

Oral MS Disease-Modifying Therapies Policy Number: C21142-A

CRITERIA EFFECTIVE DATES:

ORIGINAL EFFECTIVE DATE	LAST REVIEWED DATE	NEXT REVIEW DUE BY OR BEFORE
5/1/2019	4/15/2021	4/26/2022
J CODE	TYPE OF CRITERIA	LAST P&T APPROVAL/VERSION
NA	RxPA	Q2 2021 20210428C21142-A

PRODUCTS AFFECTED:

Mayzent (siponimod), Aubagio (teriflunomide), Gilenya (fingolimod), Mavenclad (cladribine), Tecfidera (dimethyl fumarate), Vumerity (diroximel fumarate), Bafiertam (monomethyl fumarate), dimethyl fumarate, Zeposia (ozanimod), Ponvory (ponesimod)

DRUG CLASS:

Multiple Sclerosis Disease-Modifying Agents

ROUTE OF ADMINISTRATION:

Oral

PLACE OF SERVICE:

Specialty Pharmacy

The recommendation is that medications in this policy will be for pharmacy benefit coverage and patient self-administered

AVAILABLE DOSAGE FORMS:

Mayzent 0.25mg (siponimod fumarate)- bottle of 28 tabs, Mayzent 2mg (siponimod fumarate)- bottle of 30 tabs, Aubagio 7mg tab, 14mg tab, Gilenya CAPS 0.25MG
 Gilenya CAPS 0.5MG- bottles of 30 capsules [Gilenya 0.25mg capsules are ONLY available through the Gilenya Go Program 1-800-598-1410]
 Mavenclad (4 Tabs) TBPK 10MG, Mavenclad (5 Tabs) TBPK 10MG, Mavenclad (6 Tabs) TBPK 10MG, Mavenclad (7 Tabs) TBPK 10MG, Mavenclad (8 Tabs) TBPK 10MG, Mavenclad (9 Tabs) TBPK 10MG, Mavenclad (10 Tabs) TBPK 10MG
 Tecfidera MISC 120 & 240MG, Tecfidera CPDR 120MG, Tecfidera CPDR 240MG, 30-day Starter Pack, 7-day bottle 120 mg capsules, quantity 14, 23-day bottle 240 mg capsules, quantity 46 120 mg capsules: 7-day bottle of 14 capsules, 240 mg capsules: 30-day bottle of 60 capsules
 Vumerity (Starter) CPDR 231MG (diroximel fumarate Capsule DR Starter Bottle 231 MG (bottle= 106), Vumerity CPDR 231MG (diroximel fumarate)- (bottle= 120)
 Bafiertam CPDR 95MG (120ct/bottle)
 Dimethyl Fumarate CPDR 120MG, Dimethyl Fumarate CPDR 240MG, Dimethyl Fumarate Starter Pack MISC 120 & 240MG
 Zeposia 7-Day Starter Pack CPPK 4 x 0.23MG & 3 x 0.46MG, Zeposia CAPS 0.92MG, Zeposia Starter Kit CPPK 0.23MG & 0.46MG & 0.92MG
 Ponvory Starter Kit (2,3,4,5,6,7,8,9 & 10 MG), Ponvory 20mg-bottle of 30 tabs

FDA-APPROVED USES:

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Mayzent (siponimod) 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

Aubagio (teriflunomide) 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

Gilenya(fingolimod) 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 patients 10 years of age and older

Mavenclad (cladribine) Indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease and active secondary progressive disease, in adults. Because of its safety profile, use of MAVENCLAD is generally recommended for patients who have had an inadequate response to, or are unable to tolerate, an alternate drug indicated for the treatment of MS

Limitations of Use: MAVENCLAD is not recommended for use in patients with clinically isolated syndrome (CIS) because of its safety profile

Vumerity (diroximel fumarate) 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.

Bafiertam (monomethyl fumarate) 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

Tecfidera (dimethyl fumarate) - 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

Zeposia (ozanimod) 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.

Ponvory (ponesimod) 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

COMPENDIAL APPROVED OFF-LABELED USES:

None

COVERAGE CRITERIA: INITIALAUTHORIZATION

DIAGNOSIS:

Multiple Sclerosis

REQUIRED MEDICAL INFORMATION:

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Documentation of a definitive diagnosis of a relapsing form of multiple sclerosis (MS) as defined by the McDonald criteria (see Appendix), including: Relapsing-remitting multiple sclerosis [RRMS], secondary-progressive multiple sclerosis [SPMS] with relapses, and progressive-relapsing multiple sclerosis [PRMS] or First clinical episode with MRI features consistent with multiple sclerosis

2. Prescriber attests that member is not concurrently being treated with another MS disease modifying therapy (DMT) (See Appendix for list)
AND
3. Documentation provided of drug specific pre-treatment assessment as recommended by each drug FDA label
[**Mayzent**- CYP2C9 genotype testing, ophthalmic evaluation, liver enzyme, evaluate varicella zoster virus VZV antibody status, skin examination, Assess pulmonary function and a complete blood count (CBC), cardiac evaluation. **Aubagio**- transaminase and bilirubin levels, complete blood cell count (CBC), screen patients for latent tuberculosis infection, Exclude pregnancy prior to initiation and Check blood pressure. **Mavenclad**- CBC including lymphocyte count, evaluate HIV, tuberculosis, hepatitis B (HBV) and hepatitis C (HCV) status, evaluate varicella zoster virus VZV antibody status, pregnancy test, liver function tests, MRI, and signs or symptoms of progressive multifocal leukoencephalopathy. **Gilenya**- CBC including lymphocyte counts, Baseline bilirubin and transaminase levels, ECG, heart rate, blood pressure, and signs and symptoms of bradycardia, Ophthalmologic exam and Evaluate pregnancy status, Vaccinate patients antibody negative to varicella zoster virus ; **Tecfidera/Vumerity/Bafiertam**- CBC including lymphocyte counts, MRI, latent infection screening (e.g., hepatitis, tuberculosis) and liverfunction tests; **Zeposia**- CBC, including lymphocyte counts, Hepatic monitoring: Baseline bilirubin and transaminase levels, ECG (baseline); heart rate; BP; signs and symptoms of bradycardia, Ophthalmologic exam, respiratory function, Vaccinate patients antibody negative to varicella zoster virus, latent infection screening; **Ponvory**- CBC, including lymphocyte counts, Hepatic monitoring: Baseline bilirubin and transaminase levels, ECG (baseline); heart rate; BP; signs and symptoms of bradycardia, Ophthalmologic exam, respiratory function, Vaccinate patients antibody negative to varicella zoster virus, latent infection screening]
AND
4. Prescriber attests to (or the clinical reviewer has found that) the member not having any FDA labeled contraindications that haven't been addressed by the prescriber within the documentation submitted for review [See individual contraindications in policy section- CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION]
AND
5. MAVENCLAD REQUESTS ONLY-Prescriber attests that Mavenclad (cladribine) is not being used to treat clinically isolated syndrome OR provides supportive of medical necessity for the treatment
AND
6. IF NON-FORMULARY/NON-PREFERRED: Documentation of inadequate response (6 months of therapy), intolerance or FDA labeled contraindication to TWO preferred formulary disease modify therapies. Inadequate response is defined as increase frequency, severity and/or sequelae of relapses, changes in MRI or increase in disability progression

DURATION OF APPROVAL:

Initial authorization: 12 months, Continuation of therapy: 12 months

QUANTITY:

Mayzent (siponimod)

0.25mg tablets Starter Pack – blister card of twelve 0.25 mg tablets in a calendarized blister wallet - NDC 0078-0979-12. This starter pack is only intended for patients who will receive the 2 mg maintenance dosage. Patients with CYP2C9*1/*3 or *2/*3 genotype: maintenance max dose is 1mg once daily, all others maintenance max dose is 2mg once daily

Aubagio (teriflunomide): 1 tablet per day (30 tablets per 30 days)

Gilenya (fingolimod) Maximum dosage (10 years or older OR more than 40 kg/88.2lbs): 0.5 mg

orally once daily, maximum dosage for ages 10 AND up to 88.2lbs: 0.25 mg orally once daily

Mavenclad (cladribine)

Quantity is limited to the exact number of tablets needed per body weight for each treatment course 40kg- <50kg: First Cycle- 40mg (4 tabs), Second Cycle-40mg (4 tabs)

50kg- <60kg: First Cycle- 50mg (5 tabs), Second Cycle-50mg (5 tabs) 60kg- <70kg: First Cycle- 60mg (6 tabs), Second Cycle-60mg (6 tabs) 70kg- <80kg: First Cycle- 70mg (7 tabs), Second Cycle-70mg (7 tabs) 80kg- <90kg: First Cycle- 80mg (8 tabs), Second Cycle-70mg (7 tabs) 90kg- <100kg: First Cycle- 90mg (9 tabs), Second Cycle-80mg (8 tabs) 100g- <110kg: First Cycle- 100mg (10 tabs), Second Cycle-90mg (9 tabs) 110kg: First Cycle- 100mg (10 tabs), Second Cycle-100mg (10 tabs)

Tecfidera (dimethyl fumarate)- maximum dose of 240mg twice daily

Vumerity (diroximel fumarate)- Starting dose: 231 mg twice a day, orally, for 7 days, Maintenance dose after 7 days: 462 mg (administered as two 231 mg capsules) twice a day, orally

Bafiertam (monomethyl fumarate)- 95 mg twice a day orally for 7 days. After 7 days, the dosage should be increased to the maintenance dosage of 190 mg (administered as two 95 mg capsules) twice a day orally. Maximum 120 capsules/30 days

Zeposia (ozanimod)- Days 1-4 (0.23) mg once daily Days 5-7 (0.46) mg once daily Day 8 and thereafter (0.92) mg once daily; maximum of #30 0.92mg capsules/30 days

Ponvory (ponesimod)- Days 1,2 daily dose 2mg, Days 3,4 daily dose 3 mg, Days 5,6 daily dose 4mg, Day 7 daily dose 5mg, Day 8 daily dose 6mg, Day 9 daily dose 7mg, Day 10 daily dose 8 mg, Day 11 daily dose 9mg, Days 12,13,14 daily dose 10mg, Day 15 and after daily dose 20mg

PRESCRIBER REQUIREMENTS:

Prescribed by, or in consultation with, a board-certified neurologist or a multiple sclerosis specialist. Please submit consultation notes if prescribed after consultation

AGE RESTRICTIONS:

Gilenya- For ages 10 AND up to 88.2lbs: 0.25 mg., If pt. exceeds 88.2lbs they will be recommended for the 0.5mg regardless of age

ALL OTHER DMTS: 18 years of age and older

CONTINUATION OF THERAPY:

A. RELAPSING FORM OF MULTIPLE SCLEROSIS:

1. Adherence to therapy at least 85% of the time as verified by the prescriber or member medication fill history OR adherence less than 85% of the time due to the need for surgery or treatment of an infection, causing temporary discontinuation (documentation required)
AND
2. Documentation of no intolerable adverse effects or drug toxicity
AND
3. Documentation of positive clinical response as demonstrated by low disease activity and/or improvements in the condition's signs and symptoms (i.e. Documentation of a stable number or decrease in acute attacks (relapses) within the last 6 months OR Documentation of lack of progression or sustained disability OR Recent (within last 6 months) MRI shows lack of development of new asymptomatic lesions)
AND
4. Prescriber attests to continued monitoring as required per drug specific FDA labeling

CONTRAINDICATIONS/EXCLUSIONS/DISCONTINUATION:

All other uses of oral disease-modifying therapies are considered experimental/investigational and therefore, will follow Molina's Off-Label policy.

Contraindications to Mayzent (siponimod) include: A CYP2C9*3/*3 genotype, Myocardial infarction within the last 6 months, Unstable angina within the last 6 months, Stroke or TIA within the last 6 months, Decompensated heart failure requiring hospitalization within the last 6 months, Class III or IV heart failure within the last 6 months, Mobitz type II second-degree or third-degree atrioventricular block, unless patient has a functional pacemaker and Sick-sinus syndrome, unless patient has a functional pacemaker.

Contraindications to Aubagio(teriflunomide) include: Patients with severe hepatic impairment , Pregnant women and females of reproductive potential not using effective contraception. AUBAGIO may cause fetal harm, Patients with a history of a hypersensitivity reaction to teriflunomide, leflunomide, or to any of the inactive ingredients in AUBAGIO, Coadministration with leflunomide.

Contraindications to Mavenclad (cladribine) include; Patients with current malignancy, Pregnant women, and women and men of reproductive potential who do not plan to use effective contraception during MAVENCLAD dosing and for 6 months after the last dose in each treatment course, HIV infection, Active chronic infections (e.g., hepatitis or tuberculosis), History of hypersensitivity to cladribine, Women intending to breastfeed on a MAVENCLAD treatment day and for 10 days after the last dose.

Contraindications to Gilenya(fingolimod) include: Recent myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure with hospitalization, or Class III/IV heart failure, History of Mobitz Type II 2nd degree or 3rd degree AV block or sick sinus syndrome, unless patient has a pacemaker, Baseline QTc interval \geq 500 msec, Cardiac arrhythmias requiring anti-arrhythmic treatment with Class Ia or Class III anti- arrhythmic drugs, Hypersensitivity to fingolimod or its excipients.

Contraindications to Vumerity (diroximel fumarate) include: Known hypersensitivity to diroximel fumarate, dimethyl fumarate, or to any of the excipients of VUMERITY, Co-administration with dimethyl fumarate

Contraindications to Bafiertam (monomethyl fumarate) include: Known hypersensitivity to monomethyl fumarate, dimethyl fumarate, diroximel fumarate, or any of the excipients of BAFIERTAM, Co-administration with dimethyl fumarate or diroximel fumarate

Contraindications to Tecfidera (dimethyl fumarate) include known hypersensitivity to dimethyl fumarate or any of the excipients of TECFIDERA

Contraindications to Zeposia (ozanimod) include: In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure, Presence of Mobitz type II second- degree or third degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial block, unless the patient has a functioning pacemaker, Severe untreated sleep apnea,

Concomitant use of a monoamine oxidase inhibitor

Contraindications to Ponvory (ponesimod) include: In the last 6 months, experienced myocardial infarction, unstable angina, stroke, transient ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure. Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

OTHER SPECIAL CONSIDERATIONS:**BACKGROUND:****Multiple Sclerosis (MS)**

MS is a chronic, inflammatory, autoimmune disease of the central nervous system that disrupts communications between the brain and other parts of the body. Most people experience their first symptoms of MS between the ages of 20 and 40 years of age. MS is among the most common causes of neurological disability in young adults and occurs more frequently in women than in men. MS is the most common immune-mediated inflammatory demyelinating disease of the central nervous system. MS is characterized pathologically by multifocal areas of demyelination with loss of oligodendrocytes and astroglial scarring. Axonal injury is also a prominent pathologic feature, especially in the later stages. Certain clinical features are typical of MS, but the disease has a highly variable pace and many atypical forms. For most people, MS starts with a relapsing-remitting course, in which episodes of worsening function (relapses) are followed by recovery periods (remissions). These remissions may not be complete and may leave patients with some degree of residual disability. Many, but not all, patients with MS experience some degree of persistent disability that gradually worsens over time. In some patients, disability may progress independent of relapses, a process termed secondary progressive multiple sclerosis (SPMS). In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as active SPMS. Active SPMS is one of the relapsing forms of MS, and drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. On average, up to 80% of patients with relapsing-remitting (RRMS) – the most common form of MS at diagnosis – will develop SPMS. SPMS is a form of MS characterized by progressive and irreversible neurological disability. Most patients transition from RRMS to SPMS over time, which can vary if a patient is on disease modifying drug treatment or not.

RRMS – the most common disease course – is characterized by clearly defined attacks of new or increasing neurologic symptoms. These attacks – also called relapses or exacerbations – are followed by periods of partial or complete recovery (remissions). During remissions, all symptoms may disappear, or some symptoms may continue and become permanent. However, there is no apparent progression of the disease during the periods of remission. At different points in time, RRMS can be further characterized as either active (with relapses and/or evidence of new MRI activity) or not active, as well as worsening (a confirmed increase in disability over a specified period of time following a relapse) or not worsening. An increase in disability is confirmed when the person exhibits the same level of disability at the next scheduled neurological evaluation, typically 6 to 12 months later.

Mayzent (siponimod)

The efficacy of Mayzent was demonstrated in the Phase III Expand study (Lancet, March 2018), a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry. My-MS.org⁹ Patients were randomized to receive either once daily Mayzent 2 mg or placebo, beginning with a dose titration. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected relapse. MRI evaluations were performed at screening and every 12 months. The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP), defined as at least a 1-point increase from baseline in EDSS (0.5-point

increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A pre-specified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3-month confirmed worsening of at least 20% from baseline on the timed 25-foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate (relapses/year) and MRI measures of inflammatory disease activity. Study duration was variable for individual patients (median study duration was 21 months, range 1 day-37 months). EXPAND randomized 1651 patients to either Mayzent 2 mg (N = 1105) or placebo (N = 546); 82% of Mayzent treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was 6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy. Mayzent was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.79, $p < 0.0134$; see Figure 1). Mayzent did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo. Patients treated with Mayzent had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal pvalue < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although Mayzent had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of Mayzent in patients with non-active SPMS was not statistically significant.

A total of 1737 MS patients have received Mayzent at doses of at least 2 mg daily. These patients were included in Phase III studies and in a Phase 2 placebo-controlled study in patients with MS. In Phase III Study 1, 67% of Mayzent treated patients completed the double-blind part of the study, compared to 59.0% of patients receiving placebo. Adverse events led to discontinuation of treatment in 8.5% of Mayzent treated patients, compared to 5.1% of patients receiving placebo. The most common adverse reactions (incidence at least 10%) in Mayzent treated patients were headache, hypertension, and transaminase increase.

Gilenya (fingolimod), a sphingosine 1-phosphate receptor modulator, is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS) to reduce the frequency of clinical exacerbations and to delay the accumulation of physical disability. The recommended dose of Gilenya is 0.5 mg orally once daily. The initiation of Gilenya leads to decreases in heart rate. After the first dose of Gilenya, the heart rate decreases are noted within an hour and generally are greatest at 6 hours, although the effects can be observed 24 hours after the first dose in some patients. The first dose of Gilenya should be given in a setting with resources to appropriately manage symptomatic bradycardia

Mavenclad (cladribine)

The efficacy of Mavenclad was shown in a clinical trial called CLARITY (Cladribine Tablets Treating Multiple Sclerosis Orally) which studied 1,326 patients with relapsing forms of MS who had at least one relapse in the previous 12 months. The primary outcome of CLARITY was the annualized relapse rate (ARR). Additional outcome measures included the proportion of patients with confirmed disability progression, the time to first qualifying relapse, the mean number of MRI T1 Gadolinium-enhancing (Gd+) lesions, and new or enlarging MRI T2 hyperintense lesions. Disability progression was measured in terms of a 3-month sustained change in expanded disability status scale (EDSS) score of at least one point, if baseline EDSS score was between 0.5 and 4.5 inclusively, at least 1.5 points if the baseline EDSS score was 0, or at least 0.5 point if the baseline EDSS score was at least 5, over a period of at least 3 months. Mavenclad 3.5 mg/kg resulted in a 58% relative reduction in annualized relapse rate over placebo, with 81% patients having no relapses compared to 63% placebo patients. Per the FDA, Mavenclad must be dispensed with a patient Medication Guide that describes information about the drug's uses and risks. Mavenclad has a Boxed Warning for an increased risk of malignancy and fetal harm. Mavenclad should be stopped if the patient becomes pregnant.

Other warnings include the risk of decreased lymphocyte (white blood cell) counts; lymphocyte counts

should be monitored before, during and after treatment. Mavenclad may increase the risk of infections; health care professionals should screen patients for infections, and treatment with Mavenclad should be delayed if necessary. Mavenclad may cause hematologic toxicity and bone marrow suppression, so health care professionals should measure a patient's complete blood counts before, during and after therapy. The drug has been associated with graft-versus-host-disease following blood transfusions with non-irradiated blood. Mavenclad may cause liver injury and treatment should be interrupted or discontinued, as appropriate, if clinically significant liver injury is suspected. The most common (>20%) adverse reactions reported by patients receiving Mavenclad include upper respiratory tract infection, headache, and decreased lymphocyte counts. Serious adverse reactions reported in the clinical program included malignancies (0.27 events per 100 patient years) in Mavenclad treated arms, compared to placebo patients (0.13 events per 100 patient-years), herpes zoster infections (2.0% vs. 0.2%), and oral herpes (2.6% vs. 1.2%).

Tecfidera (dimethyl fumarate) is indicated for the treatment of patients with relapsing forms of multiple sclerosis. The mechanism by which DMF exerts its therapeutic effect in multiple sclerosis is unknown. DMF and its active metabolite, monomethyl fumarate (MMF), have been shown to activate the Nuclear factor (erythroid derived 2)-like 2 (Nrf2) pathway in vitro and in vivo in animals and humans. The Nrf2 pathway is involved in the cellular response to oxidative stress. MMF has been identified as a nicotinic acid receptor agonist in vitro. DMF and MMF are postulated to decrease oxidative stress and protect axons from inflammatory mediators.

Vumerity (diroximel fumarate)

The efficacy of Vumerity is based upon bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing Tecfidera to Vumerity. After oral administration of Vumerity, diroximel fumarate undergoes rapid presystemic hydrolysis by esterases and is converted to its active metabolite, monomethyl fumarate (MMF). Diroximel fumarate is not quantifiable in plasma following oral administration of Vumerity. Therefore, all pharmacokinetic analyses related to Vumerity were performed with plasma MMF concentrations. Pharmacokinetic data were obtained in subjects with relapsing forms of multiple sclerosis (MS) and healthy volunteers. All bioavailability studies met their endpoints. The key study for Biogen in providing differentiation from Tecfidera is the EVOLVE-MS-2 study. In July 2019, Biogen announced positive results from EVOLVE-MS-2, a randomized, double-blind, five-week, Phase 3 study of diroximel fumarate compared to Tecfidera. According to the company's press release, diroximel fumarate was statistically superior to dimethyl fumarate on the study's pre-specified primary endpoint, with patients treated with diroximel fumarate self-reporting significantly fewer days of key gastrointestinal (GI) symptoms with intensity scores ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS), as compared to dimethyl fumarate ($p=0.0003$). The most common adverse events (AEs) reported in the study for both treatment groups were flushing, diarrhea and nausea (32.8%, 15.4%, and 14.6% for diroximel fumarate; 40.6%, 22.3%, and 20.7% for dimethyl fumarate). The overall proportion of patients with AEs leading to study discontinuation were 1.6% for diroximel fumarate and 6.0% for dimethyl fumarate. Of those, the proportion of patients who discontinued due to GI adverse events during the five-week treatment period were 0.8% for diroximel fumarate and 4.8% for dimethyl fumarate.

Zeposia (ozanimod)

The approval of Zeposia, a sphingosine 1-phosphate (S1P) receptor modulator, was based on data from 2 double-blind, parallel-group, active comparator-controlled clinical trials in patients with relapsing forms of MS. Results showed that in both trials, the annualized relapse rate was statistically significantly lower in patients treated with Zeposia than in patients who received interferon beta-1a. With regard to safety, the most common adverse reactions reported included upper respiratory tract infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

Aubagio (teriflunomide)

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The approval was based on efficacy data from the Phase 3 TEMSO (Teriflunomide Multiple Sclerosis Oral) trial evaluating more than 5,000 patients in 36 countries. Aubagio 14mg significantly reduced the annualized relapse rate (P=0.0005) and the time to disability progression (P=0.0279) at two years vs. placebo in patients with relapsing forms of MS. Additionally, Aubagio 7mg significantly reduced the annualized relapse rate (P=0.0002) in the trial.

Bafiertam (monomethyl fumarate)

Bafiertam is similar to Tecfidera® and Vumerity® but has a distinct chemical structure. Although their exact mechanisms of action are not known, fumarate therapies are thought to modulate the immune response underlying MS to be less inflammatory and may have antioxidant properties that could be protective against damage to the brain and spinal cord. Because of its similarity to Tecfidera, Bafiertam's approval was based largely on the FDA's findings of safety and efficacy for Tecfidera and "bioavailability" studies in healthy subjects comparing dimethyl fumarate to Bafiertam. Twice-daily Tecfidera was shown in clinical trials to significantly reduce relapses and disease activity on MRIs, and in one trial it reduced progression of disability.

Ponvory (ponesimod)

Ponesimod is a once-daily oral selective sphingosine-1-phosphate receptor 1 (S1P1) modulator. The approval was based on results from a phase 3 head-to-head, randomized trial of ponesimod vs teriflunomide. A total of 1133 patients with relapsing MS, were randomly assigned to either ponesimod 20mg once daily or teriflunomide 14mg once daily. Results showed that the annualized relapse rate from baseline to Week 108 was reduced by 30.5% for the ponesimod group vs the teriflunomide group, meeting the trial's primary endpoint. The Company stated that 71% of patients treated with ponesimod had no confirmed relapses, compared to 61% in the teriflunomide group. Moreover, ponesimod showed superiority in reducing the number of new gadolinium-enhancing (GdE) T1 and T2 lesions compared with teriflunomide by 59% and 56%, respectively. As for adverse events, overall rates were similar to teriflunomide. The most common adverse events observed in the phase 3 trial in ponesimod-treated patients were upper respiratory infection, hepatic transaminase elevation, and hypertension.

APPENDIX:

Disease-modifying therapies for MS include: glatiramer acetate (Copaxone®), Glatopa®), interferon beta-1a (Avonex®, Rebif®), interferon beta-1b (Betaseron®, Extavia®), peginterferon beta-1a (Plegridy®), dimethyl fumarate (Tecfidera®), fingolimod (Gilenya™), teriflunomide (Aubagio®), alemtuzumab (Lemtrada®), mitoxantrone (Novantrone®), natalizumab (Tysabri®), ocrelizumab (Ocrevus™), siponimod (Mayzent®), Ponvory (ponesimod) and cladribine (Mavenclad®).

Summary of 2017 McDonald Criteria for the Diagnosis of MS

CLINICAL PRESENTATION	ADDITIONAL CRITERIA TO MAKE MS DIAGNOSIS
...in a person who has experienced a typical attack/CIS at onset	
<ul style="list-style-type: none"> 2 or more attacks and clinical evidence of 2 or more lesions; OR 2 or more attacks and clinical evidence of 1 lesion with clear historical evidence of prior attack involving lesion in different location 	None. DIS and DIT have been met.
<ul style="list-style-type: none"> 2 or more attacks and clinical evidence of 1 lesion 	DIS shown by <u>one</u> of these criteria: <ul style="list-style-type: none"> - additional clinical attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord
<ul style="list-style-type: none"> 1 attack and clinical evidence of 2 or more lesions 	DIT shown by <u>one</u> of these criteria: <ul style="list-style-type: none"> - Additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
<ul style="list-style-type: none"> 1 attack and clinical evidence of 1 lesion 	DIS shown by <u>one</u> of these criteria: <ul style="list-style-type: none"> - Additional attack implicating different CNS site - 1 or more MS-typical T2 lesions in 2 or more areas of CNS: periventricular, cortical, juxtacortical, infratentorial or spinal cord AND DIT shown by <u>one</u> of these criteria: <ul style="list-style-type: none"> - additional clinical attack - Simultaneous presence of both enhancing and non-enhancing MS-typical MRI lesions, or new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) - CSF oligoclonal bands
...in a person who has steady progression of disease since onset	
1 year of disease progression (retrospective or prospective)	DIS shown by at least <u>two</u> of these criteria: <ul style="list-style-type: none"> - 1 or more MS-typical T2 lesions (periventricular, cortical, juxtacortical or infratentorial) - 2 or more T2 spinal cord lesions - CSF oligoclonal bands

DIT = Dissemination in time CNS = central nervous system CSF = cerebrospinal fluid
 DIS = Dissemination in space T2 lesion = hyperintense lesion on T2-weighted MRI

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