U.S. Food and Drug Administration Approves Bristol Myers Squibb’s ZEPOSIA® (ozanimod), a New Oral Treatment for Relapsing Forms of Multiple Sclerosis

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In clinical trials, ZEPOSIA demonstrated efficacy on a key clinical marker of disease activity – annualized relapse rate (ARR) – as compared to AVONEX ® (interferon beta-1a)\(^1,2,3\)

**ZEPOSIA is a sphingosine-1-phosphate (S1P) receptor modulator that requires no label-based first dose observation**

**ZEPOSIA adds to Bristol Myers Squibb’s legacy immunology franchise and marks the first FDA-approved New Drug Application since the Celgene acquisition**

PRINCETON, N.J.--(BUSINESS WIRE)--Bristol-Myers Squibb Company (NYSE: BMY) today announced that the U.S. Food and Drug Administration (FDA) approved ZEPOSIA® (ozanimod) 0.92 mg for the treatment of adults with relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease.\(^1\) ZEPOSIA, an oral medication taken once daily, is the only approved sphingosine-1-phosphate (S1P) receptor modulator that offers RMS patients an initiation with no genetic test and no label-based first-dose observation required for patients.\(^1,4,5\) An up-titration scheme should be used to reach the maintenance dosage of ZEPOSIA, as a transient decrease in heart rate and atrioventricular conduction delays may occur.\(^1\)

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.\(^6,7\) This “signal breakdown” can lead to symptoms and relapses.\(^6,8\)

"With the FDA approval of ZEPOSIA, appropriate patients with relapsing forms of multiple sclerosis will have another oral treatment option with meaningful efficacy to help address the disease’s hallmark relapses and brain lesions," said Samit Hirawat, M.D., chief medical officer, Bristol Myers Squibb. "ZEPOSIA has substantial clinical potential, and we are well positioned with our heritage in transformational science to ensure this innovative compound ultimately benefits as many patients as possible."

The approval is based on data from the largest pivotal, head-to-head RMS studies with an active comparator to date: the randomized, active-controlled Phase 3 SUNBEAM™ (safety and efficacy of ZEPOSIA versus interferon beta-1a in relapsing multiple sclerosis) and RADIANCE™ (safety and efficacy of the selective sphingosine 1-phosphate receptor modulator ZEPOSIA in relapsing multiple sclerosis) Part B clinical trials of more than 2,600 adults.\(^1,2,3,10\) In both trials – 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.\(^1,2,3\)

- ZEPOSIA demonstrated a relative reduction in ARR versus AVONEX of 48% through one year and 38% at two years (absolute ARR of 0.18 versus 0.35 and 0.17 versus 0.28, respectively).\(^1,2,3\)
- At one year, 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 lesions (1.47 vs. 2.84), a relative reduction of 48%.\(^1,3\)
- At two years, treatment with ZEPOSIA reduced the number of T1-weighted gadolinium-enhanced (GdE) brain lesions more than AVONEX (0.18 vs 0.37), a relative reduction of 53%.\(^1,2\) ZEPOSIA also reduced the number of new or enlarging...
Multiple sclerosis (MS) is a disease in which the immune system attacks the protective myelin sheath that covers the
nerve fibers of the brain and spinal cord. This damage can lead to a range of symptoms, including weakness, fatigue, and
problems with balance, coordination, walking, speech, and vision.

**About Multiple Sclerosis**

ZEPOSIA demonstrated acceptable safety and tolerability in the Phase 3 SUNBEAM and RADIANCE Part B trials. ZEPOSIA
is contraindicated in patients who in the last six months experienced myocardial infarction, unstable angina, stroke, transient
ischemic attack (TIA), decompensated heart failure requiring hospitalization, or Class III/IV heart failure; patients who 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; and patients taking a monoamine oxidase
inhibitor. ZEPOSIA is associated with the following Warnings and Precautions: increased risk of infections, bradyarrhythmia
and atrioventricular conduction delays, liver injury, fetal risk, increased blood pressure, respiratory effects, macular edema,
posterior reversible encephalopathy syndrome, additive immunosuppressive effects from prior immune-modulating
treatments, severe increase in disability after stopping ZEPOSIA, and immune system effects after stopping ZEPOSIA. Please
see Important Safety Information for additional details.

Before initiation of treatment with ZEPOSIA, all patients require assessments including a recent complete blood count
involving lymphocyte count (within six months or after discontinuation of prior MS therapy), an ECG to determine whether
preexisting conduction abnormalities are present, a recent liver function test (within six months), and consideration of
current and prior medications, including vaccinations. For patients with a history of uveitis or macular edema, an ophthalmic
assessment is required.

“Treatment for relapsing forms of multiple sclerosis is critical to address this devastating neurological disease,” said Bruce Cree, M.D., Ph.D., M.A.S., professor of clinical neurology, University of California San Francisco (UCSF) Weill Institute for Neurosciences and clinical research director, UCSF MS Center.

“Multiple sclerosis is an unpredictable and often disabling disease that affects nearly one million people in the United
States.” Ongoing treatment with disease-modifying therapy can reduce the number of disease attacks, said Bruce Bebo, executive vice president of research, National Multiple Sclerosis Society. “Each person can respond differently to these medications, which is why having treatment options is so important. We are pleased that there will now be another effective treatment option for people with MS.”

As the country’s healthcare system is dealing with the unprecedented COVID-19 pandemic, Bristol Myers Squibb has made
the decision to delay commercialization of ZEPOSIA. The Company made the decision based on what’s in the best health
interest of our patients, customers and employees. Bristol Myers Squibb will continue to monitor the environment and will
partner with the neurology community to inform launch timing.

A Marketing Authorization Application for ZEPOSIA for the treatment of adults with relapsing-remitting multiple sclerosis in
the European Union is currently under review with the European Medicines Agency (EMA). A regulatory decision from the EMA
is expected in the first half of 2020.

**About SUNBEAM™**

SUNBEAM is a pivotal, phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled trial evaluating the
efficacy, safety and tolerability of oral ZEPOSIA (0.92 mg, equivalent to 1 mg) against weekly intramuscular AVONEX
(interferon beta-1a) for at least a 12-month treatment period. The study included 1,346 people living with RMS across 152
sites in 20 countries.

The primary endpoint of the trial was annualized relapse rates (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 and number
of gadolinium-enhanced brain MRI lesions at month 12.

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 oral ZEPOSIA (0.92 mg, equivalent to 1 mg) 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 21 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.

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 Multiple Sclerosis**

Multiple sclerosis (MS) is a disease in which the immune system attacks the protective myelin sheath that covers the
nerve fibers of the brain and spinal cord. This damage can lead to a range of symptoms, including weakness, fatigue, and
problems with balance, coordination, walking, speech, and vision.
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.

RMS, including clinically isolated syndrome, relapsing remitting disease, and active secondary progressive disease, is characterized by clearly defined attacks of worsening neurologic function. These attacks — often called relapses, flares, or exacerbations — are followed by partial or complete recovery periods (remissions), during which symptoms improve partially or completely with no apparent progression of disease. RMS is the most common disease course at the time of diagnosis. Approximately 85% of patients are initially diagnosed with RMS, compared with 10-15% with progressive forms of the disease.

About ZEPOSIA® (ozanimod)

ZEPOSIA® is a 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 ozanimod exerts therapeutic effects in multiple sclerosis is unknown but may involve the reduction of lymphocyte migration into the central nervous system.

ZEPOSIA is also in development for additional immune-inflammatory indications, including ulcerative colitis and Crohn's disease.

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.
- 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.

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, othostatic 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, Twitter, YouTube, Facebook and Instagram.

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, whether ZEPOSIA (ozanimod) for the indication described in this release will be commercially successful and that continued approval of ZEPOSIA for such indication described in this release may be contingent upon verification and description of clinical benefit in confirmatory trials. 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.


McCann Agency. Pivotal Trials for MS Therapies: ZEPOSIA –2 head-to-head with Active Comparator Based on PIs. March 2020.


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#FDA approves new $BMY oral treatment option for #MultipleSclerosis #MS