

Monomethyl Fumarate (Bafiertam™) Abbreviated New Drug Update (ANDU)

July 2020

OVERVIEW¹

- Indication
 - Monomethyl fumarate (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
- Contraindications/Warnings
 - Contraindications – history of hypersensitivity to monomethyl fumarate (MMF), dimethyl fumarate, diroximel fumarate, or to any inactive ingredients of Bafiertam; monomethyl fumarate should not be administered with dimethyl fumarate (Tecfidera®) or diroximel fumarate (Vumerity™)
 - Warnings – anaphylaxis and angioedema; progressive multifocal leukoencephalopathy (PML); herpes zoster and other serious opportunistic infections; lymphopenia; liver injury; flushing
- Drug Interactions
 - Coadministration with diroximel fumarate or dimethyl fumarate is contraindicated as these agents are metabolized to monomethyl fumarate; monomethyl fumarate can be started the day following discontinuation of either of these medications
- Common Adverse Effects – common adverse reactions ($\geq 10\%$), shown as the incidence for dimethyl fumarate (prodrug for monomethyl fumarate) versus placebo ($\geq 2\%$ more than placebo) include flushing (40% versus 6%), abdominal pain (18% versus 10%), diarrhea (14% versus 11%), and nausea (12% versus 9%)
- Special Populations
 - Pregnancy – there are no adequate data in pregnant women to inform of the drug-related risk with monomethyl fumarate; animal data with dimethyl fumarate suggests it may cause fetal harm when administered during pregnancy
 - Pediatrics – safety and efficacy in pediatric patients have not been determined
 - Geriatrics – clinical studies of dimethyl fumarate and monomethyl fumarate did not include adequate numbers of patients ≥ 65 years old to determine if their response differs from that of younger patients

- Hepatic Impairment – there have been no studies conducted in patients with hepatic impairment; hepatic impairment would not be expected to impact exposure to MMF, and therefore no dosage adjustment is required
- Renal Impairment – there have been no studies conducted in patients with renal impairment; renal impairment would not be expected to impact exposure to MMF, and therefore no dosage adjustment is required
- Availability
 - 95 mg delayed-release capsules for oral administration
- Dosages
 - Administer a starting dose of 95 mg orally twice daily for 7 days, then increase to the maintenance dose of 190 mg orally twice daily taken with or without food; capsules should be swallowed whole and intact and should not be crushed, chewed, or mixed with food; a dose of non-enteric coated aspirin (up to 325 mg) 30 minutes before monomethyl fumarate may decrease the incidence or severity of flushing
 - A temporary dose reduction to 95 mg twice daily may be considered in patients who do not tolerate the maintenance dose; the recommended maintenance dose of 190 mg orally twice daily should be resumed within 4 weeks. Discontinuation of therapy should be considered for patients who are unable to tolerate the return to the maintenance dose.
 - A complete blood cell count (CBC), including lymphocyte count as well as serum aminotransferase, alkaline phosphatase (ALP), and total bilirubin levels are recommended before starting monomethyl fumarate. Following initiation, a CBC, including lymphocyte count, should be assessed 6 months after initiation, then every 6 to 12 months thereafter, as clinically warranted. Serum aminotransferase, ALP, and total bilirubin levels should be monitored during treatment and as clinically warranted.
- Clinical Trials²
 - Bafiertam was approved via the 505(b)(2) pathway, hence at least a portion of the data supporting its approval may have been derived from dimethyl fumarate/another manufacturer. Following oral administration, dimethyl fumarate is rapidly hydrolyzed and converted to the active metabolite, monomethyl fumarate. Bioavailability studies in healthy subjects compared monomethyl fumarate administered orally as 190 mg (two 95 mg delayed-release capsules) in a fasting state to 240 mg orally of dimethyl fumarate delayed-release capsule. The median time to maximum concentration (T_{max}), maximum plasma concentration (C_{max}), and overall exposure as measured by the area-under-the-curve (AUC) were found to be bioequivalent.

CLINICAL CONSIDERATIONS^{3,4,5,6,7,8,9}

- The 2018 American Academy of Neurology (AAN) practice guidelines for disease-modifying therapies for adults with multiple sclerosis outline recommendations for starting, switching, and stopping disease-modifying therapy (DMT).

- When starting DMT, the following recommendations offer guidance in selecting the appropriate agent:
 - The safety, route of administration, lifestyle, cost, efficacy, common adverse effects (AEs), and tolerability should be evaluated (Level A).
 - Women of childbearing potential with MS should discuss their reproductive plans and be counseled regarding reproductive risks and use of birth control during DMT (Level B).
 - Men with MS planning to initiate treatment with teriflunomide or cyclophosphamide should be counseled on their reproductive plans regarding the potential effects of treatment prior to the initiation of these agents (Level B).
 - Mitoxantrone should not be used for MS unless the potential benefits greatly outweigh the risks due to the likelihood of severe AEs such as cardiomyopathy, ovarian failure, male infertility, chromosomal aberrations, and promyelocytic leukemia (Level B).
 - Patients with highly active MS should be prescribed alemtuzumab, fingolimod, or natalizumab (Level B) because these therapies showed more favorable outcomes compared to interferon-beta therapy.
 - Ocrelizumab should be offered to patients with primary progressive multiple sclerosis (PPMS) expected to benefit, unless the risks of treatment outweigh the benefits (Level B).
 - Treatment with natalizumab should only be initiated in patients with positive anti- John Cunningham virus (JCV) antibody indexes above 0.9 if the benefits outweigh the risk for PML (Level C).
 - Patients should be counseled regarding the PML risk associated with natalizumab, fingolimod, rituximab, ocrelizumab, and dimethyl fumarate (Level B).
- When switching DMT, the following recommendation offers guidance for patients on dimethyl fumarate:
 - If a patient using a DMT develops a malignancy, switching to an alternate DMT should be considered especially for patients taking azathioprine, methotrexate, mycophenolate, cyclophosphamide, fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B).
- Monomethyl fumarate has not yet been addressed in the guidelines.
- A study is comparing the safety and gastrointestinal (GI) tolerability within the first 5 weeks of treatment with MMF and dimethyl fumarate in healthy individuals when dosed at bioequivalent doses. Final published results may assist in determining the incidence of flushing and GI AEs.
- MMF offers another oral formulation for MS and avoids injections and infusions.
- MMF is dosed as 2 capsules twice daily, and dimethyl fumarate is the prodrug of MMF. A dose of 190 mg of MMF has been found to be bioequivalent to 240 mg of dimethyl fumarate (Tecfidera®).
 - For the flushing side effects, can administer non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes before dosing.
 - Banner Life Sciences received approval for Bafiertam on April 28, 2020.

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Multiple Sclerosis Agents
Clinical Edit	<p>Initial Approval Criteria</p> <ul style="list-style-type: none"> ▪ Patient is ≥ 18 years old; AND ▪ Must be used as single agent therapy; AND ▪ Will NOT be given concomitantly with other fumarate class drugs (e.g., dimethyl fumarate, diroximel fumarate); AND ▪ Patient lymphocyte and liver function tests were obtained prior to initiation of therapy and periodically thereafter; AND ▪ Patient has been diagnosed with a relapsing form of multiple sclerosis (e.g., relapsing remitting disease [RRMS], active secondary progressive disease [SPMS], or clinically isolated syndrome [CIS]); AND ▪ Confirmed diagnosis of MS as documented by laboratory report (e.g., MRI). <p>Renewal Criteria</p> <ul style="list-style-type: none"> ▪ Patient continues to meet initial approval criteria; AND ▪ Absence of unacceptable toxicity from the drug (e.g., anaphylaxis and angioedema; prolonged [> 6 months] lymphopenia [$< 0.5 \times 10^9/L$]; herpes zoster and other serious opportunistic infections; serious flushing reactions; progressive multifocal leukoencephalopathy [PML]; liver injury); AND ▪ Continuous monitoring of response to therapy (manifestations of MS disease activity include, but are not limited to, an increase in annualized relapse rate [ARR], development of new/worsening T2 hyperintensities or enhancing lesions on brain/spinal MRI, and progression of sustained impairment as evidenced by expanded disability status scale [EDSS], timed 25-foot walk [T25-FW], 9-hole peg test [9-HPT]).
Quantity Limit	120 capsules per 30 days
Duration of Approval	Initial: 12 months Renewal: 12 months
Drug to Disease Hard Edit	N/A

REFERENCES

1 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.

2 Bafiertam [package insert]. High Point, NC; Banner Life Sciences; April 2020.

3 National Multiple Sclerosis Society. Available at: <https://www.nationalmssociety.org/What-is-MS/MS-FAQ-s>. Accessed July 1, 2020.

4 Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2018; 90(17): 777-788. DOI: 10.1212/WNL.0000000000005347.

5 Thomas RH, Wakefield RA. Oral disease-modifying therapies for relapsing-remitting multiple sclerosis. *Am J Health Syst Pharm*. 2015; 72(1): 25-38. DOI: 10.2146/ajhp140023.

6 FDA approves Bafiertam fumarate bioequivalent for relapsing multiple sclerosis. <https://www.neurologylive.com/clinical-focus/fda-approves-bafiertam-fumarate-bioequivalent-for-relapsing-multiple-sclerosis>. Accessed July 1, 2020

7 Study to compare GI tolerability following oral administration of Bafiertam or Tecfidera to healthy volunteers. NCT04022473. Available at <https://clinicaltrials.gov/ct2/show/NCT04022473>. Accessed July 1, 2020.

8 Bafiertam oral capsules approved by the FDA for relapsing forms of MS. Available at: <https://mymsaa.org/news/bafiertam-oral-capsules-approved-by-the-fda-for-relapsing-forms-of-ms/>. Accessed July 1, 2020.

9 FDA approves oral Bafiertam (monomethyl fumarate), similar to Tecfidera, for relapsing MS. Available at: [https://www.nationalmssociety.org/About-the-Society/News/FDA-Approves-Oral-Bafiertam%E2%84%A2-\(Monomethyl-Fumarate\)](https://www.nationalmssociety.org/About-the-Society/News/FDA-Approves-Oral-Bafiertam%E2%84%A2-(Monomethyl-Fumarate)). Accessed July 1, 2020.