

Novartis receives FDA approval for Mayzent® (siponimod), the first oral drug to treat secondary progressive MS with active disease

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- - Mayzent® (siponimod) is the first and only oral treatment specifically indicated for active secondary progressive multiple sclerosis (SPMS) in adults
- - Up to 80% of patients with relapsing remitting MS (RRMS) will develop SPMS(1); Mayzent addresses a critical unmet need for RRMS patients in transition and those with active SPMS who have transitioned
- - Approval is based on the Phase III EXPAND trial, the largest controlled clinical study of SPMS patients, showing Mayzent significantly reduced the risk of three-month confirmed disability progression in patients with active disease(2)
- - Mayzent is approved across the MS spectrum for clinically isolated syndrome (CIS), RRMS and active SPMS, with most patients not requiring a first dose observation

EAST HANOVER, N.J., March 27, 2019 /PRNewswire/ -- Novartis today announced that the US Food and Drug Administration (FDA) has approved Mayzent® (siponimod) for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome (CIS, is defined as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system (CNS)³), relapsing remitting disease, and active secondary progressive disease, in adults. SPMS is a debilitating form of multiple sclerosis (MS) characterized by progressive and irreversible neurological disability⁴. Mayzent is expected to be available in the US in approximately one week.* Patients will not require a first dose observation (FDO, cardiac monitoring upon initiation) unless they have certain pre-existing cardiac conditions.

"Delaying disability progression is a critical goal of MS treatment, and historically, patients with advancing disease have had very few options to help them," said Fabrice Chouraqui, President, Novartis Pharmaceuticals Corporation. "We've had a longstanding mission to enhance the understanding of MS and help reimagine treatment options, and we're excited to expand on our legacy with Mayzent for patients with relapsing forms of MS, including SPMS with active disease."

Most patients transition from RRMS to SPMS over time¹. Therefore, starting therapy early is critical for patients to help slow the rate of disability progression. Disability progression most frequently includes – but is not limited to – an impact on ambulation, which could lead to patients needing a walking aid or a wheelchair⁵.

"We are grateful that there is a new treatment option for adults with active secondary progressive MS," said Bruce Bebo, PhD, Executive Vice President, Research, National MS Society. "We are hopeful this approval will stimulate a conversation between patients and healthcare professionals about disability progression after relapsing remitting MS and its early management."

The approval of Mayzent is based on results from the Phase III EXPAND study, a randomized, double-blind, placebo-controlled study, comparing the efficacy and safety of Mayzent versus placebo in people living with SPMS. Patients enrolled in EXPAND were representative of a typical SPMS population: at study initiation, patients had a mean age of 48 years, had been living with MS for approximately 16 years and more than 50% had a median Expanded Disability Status Scale (EDSS) score of 6.0 and relied on a walking aid². Mayzent significantly reduced the risk of three-month confirmed disability progression (CDP) (primary endpoint; 21% reduction versus placebo, $p=0.013$; 33% reduction versus placebo in patients with relapse activity in the two years prior to screening, $p=0.01$)². Mayzent also reduced the annualized relapse rate (ARR) by 55%².

Most common adverse reactions (incidence greater than 10%) are headache, hypertension, and transaminase increase.

"With the approval of Mayzent, we now have a much-needed therapeutic option to address SPMS with active disease," said EXPAND Steering Committee member Bruce Cree, MD, PhD, MAS, Clinical Research Director and George A. Zimmermann Endowed Professor in Multiple Sclerosis, University of California, San Francisco, School of Medicine. "Importantly, healthcare professionals now have even more reason to help patients identify changing symptoms and uncover early signs of progression."

Novartis is committed to bringing Mayzent to patients worldwide, and additional regulatory filings are currently underway with other health authorities outside the US. Regulatory action for Mayzent in the European Union is anticipated in late 2019, with additional regulatory action anticipated in Switzerland, Japan, Australia, and Canada this year.

*Time of availability may vary as healthcare providers integrate Mayzent into their practices.

About the EXPAND Study

EXPAND is a randomized, double-blind, placebo-controlled Phase III study, comparing the efficacy and safety of Mayzent versus placebo in people with SPMS with varying levels of disability, EDSS scores of 3.0–6.5². It is the largest randomized, prospective, controlled study in SPMS to date, including 1,651 people with a diagnosis of SPMS from 31 countries². Mayzent demonstrated a safety profile that was overall consistent with the known effects of S1P receptor modulation. It reduced the risk of three-month CDP by a statistically significant 21% ($p=0.013$; primary endpoint)². CDP was defined as a 1-point increase in EDSS, if the baseline score was 3.0–5.0, or a 0.5-point increase, if the baseline score was 5.5–6.5². No significant differences were found in the T25FW, however, T2 lesion volume was reduced by 79% as compared to placebo². Additional secondary endpoints data included a 55% relative reduction in ARR and, compared to placebo, more patients were free from gadolinium-enhancing lesions (89%) and from new or enlarging T2 lesions (57%)².

About Mayzent® (siponimod)

Mayzent is a next generation, selective sphingosine 1-phosphate receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome (CIS, is defined as a first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the central nervous system (CNS)³), relapsing remitting disease, and active secondary progressive disease, in adults. Mayzent selectively binds to S1P1 and S1P5 receptors. In relation to the S1P1 receptor, it prevents 1/5 lymphocytes from egressing the lymph nodes and as a consequence, from

entering the CNS of patients with MS. This leads to the anti-inflammatory effects of Mayzent². Mayzent also enters the CNS and directly binds to the S1P5 and S1P1 sub-receptors on specific cells in the CNS (oligodendrocytes and astrocytes)⁶ to prevent inflammation.

About Multiple Sclerosis

MS is a chronic disorder of the CNS that affects around 400,000 people in the US⁷. Patients can be diagnosed with the following types of MS: RRMS (the most common form of the condition at diagnosis), SPMS and primary progressive MS (PPMS)⁸. MS disrupts the normal functioning of the brain, optic nerves and spinal cord through inflammation and tissue loss⁹.

SPMS follows an initial form of RRMS, which accounts for approximately 85% of all MS diagnoses, and is characterized by gradual worsening of neurological function over time³. This leads to a progressive accumulation of neurological disability. There remains a high unmet need for safe and effective treatments to help delay disability progression in SPMS with active disease (with relapses and/or evidence of new MRI activity)⁴.

Novartis in Neuroscience

Novartis has a strong ongoing commitment to neuroscience and to bringing innovative treatments to patients suffering from neurological conditions where there is a high unmet need. We are committed to supporting patients and physicians in multiple disease areas, including MS, migraine, Alzheimer's disease, Parkinson's disease, epilepsy and attention deficit hyperactivity disorder, and have a promising pipeline in MS, Alzheimer's disease, spinal muscular atrophy and specialty neurology.

MAYZENT US INDICATION

What is MAYZENT® (siponimod) tablets?

MAYZENT is a prescription medicine that is used to treat relapsing forms of multiple sclerosis, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

It is not known if MAYZENT is safe and effective in children.

IMPORTANT SAFETY INFORMATION:

Do not take MAYZENT if you:

- have a CYP2C9*3/*3 genotype. Before starting treatment with MAYZENT, your CYP2C9 genotype should be determined by your health care provider. Ask your health care provider if you are not sure.
- have had a heart attack, chest pain called unstable angina, stroke or mini-stroke (transient ischemic attack or TIA), or certain types of heart failure in the last 6 months
- have certain types of heart block or irregular or abnormal heartbeat (arrhythmia), unless you have a pacemaker

MAYZENT may cause serious side effects, including:

1. Slow heart rate (bradycardia or bradyarrhythmia) when you start taking MAYZENT. MAYZENT can cause your heart rate to slow down, especially after you take your first dose. You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of MAYZENT.
During the initial updosing period (4 days for the 1-mg daily dose or 5 days for the 2-mg daily dose), if you miss 1 or more doses of MAYZENT, you need to restart the updosing. Call your health care provider if you miss a dose of MAYZENT.
2. Infections. MAYZENT can increase your risk of serious infections that can be life-threatening and cause death. MAYZENT lowers the number of white blood cells (lymphocytes) in your blood. This will usually go back to normal within 3 to 4 weeks of stopping treatment. Your health care provider should review a recent blood test of your white blood cells before you start taking MAYZENT.
Call your health care provider right away if you have any of these symptoms of an infection during treatment with MAYZENT and for 3 to 4 weeks after your last dose of MAYZENT:
 - fever
 - tiredness
 - body aches
 - chills
 - nausea
 - vomiting
 - headache with fever, neck stiffness, sensitivity to light, nausea, confusion (these may be symptoms of meningitis, an infection of the lining around your brain and spine)
3. A problem with your vision called macular edema. Macular edema can cause some of the same vision symptoms as a multiple sclerosis (MS) attack (optic neuritis). You may not notice any symptoms with macular edema. If macular edema happens, it usually starts in the first 1 to 4 months after you start taking MAYZENT. Your health care provider should test your vision before you start taking MAYZENT and any time you notice vision changes during treatment with MAYZENT. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis.
Call your health care provider right away if you have any of the following: blurriness or shadows in the center of your vision, a blind spot in the center of your vision, sensitivity to light, or unusually colored (tinted) vision.

Before taking MAYZENT, tell your health care provider about all of your medical conditions, including if you:

- have an irregular or abnormal heartbeat
- have a history of stroke or other diseases related to blood vessels in the brain
- have breathing problems, including during your sleep
- have a fever or infection, or you are unable to fight infections due to a disease or are taking medicines that lower your immune system. Tell your health care provider if you have had chicken pox or have received the vaccine for chicken pox. Your health care provider may do a blood test for chicken pox virus. You may need to get the full course of vaccine for chicken pox and then wait 1 month before you start taking MAYZENT.
- have slow heart rate
- have liver problems
- have diabetes

- have eye problems, especially an inflammation of the eye called uveitis
- have high blood pressure
- are pregnant or plan to become pregnant. MAYZENT may harm your unborn baby. Talk to your health care provider right away if you become pregnant while taking MAYZENT or if you become pregnant within 10 days after you stop taking MAYZENT.
- o If you are a woman who can become pregnant, you should use effective birth control during your treatment with MAYZENT and for at least 10 days after you stop taking MAYZENT.
- are breastfeeding or plan to breastfeed. It is not known if MAYZENT passes into your breast milk. Talk to your health care provider about the best way to feed your baby if you take MAYZENT.

Tell your doctor about all the medicines you take, including prescription medicines, over-the-counter medicines, vitamins, and herbal supplements. Especially tell your health care provider if you take medicines to control your heart rhythm (antiarrhythmics), or blood pressure (antihypertensives), or heart beat (such as calcium channel blockers or beta-blockers); take medicines that affect your immune system, such as beta-interferon or glatiramer acetate, or any of these medicines that you took in the past.

Tell your doctor if have recently received a live vaccine. You should avoid receiving live vaccines during treatment with MAYZENT. MAYZENT should be stopped 1 week before and for 4 weeks after receiving a live vaccine. If you receive a live vaccine, you may get the infection the vaccine was meant to prevent. Vaccines may not work as well when given during treatment with MAYZENT.

MAYZENT may cause possible side effects, including:

- increased blood pressure. Your health care provider should check your blood pressure during treatment with MAYZENT.
- liver problems. MAYZENT may cause liver problems. Your health care provider should do blood tests to check your liver before you start taking MAYZENT. Call your health care provider right away if you have any of the following symptoms of liver problems:
 - o nausea
 - o vomiting
 - o stomach pain
 - o tiredness
 - o loss of appetite
 - o your skin or the white of your eyes turn yellow
 - o dark urine
- breathing problems. Some people who take MAYZENT have shortness of breath. Call your health care provider right away if you have new or worsening breathing problems.
- swelling and narrowing of the blood vessels in your brain. A condition called PRES (Posterior Reversible Encephalopathy Syndrome) has happened with drugs in the same class. Symptoms of PRES usually get better when you stop taking MAYZENT. However, if left untreated, it may lead to a stroke. Call your health care provider right away if you have any of the following symptoms: sudden severe headache, sudden confusion, sudden loss of vision or other changes in vision, seizure.
- severe worsening of multiple sclerosis after stopping MAYZENT. When MAYZENT is stopped, symptoms of MS may return and become worse compared to before or during treatment. Always talk to your doctor before you stop taking MAYZENT for any reason. Tell your health care provider if you have worsening symptoms of MS after stopping MAYZENT.

The most common side effects of MAYZENT include: headache, high blood pressure (hypertension), and abnormal liver tests.

These are not all of the possible side effects of MAYZENT. Call your doctor for medical advice about side effects.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see full [Prescribing Information](#), including Medication Guide.

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About Novartis

Novartis is reimagining medicine to improve and extend people's lives. As a leading global medicines company, we use innovative science and digital technologies to create transformative treatments in areas of great medical need. In our quest to find new medicines, we consistently rank among the world's top companies investing in research and development. Novartis products reach more than 800 million people globally and we are finding innovative ways to

expand access to our latest treatments. About 130,000 people of nearly 150 nationalities work at Novartis around the world. Novartis Pharmaceuticals Corporation, a US affiliate of Novartis, is located in East Hanover, NJ. Find out more at www.novartis.com.

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