups decreased white cell and lymphocyte counts occurred during the first year of therapy, with one patient in the BG-12 three times daily group discontinuing the study.

Limitations: The data was analyzed by the sponsors (Biogen Idec). The study used an active control, glatiramer however, the study was not designed to test the superiority or non-inferiority of BG-12 versus glatiramer acetate. The investigators dispensing the medications were not blinded to treatment groups. This could change the patient's perception on the quality of care they were receiving, especially if the patient had previously tried glatiramer acetate with poor results. The percentage of patients previously receiving glatiramer acetate therapy was not reported. The study was supported by Biogen Idec, several authors have potential conflicts of interest with this company including receiving grant and travel support, consulting and lecture fees, and employment.

Conclusion: The study could have resulted in more clinically useful data if it would have been designed to also include analyses of BG-12 versus glatiramer acetate. This would have helped to decide where in a treatment algorithm BG-12 should be placed. The study did evaluate BG-12 versus glatiramer acetate in a post hoc direct evaluation with some findings statistically significant, especially with the BG-12 three times daily treatment group. This data would suggest that BG-12 three times daily is at least as efficacious as glatiramer acetate with respect to the annualized relapse rate, the number of new or enlarging hyperintense lesions on T2 weighted images, and the number of new hypointense lesions on T1 weighted images of relapsing-remitting multiple sclerosis. However, current FDA approval is for a maximum dose of BG-12 240 mg two times daily, making this data less clinically significant. A study designed directly comparing BG-12 and glatiramer would be useful to further develop BG-12's place in treatment. Blinding could only remain if all patients were given BG-12 treatment and a placebo injection or oral placebo tablet and glatiramer acetate injection. One major benefit of BG-12 compared to current standard treatments is the oral dosage route which may be more appealing to many patients instead of daily injections. Overall in this study BG-12 twice or three times daily was relatively well tolerated and effective for relapsing-remitting multiple sclerosis in comparison to placebo.

Contraindications[1,2,3,4,5]:

None well documented

Precautions:

Flushing: usually mild to moderate flushing occurs when initiating therapy and a decreased incidence occurs over time; symptoms include warmth, redness, itching, and/or a burning sensation.[1,2,3,4] Taking the medication with food may decrease the incidence of flushing. [1,3,4]

Lymphopenia: dimethyl fumarate may decrease lymphocyte counts, a complete blood count is recommended within the past 6 months before therapy initiation, and to be repeated annually.[1,2,3,45] Consider withholding treatment in patients with serious infections until resolved.[1,2,3,4] In controlled trials, mean lymphocyte counts decreased by approximately 30% within the first year of therapy and then remained stable. Discontinuation of dimethyl fumarate resulted in increased lymphocyte counts within 4 weeks but it was still less than baseline.[1,3,4] The drug has not been studied in patients with preexisting low lymphocyte counts.[1,3]

Hepatic effects: transaminase elevations may occur within the first 6 months of treatment; elevations are typically less than 3 times the upper normal limit[3]

Gastrointestinal events: nausea, vomiting, diarrhea, abdominal pain, and dyspepsia commonly occur with dimethyl fumarate upon initiation of therapy and decrease with continued use after approximately a month of therapy[3]

Adverse Effects[1,2,3,4,5]:

Occurring in > 10% of patients

- Gastrointestinal Disorders:
  - Abdominal pain (18%)
  - Diarrhea (14%)
  - Nausea (12%)
- Vascular Disorders:
  - Flushing (40%)

Occurring in >1% to < 10% of patients

Blood and Lymphatic System Disorders:
Lymphopenia (2-6%)

Gastrointestinal Disorders:
Vomiting (9%)
Dyspepsia (5%)
Skin and Subcutaneous Tissue Disorders:
Pruritus (8%)
Rash (8%)
Erythema (5%)
Renal Effects:
Albumin urine present (6%)
Hepatic Effects:
Asparate aminotransferase increased (4%)

Drug Interactions[1,2,3,4,5]:

Drug-Drug Interactions:
None well documented
Drug-Food Interactions:
High fat, high calorie meals decrease C_{max} by 40% and the T_{max} is delayed 3-3.5 hours.

Dosing/Administration:

Adult dose[1,2,3,4,5]:
Initial dose: 120 mg by mouth twice daily
Titrating dose: after 7 days the dose may be increased to the maintenance dose
Maintenance dose: 240 mg by mouth twice daily
Maximum daily dose: 480 mg/day
Geriatric dose[1,3,4,5]:
No known dosage adjustment necessary. Clinical studies did not include a significant number of patients aged 65 years or older.[1]
Pediatric dose[1,2,4,5]:
Safety and efficacy in neonates, infants, children, or adolescents has not been established
Renal impairment dose[2,3,4,5]:
No dosage adjustment necessary
Hepatic impairment dose[2,3,4,5]:
No dosage adjustment necessary

Use in special circumstances:

Pregnancy[1,2,3,4,5]:
Pregnancy category C – there have not been any well controlled studies in pregnant women, but adverse effects (including embryofetal toxicity, offspring survival, growth, sexual maturation, and decreased neurobehavioral function) have occurred in animals. Dimethyl fumarate use in pregnancy is currently only recommended if potential benefits outweigh the risk to the fetus.
Lactation[1,2,3.4.5]:
It is unknown if dimethyl fumarate is excreted in human milk, caution should be exercised when dimethyl fumarate is administered to a mother that is breastfeeding. Before using dimethyl fumarate in lactation potential benefits must outweigh the potential risk to the fetus. Offspring survival, growth, sexual maturation, and neurobehavioral function adverse effects have been reported with use of dimethyl fumarate during lactation in animals.[4,5]

Serious infection[1,2,3,4]:

Consider withholding treatment until infection resolves.

Conclusion:

Dimethyl fumarate offers patients an oral dosage route for the treatment of relapsing-remitting multiple sclerosis. Based off current clinical trials the proper warnings, precautions, and adverse effects are reflected in package labeling. Overall the medication is well tolerated with flushing and gastrointestinal reactions being the most frequent reported. These effects appear to dissipate with time and are most severe during the initial month of treatment. White cell and lymphocyte counts were shown to decrease within the first year of treatment, but then remain steady. Current recommendations for CBC are included in the labeling and appropriate. More frequent monitoring during the first year of therapy may be indicated. Patients have been studied in clinical trials with dimethyl fumarate 240mg three times daily, however current packaging limits patients total daily dosage to 480 mg daily. Based off the clinical trials adverse effects were not reported to be more severe in the patients treated with a daily dose of 720 mg. However, there was not a statistical analysis comparing the two treatment groups with each other. Further studies may need to be conducted to evaluate if the higher dosage provides more benefit with minimal risk of additional adverse effects. Dimethyl fumarate is currently not recommended in pregnancy and lactation, unless potential benefits outweigh risk. All patients should be aware of all risks versus possible benefits before beginning treatment with dimethyl fumarate. Overall, the medication provides a relatively safe and effective oral option for patients suffering from relapsing-remitting multiple sclerosis. Further studies may need to be conducted to find the best place in therapy for dimethyl fumarate in relapsing-remitting multiple sclerosis as well as to see if it the medication can benefit patients with other types of multiple sclerosis.

Recommended References:

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