Template Letter of Appeal
(for Patients Currently on MS Treatment)

The following example template may be used to support an appeal for ZEPOSIA® (ozanimod). The letter should be submitted with relevant medical records, on your letterhead, and signed by the HCP.

Health plans may allow multiple levels of appeal. You should refer to the health plan's specific appeal guidelines. If you are submitting a second- or third-level appeal, include the letter of denial and medical notes in response to the denial.

Disease summary may include the following: 1

- Relapse history including number of relapses within 12 months and/or number of relapses within the past 2 years plus evidence of at least 1 GdE lesion in the prior year
- MRI scan documentation and findings (eg, brain lesions)
- Neurological exam findings
- RMS severity overview including disability status. Include Expanded Disability Status Scale (EDSS) score, if available. Scores from 0 to 5.0 were studied in clinical trial populations
- Intolerability to alternate RMS therapies (eg, flushing and intolerable gastrointestinal side effects, severe skin reactions, or difficulty with injections)
- Past drugs and treatments that were tried and failed (eg, failed interferon therapy)
- Activities of daily living affected by current RMS disease
- Patient's RMS symptoms are worsening
- Documentation of required pre-initiation tests including:
  - Complete blood count including lymphocyte count (within the last 6 months or after discontinuation of prior MS therapy)
  - ECG to determine whether preexisting conduction abnormalities are present
  - Transaminase and bilirubin levels (within the last 6 months)
  - An ophthalmic assessment is required for patients with a history of uveitis or macular edema
- Clinical trial efficacy, safety, and tolerability endpoints that may be relevant to patient's treatment
- Other relevant medical information

List and attach additional documents, as appropriate: 2

- Denial letter
- Prescribing Information
- FDA approval letter
- Clinical practice guidelines
- Clinical notes/medical records

Please see Important Safety Information on pages 3–6 and full Prescribing Information and Medication Guide at www.ZEPOSIAhcp.com.

Template Letter of Appeal
(for Patients Currently on MS Treatment)

[Date]
[Health Plan Name]
ATTN: [Department]
[Medical/Pharmacy Director Name (if available)]
[Health Plan Address]
[City, State ZIP]

[Patient's Name]
[Date of Birth]
Patient Policy ID Number: [ID #]
Reference Number: [# if available]
[Dates of Service]

Re: Letter of Appeal for ZEPOSIA® (ozanimod) capsules for [Patient Name]

Dear [Medical/Pharmacy Director Name],

I am writing on behalf of [patient's name] to request reconsideration of your denial of coverage for ZEPOSIA® (ozanimod) which I have prescribed to my patient for the treatment of [indication], ICD-10-CM diagnosis code [diagnosis code]. Your reason(s) for the denial [is/are] [reason(s) for the denial].

Based on my experience with treating patients with [indication], ICD-10-CM diagnosis code [diagnosis code], and the patient's condition and medical history, I believe treatment with [current drug name] should be discontinued and replaced with ZEPOSIA as it is appropriate and medically necessary. This letter provides the clinical rationale and relevant information about the patient's medical history and treatment.

ZEPOSIA is a sphingosine 1-phosphate (S1P) receptor agonist that was approved by the US Food and Drug Administration (FDA) in 2020 for treatment of patients with relapsing forms of multiple sclerosis (MS) and in my clinical opinion would be beneficial to the patient.

The patient is a [age]-year-old [male/female/other gender identification] who was diagnosed with RMS on [date]. Below is a rationale for prescribing ZEPOSIA based on my patient's disease summary.

1
- [Insert disease summary]
- [Support information as requested by the plan in their denial letter]
- [Clinical attributes of ZEPOSIA and relevance to the patient]
- [Past drugs and treatments that were tried and failed (eg, failed interferon therapy)]
- [Duration of previous therapies]

This is my [level of request] prior authorization appeal. A copy of the [level of denial] denial letter is included along with medical notes in response to the denial. Considering the patient's history and condition, I believe treatment with ZEPOSIA is medically necessary for my patient. Please contact me at [physician's phone number] or via email at [physician's email] should you have questions or need additional information.

Thank you for your time and immediate attention to this request.

Sincerely,
[Provider name, contact information, and signature]

2 Enclosures: [List and attach additional documents to support your treatment rationale]

Please see Important Safety Information on pages 3–6 and full Prescribing Information and Medication Guide at www.ZEPOSIAhcp.com.

Indication and Important Safety Information for ZEPOSIA® (ozanimod)

INDICATION

ZEPOSIA 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.

IMPORTANT SAFETY INFORMATION

Contraindications:

- Patients who 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 or have a presence of Mobitz type II second or third-degree atrioventricular (AV) block, sick sinus syndrome, or sino-atrial, unless the patient has a functioning pacemaker
- Patients with severe untreated sleep apnea
- Patients taking a monoamine oxidase (MAO) inhibitor

Infections: ZEPOSIA may increase the susceptibility to infections. Life-threatening and rare fatal infections have occurred in patients receiving ZEPOSIA. Obtain a recent (i.e., within 6 months or after discontinuation of prior MS therapy) complete blood count (CBC) including lymphocyte count before initiation of ZEPOSIA. Delay initiation of ZEPOSIA in patients with an active infection until the infection is resolved. Consider interruption of treatment with ZEPOSIA if a patient develops a serious infection. Continue monitoring for infections up to 3 months after discontinuing ZEPOSIA

- Herpes zoster was reported as an adverse reaction in ZEPOSIA-treated patients. Herpes simplex encephalitis and varicella zoster meningitis have been reported with sphingosine 1-phosphate (S1P) receptor modulators. Patients without a healthcare professional-confirmed history of varicella (chickenpox), or without documentation of a full course of vaccination against varicella zoster virus (VZV), should be tested for antibodies to VZV before initiating ZEPOSIA. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with ZEPOSIA
- Cases of fatal cryptococcal meningitis (CM) were reported in patients treated with another S1P receptor modulator. If CM is suspected, ZEPOSIA should be suspended until cryptococcal infection has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

Important Safety Information for ZEPOSIA® (ozanimod) (cont.)

Infections (cont.):

- Progressive Multifocal Leukoencephalopathy (PML) is an opportunistic viral infection of the brain that typically occurs in patients who are immunocompromised, and that usually leads to death or severe disability. No cases of PML were identified in active-controlled MS clinical trials with ZEPOSIA. PML has been reported in patients treated with S1P receptor modulators and other MS therapies and has been associated with some risk factors. If PML is suspected, withhold ZEPOSIA and perform an appropriate diagnostic evaluation. If confirmed, treatment with ZEPOSIA should be discontinued
- In clinical studies, patients who received ZEPOSIA were not to receive concomitant treatment with antineoplastic, non-corticosteroid immunosuppressive, or immune-modulating therapies used for treatment of MS. Concomitant use of ZEPOSIA with any of these therapies would be expected to increase the risk of immunosuppression. When switching to ZEPOSIA from immunosuppressive medications, consider the duration of their effects and their mode of action to avoid unintended additive immunosuppressive effects
- Use of live *attenuated* vaccines should be avoided during and for 3 months after treatment with ZEPOSIA. If live *attenuated* vaccine immunizations are required, administer at least 1 month prior to initiation of ZEPOSIA

Bradyarrhythmia and Atrioventricular Conduction Delays: Since initiation of ZEPOSIA may result in a transient decrease in heart rate and atrioventricular conduction delays, dose titration is recommended to help reduce cardiac effects. Initiation of ZEPOSIA without dose escalation may result in greater decreases in heart rate. If treatment with ZEPOSIA is considered, advice from a cardiologist should be sought for those individuals:

- with significant QT prolongation
- with arrhythmias requiring treatment with Class 1a or III anti-arrhythmic drugs
- with ischemic heart disease, heart failure, history of cardiac arrest or myocardial infarction, cerebrovascular disease, and uncontrolled hypertension
- with a history of Mobitz type II second-degree or higher AV block, sick-sinus syndrome, or sinoatrial heart block

Liver Injury: Elevations of aminotransferases may occur in patients receiving ZEPOSIA. Obtain liver function tests, if not recently available (i.e., within 6 months), before initiation of ZEPOSIA. Patients who develop symptoms suggestive of hepatic dysfunction should have hepatic enzymes checked and ZEPOSIA should be discontinued if significant liver injury is confirmed. Caution should be exercised when using ZEPOSIA in patients with history of significant liver disease

Important Safety Information for ZEPOSIA® (ozanimod) (cont.)

Fetal Risk: There are no adequate and well-controlled studies in pregnant women. Based on animal studies, ZEPOSIA may cause fetal harm. Women of childbearing potential should use effective contraception to avoid pregnancy during treatment and for 3 months after stopping ZEPOSIA

Increased Blood Pressure: Increase in systolic pressure was observed after about 3 months of treatment and persisted throughout treatment. Blood pressure should be monitored during treatment and managed appropriately. Certain foods that may contain very high amounts of tyramine could cause severe hypertension in patients taking ZEPOSIA. Patients should be advised to avoid foods containing a very large amount of tyramine while taking ZEPOSIA

Respiratory Effects: ZEPOSIA may cause a decline in pulmonary function. Spirometric evaluation of respiratory function should be performed during therapy, if clinically indicated

Macular edema: S1P modulators have been associated with an increased risk of macular edema. Patients with a history of uveitis or diabetes mellitus are at increased risk. Patients with a history of these conditions should have an ophthalmic evaluation of the fundus, including the macula, prior to treatment initiation and regular follow-up examinations. An ophthalmic evaluation is recommended in all patients at any time if there is a change in vision. Continued use of ZEPOSIA in patients with macular edema has not been evaluated; potential benefits and risks for the individual patient should be considered if deciding whether ZEPOSIA should be discontinued

Posterior Reversible Encephalopathy Syndrome (PRES): Rare cases of PRES have been reported in patients receiving a S1P receptor modulator. If a ZEPOSIA-treated patient develops unexpected neurological or psychiatric symptoms or any symptom/sign suggestive of an increase in intracranial pressure, a complete physical and neurological examination should be conducted. Symptoms of PRES are usually reversible but may evolve into ischemic stroke or cerebral hemorrhage. Delay in diagnosis and treatment may lead to permanent neurological sequelae. If PRES is suspected, treatment with ZEPOSIA should be discontinued

Unintended Additive Immunosuppressive Effects From Prior Immunosuppressive or Immune-Modulating Drugs: When switching from drugs with prolonged immune effects, the half-life and mode of action of these drugs must be considered to avoid unintended additive immunosuppressive effects while at the same time minimizing risk of disease reactivation. Initiating treatment with ZEPOSIA after treatment with alemtuzumab is not recommended

Important Safety Information for ZEPOSIA® (ozanimod) (cont.)

Severe Increase in Disability After Stopping ZEPOSIA: Severe exacerbation of disease, including disease rebound, has been rarely reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping ZEPOSIA treatment so patients should be monitored upon discontinuation

Immune System Effects After Stopping ZEPOSIA: After discontinuing ZEPOSIA, the median time for lymphocyte counts to return to the normal range was 30 days with approximately 90% of patients in the normal range within 3 months. Use of immunosuppressants within this period may lead to an additive effect on the immune system, therefore caution should be applied when initiating other drugs 4 weeks after the last dose of ZEPOSIA

Most common Adverse Reactions (≥ 4%): upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain, and hypertension.

For additional safety information, please see the full Prescribing Information and Medication Guide, available at www.ZEPOSIAhcp.com.

Bristol Myers Squibb™

once-daily ZEPOSIA® (ozanimod) 0.92 mg capsules