PDL DRUG REVIEW

Proprietary Name: Bafiertam®
Common Name: monomethyl fumarate
PDL Category: Multiple Sclerosis Agents

Comparable Products	Preferred Drug List Status
Tecfidera	Preferred with Conditions
Vumerity	Non-Preferred with Conditions

Summary

Pharmacology/Usage: Monomethyl fumarate (MMF), the active ingredient of Bafiertam® has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway in vitro and in vivo. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist in vitro. However, the mechanism by which MMF exerts its therapeutic effect in multiple sclerosis is not known.

Indication: For the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

There is no pregnancy category for this product; however, the risk summary indicates that there are no adequate data on the developmental risk associated with the use of Bafiertam® or dimethyl fumarate (the prodrug of Bafiertam®) in pregnant women. The safety and efficacy of use in the pediatric population have not been established.

Dosage Form: Soft Gelatin Delayed-Release Capsules: 95mg. Swallow whole; do not chew, crush, or mix the contents with food.

Recommended Dosage: Obtain the following prior to treatment with Bafiertam®:

- A complete blood cell count (CBC), including lymphocyte count. In addition, obtain these labs 6 months after initiation of treatment and then every 6 to 12 months thereafter, as clinically indicated.
- Serum aminotransferase, alkaline phosphatase, and total bilirubin levels. In addition, obtain these labs during treatment, as clinically indicated.

Take 95mg PO BID for 7 days. After 7 days, increase to the maintenance dose of 190mg PO BID. Temporary dosage reductions to 95mg BID may be considered for individuals who do not tolerate the maintenance dosage. Within 4 weeks, the recommended dosage of 190mg BID should be resumed. Discontinuation of Bafiertam® should be considered for patients unable to tolerate return to the maintenance dosage. Administration of non-enteric coated aspirin (up to a dose of 325mg) 30 minutes prior to Bafiertam® dosing may reduce the incidence or severity of flushing.

No studies have been conducted in subjects with renal or hepatic impairment; however, neither condition would be expected to affect plasma exposure to MMF and thus no dosage adjustment is needed.

Drug Interactions: Both dimethyl fumarate and diroximel fumarate are metabolized to monomethyl fumarate. Thus, Bafiertam® is contraindicated in patients currently taking dimethyl fumarate or diroximel fumarate. Bafiertam® may be initiated the day following discontinuation of either of these drugs.

Box Warning: There is no box warning listed with this product.

Common Adverse Drug Reactions: *Listed % incidence for adverse drug reactions= reported % incidence for drug (dimethyl fumarate) minus reported % incidence for placebo. Please note that an incidence of 0% means the incidence was the same as or less than placebo.* The most frequently reported adverse events included flushing (34%), abdominal pain (8%), diarrhea (3%), nausea (3%), vomiting (4%), pruritus (4%), rash (5%), albumin urine present (2%), erythema (4%), dyspepsia (2%), aspartate aminotransferase increased (2%), and lymphopenia (>1%).

In clinical studies, a total of 178 healthy subjects have received single doses of Bafiertam®. The adverse reaction profile of Bafiertam® was consistent with the experience in the placebo-controlled trials with dimethyl fumarate. Taking Bafiertam® without food may reduce the incidence of GI events.

Bafiertam® cay cause anaphylaxis and angioedema after the first dose or at any time during treatment. Discontinue treatment and seek immediate medical care if signs or symptoms of anaphylaxis or angioedema occur.

Progressive multifocal leukoencephalopathy (PML) has occurred in patients with MS treated with dimethyl fumarate (the prodrug of Bafiertam®). PML has also occurred in patients taking dimethyl fumarate in the post marketing setting in the presence of lymphopenia. At the first sign or symptom suggestive of PML, withhold Bafiertam® and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms.

Serious cases of herpes zoster have occurred with dimethyl fumarate (the prodrug of Bafiertam®). These events may occur at any time during treatment. Monitor patients for signs and symptoms of herpes zoster. Other serious opportunistic infections have occurred with dimethyl fumarate, such as West Nile, cytomegalovirus, *Aspergillus,* or *Listeria*. These infections have been reported in patients with reduced absolute lymphocyte counts, as well as in patients with normal absolute lymphocyte counts. Consider withholding Bafiertam® treatment in patients with herpes zoster or other serious infections until the infection has resolved.

Bafiertam® may decrease lymphocyte counts. Obtain a CBC, including lymphocyte count, as discussed in the recommended dosage section. Consider interruption of Bafiertam® in patients with lymphocyte counts less than 0.5 X 10^9/L persisting for more than 6 months.

Clinically significant cases of liver injury have been reported in patients treated with dimethyl fumarate (the prodrug of Bafiertam®) in the post marketing setting. The onset has ranged from a few days to several months after the start of treatment with dimethyl fumarate. None of the reported cases resulted in liver failure, liver transplant, or death. Elevations of hepatic transaminases were observed during controlled trials with dimethyl fumarate. Obtain labs as discussed in the recommended dosage section and discontinue Bafiertam® if clinically significant liver injury induced by Bafiertam® is suspected.

Bafiertam® may cause flushing. In clinical trials of dimethyl fumarate (the prodrug of Bafiertam®), 40% of dimethyl fumarate patients experienced flushing. Flushing symptoms generally began soon after starting dimethyl fumarate and usually improved or resolved over time. In most who experienced flushing, it was mild or moderate in severity. However, 3% of patients discontinued dimethyl fumarate for flushing. Studies with dimethyl fumarate demonstrate that administration of non-enteric coated aspirin (up to a 325mg dose) 30 minutes prior to dosing may reduce the incidence or severity of flushing. In the Bafiertam® studies, the presence of food did not impact the incidence of flushing.

Contraindications: With known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or to any of the excipients of Bafiertam®; Taking dimethyl fumarate or diroximel fumarate.

Manufacturer: Banner Life Sciences

Analysis: The efficacy of Bafiertam® is based upon bioavailability studies in healthy subjects comparing oral dimethyl fumarate delayed-release capsules to Bafiertam® delayed-release capsules. The clinical studies included in the prescribing information for Bafiertam® were conducted using dimethyl fumarate. Dimethyl fumarate, under the brand name Tecfidera®, is available as a hard gelatin delayed-release capsule (120mg or 240mg) with the same indication as Bafiertam®, has been available for numerous years, and has been found to be safe and effective. In addition, Tecfidera® now has a generic available.

Dimethyl fumarate is the prodrug of Bafiertam®. After oral administration, dimethyl fumarate undergoes rapid pre-systemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate. Following oral administration of Bafiertam® 190mg under fasting conditions, the median Tmax is 4.03 hours. In addition, the peak plasma concentration and the overall exposure (AUC) of monomethyl fumarate are bioequivalent to those after oral administration of 240mg dimethyl fumarate delayed-release capsules.

In a 5-week, randomized, double-blind phase 1 study by Wynn et al[3] assessing the gastrointestinal tolerability of MMF 190mg as compared with dimethyl fumarate 240mg in healthy subjects, the first primary endpoint of abdominal pain was not statistically significant between treatments. The primary endpoint was the area under the curve (AUC) in each of the individual symptoms in the self-administered Modified Overall Gastrointestinal Symptom Scale (MOGISS). The 'upper abdominal pain' and 'lower abdominal pain' scores were averaged for analysis of abdominal pain. Other MOGISS symptoms included vomiting, diarrhea, nausea, flatulence, bloating, and constipation. As the first primary endpoint of abdominal pain was not statistically different between treatments, all subsequent statistical analyses in the hierarchical testing were exploratory. There were no statistically significant differences in any of the other primary endpoints between Bafiertam® and Tecfidera® for each symptom, but the least square mean AUC values were lower for Bafiertam® than Tecfidera®. The vomiting AUC in females was statistically significantly lower for Bafiertam® in females than males (p=0.043). None of the other differences between treatments in other MOGISS symptom AUC reached statistical significance for either gender. Nevertheless, for most symptoms in both genders the trend was in favor of Bafiertam®.

There were no subjects in either group with GI adverse events who discontinued treatment. The authors concluded that while the study did not reach statistical significance for the main analyses, based on the tolerability data, Bafiertam® seems to demonstrate improved GI tolerability in terms of incidence, severity, and duration.

Place in Therapy: Bafiertam® is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. The efficacy of Bafiertam® is based upon bioavailability studies in healthy subjects comparing oral dimethyl fumarate delayed-release capsules to Bafiertam® delayed-release capsules.

There is no evidence at this time to suggest that Bafiertam® is safer or more effective than the other currently preferred, more cost-effective medications. It is therefore recommended that Bafiertam® remain non-preferred and require prior authorization and be available to those who are unable to tolerate or who have failed on preferred medications.

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

References

[1] Bafiertam [package insert]. High Point, NC: Banner Life Sciences LLC; 2020.
[2] Tecfidera [package insert]. Cambridge, MA: Biogen Inc; 2020.
[3] Wynn D, Lategan TW, Sprague TN, et al. Monomethyl fumarate has better gastrointestinal tolerability profile compared with dimethyl fumarate. *Mult Scler Relat Disord*. 2020; 45:102335.