Bristol Myers Squibb Receives European Commission Approval for Zeposia (ozanimod) for the Treatment of Adult Patients with Relapsing Remitting Multiple Sclerosis with Active Disease

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Zeposia offers relapsing remitting multiple sclerosis (RRMS) patients with active disease in the European Union a new oral option to help address the disease’s hallmark relapses and brain lesions

Zeposia is the only approved sphingosine-1-phosphate (S1P) receptor modulator for RRMS patients with active disease

Zeposia adds to Bristol Myers Squibb’s immunology franchise and marks the first European Commission marketing authorization since the Celgene acquisition

PRINCETON, N.J.-(BUSINESS WIRE)--Bristol Myers Squibb (NYSE:BMY) today announced that the European Commission (EC) has approved Zeposia (ozanimod) for the treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease as defined by clinical or imaging features. With the EC marketing authorization, Zeposia, an oral medication taken once daily, becomes the only approved sphingosine-1-phosphate (S1P) receptor modulator for RRMS patients with active disease. The approval is based on data from the SUNBEAM™ and RADIANCE™ Part B clinical trials showing that, as compared to AVONEX® (interferon beta-1a), Zeposia delivered powerful efficacy as measured by annualized relapse rate (ARR), as well as on the number and size of brain lesions.

“Today’s European Commission approval provides the opportunity for patients with RRMS with active disease to be offered Zeposia as a new first-line treatment option, which is an important advancement based on Phase 3 trial results showing significant improvements in relapses and brain lesions caused by this devastating disease,” said Samit Hirawat, M.D., chief medical officer, Bristol Myers Squibb. “We share this achievement with the courageous multiple sclerosis patient community in Europe and around the globe, and are working closely with all stakeholders to ensure that eligible European patients can start benefitting from Zeposia as quickly as possible.”

Multiple sclerosis (MS) is a disease in which the immune system attacks the protective myelin sheath that covers the nerves, creating damaging lesions that make it harder for signals to travel between each nerve cell. This “signal breakdown” can lead to symptoms and relapses.

The approval was based on data from the randomized, active-controlled Phase 3 SUNBEAM and RADIANCE Part B clinical trials, which enrolled more than 2,600 patients across 150 sites in more than 20 countries. Key findings from the trials include:

- Zeposia demonstrated a relative reduction in ARR versus AVONEX of 48% through one year in the SUNBEAM study and 38% at two years in the RADIANCE study (absolute ARR of 0.18 versus 0.35 and 0.17 versus 0.28, respectively).
- At one year in the SUNBEAM study, treatment with Zeposia reduced the number of T1-weighted gadolinium-enhanced (GdE) brain lesions more than AVONEX (0.16 vs 0.43), a relative reduction of 63%, and reduced the number of new or enlarging T2 brain lesions (1.47 versus 2.84), a relative reduction of 48%.
- At two years in the RADIANCE study, treatment with Zeposia reduced the number of T1-weighted GdE brain lesions more than AVONEX (0.18 versus 0.37), a relative reduction of 53%. Zeposia also reduced the number of new or enlarging T2 lesions versus AVONEX (1.84 versus 3.18), a relative reduction of 42%.
- Zeposia demonstrated a reduction in percent change from baseline in whole brain volume as compared to AVONEX at one year in the SUNBEAM study (-0.41% versus -0.61%) and at two years in the RADIANCE study (-0.71% versus -
Multiple sclerosis (MS) is a disease in which the immune system attacks the protective myelin sheath that covers the nerves. The myelin damage disrupts communication between the brain and the rest of the body. Ultimately, the nerves themselves may deteriorate — a process that's currently irreversible. MS affects 700,000 people in Europe and approximately 2.5 million people worldwide.

Relapsing remitting MS (RRMS) is characterized by clearly defined attacks of worsening neurologic function. These attacks — often called relapses, flare-ups or exacerbations — are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely with no apparent progression of disease. At different points in time, RRMS can be characterized as 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. RRMS is the most common disease course at the time of diagnosis. Approximately 85 percent of patients are initially diagnosed with RRMS, compared with 10-15 percent with progressive forms of the disease.

About Zeposia (ozanimod)

Zeposia® is the only approved S1P receptor modulator that offers RRMS patients with active disease an initiation with no first-dose observation required for the majority of patients. First-dose monitoring is only recommended for high-risk patients with certain pre-existing cardiac conditions. A dose escalation regimen from day 1 to day 7 should be used to reach the maintenance dose of Zeposia, as a transient decrease in heart rate and ativoventricular conduction delays may occur.

Zeposia® demonstrated manageable safety and tolerability in the Phase 3 SUNBEAM and RADIANCE Part B trials. Zeposia® is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients, as listed in the Summary of Product Characteristics (SmPC); immunodeficient state; patients who in the last six months experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization or New York Heart Association (NYHA) Class III/IV heart failure; patients with history or presence of second-degree atrioventricular (AV) block Type II or third-degree AV block or sick sinus syndrome unless the patient has a functioning pacemaker; severe active infections; active chronic infections such as hepatitis and tuberculosis; active malignancies; severe hepatic impairment (Child-Pugh class C); and during pregnancy and in women of childbearing potential not using effective contraception. Zeposia® is associated with the following Special Warnings and Precautions for Use: bradycard rhythmicity, liver injury, immunosuppressive effects, increased risk of infections, progressive multifocal leukoencephalopathy, cutaneous neoplasms, macular oedema, posterior reversible encephalopathy syndrome, increased blood pressure, respiratory effects and severe increase in disability after stopping Zeposia®. The most common adverse reactions (incidence ≥4%) were upper respiratory infection, hepatic transaminase elevation, orthostatic hypotension, urinary tract infection, back pain and hypertension.

“Multiple sclerosis is an unpredictable and often disabling disease that affects about 700,000 people in Europe. We are delighted by the news that there is now another treatment option available to potentially delay the progression of this debilitating disease,” said Pedro Carrascal, President of the European Multiple Sclerosis Platform.

About SUNBEAM™

SUNBEAM® is a pivotal, Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trial evaluating the efficacy, safety and tolerability of two doses of oral Zeposia® (0.92 mg and 0.46 mg, equivalent to 1 mg and 0.5 mg ozanimod HCl, respectively) against weekly intramuscular AVONEX® (interferon beta-1a) for at least a 12-month treatment period. The study included 1,346 people living with relapsing forms of multiple sclerosis (RMS) across 152 sites in 20 countries.

The primary endpoint of the trial was ARR during the treatment period. The secondary MRI endpoints included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 12 months, number of gadolinium-enhanced brain MRI lesions at month 12 and percent change from baseline in whole brain volume at month 12. Cortical grey and thalamic volume changes were also prospectively assessed versus active comparator.

An analysis of the time to onset of three-month confirmed disability progression was pre-specified using pooled data from both the SUNBEAM and RADIANCE Part B Phase 3 trials.

About RADIANCE™

RADIANCE Part B is a pivotal, Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trial evaluating the efficacy, safety and tolerability of two doses of oral Zeposia® (0.92 mg and 0.46 mg, equivalent to 1 mg and 0.5 mg ozanimod HCl, respectively) against weekly intramuscular AVONEX® (interferon beta-1a) over a 24-month treatment period. The study included 1,320 people living with RMS across 150 sites in 20 countries.

The primary endpoint of the trial was ARR over 24 months. The secondary MRI endpoints included the number of new or enlarging hyperintense T2-weighted brain MRI lesions over 24 months, number of gadolinium-enhanced brain MRI lesions at month 24 and percent change from baseline in whole brain volume at month 24. Cortical grey and thalamic volume changes were also prospectively assessed versus active comparator.

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About Multiple Sclerosis

Multiple sclerosis is a disease in which the immune system attacks the protective myelin sheath that covers the nerves. The myelin damage disrupts communication between the brain and the rest of the body. Ultimately, the nerves themselves may deteriorate — a process that’s currently irreversible. MS affects 700,000 people in Europe and approximately 2.5 million people worldwide.

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Zeposia (ozanimod) is an oral, sphingosine 1-phosphate (S1P) receptor modulator that binds with high affinity to S1P receptors 1 and 5. Zeposia blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which Zeposia exerts therapeutic effects in multiple sclerosis is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

The U.S. Food and Drug Administration (FDA) approved Zeposia for the treatment of adults with relapsing forms of multiple sclerosis (RMS) in March 2020. Zeposia is also in development for additional immune-inflammatory indications, including ulcerative colitis and Crohn's disease.

U.S. FDA-APPROVED INDICATION FOR ZEPOSIA

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 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.
- 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

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

**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, otochastic hypotension, urinary tract infection, back pain, and hypertension.

For additional safety information, please see the full [Prescribing Information and Medication Guide](#).

### About Bristol Myers Squibb

Bristol Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol Myers Squibb, visit us at BMS.com or follow us on [LinkedIn](https://www.linkedin.com), [Twitter](https://twitter.com), [YouTube](https://www.youtube.com), [Facebook](https://www.facebook.com), and [Instagram](https://www.instagram.com).

Celgene and Juno Therapeutics are wholly owned subsidiaries of Bristol-Myers Squibb Company. In certain countries outside the U.S., due to local laws, Celgene and Juno Therapeutics are referred to as, Celgene, a Bristol Myers Squibb company and Juno Therapeutics, a Bristol Myers Squibb company.

### Cautionary Statement Regarding Forward-Looking Statements

This press release contains “forward-looking statements” within the meaning of the Private Securities Litigation Reform Act of 1995 regarding, among other things, the research, development and commercialization of pharmaceutical products. All statements that are not statements of historical facts are, or may be deemed to be, forward-looking statements. Such forward-looking statements are based on historical performance and current expectations and projections about our future financial results, goals, plans and objectives and involve inherent risks, assumptions and uncertainties, including internal or external factors that could delay, divert or change any of them in the next several years, that are difficult to predict, may be beyond our control and could cause our future financial results, goals, plans and objectives to differ materially from those expressed in, or implied by, the statements. These risks, assumptions, uncertainties and other factors include, among others, that the outcome of pricing and reimbursement negotiations in individual countries in Europe may delay or limit the commercial potential of Zeposia (ozanimod) for the indication described in this release, and whether Zeposia (ozanimod) for the indication described in this release will be commercially successful. No forward-looking statement can be guaranteed. Forward-looking statements in this press release should be evaluated together with the many risks and uncertainties that affect Bristol Myers Squibb’s business and market, particularly those identified in the cautionary statement and risk factors discussion in Bristol Myers Squibb’s Annual Report on Form 10-K for the year ended December 31, 2019, as updated by our subsequent Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and other filings with the Securities and Exchange Commission. The forward-looking statements included in this document are made only as of the date of this document and except as otherwise required by applicable law, Bristol Myers Squibb undertakes no obligation to publicly update or revise any forward-looking statement, whether as a result of new information, future events, changed circumstances or otherwise.

### References


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**Contact:**

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