Mayzent® (siponimod) – New drug approval

- On March 26, 2019, the FDA announced the approval of Novartis' Mayzent (siponimod), 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.

- MS is a chronic disorder of the central nervous system (CNS) that affects around 2.3 million people worldwide. 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 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 MS (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. Later, many patients with SPMS stop experiencing new relapses, but disability continues to progress, a phase called non-active SPMS.

- Mayzent is a selective sphingosine 1-phosphate receptor modulator. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown, but may involve reduction of lymphocyte migration into the CNS.

- The efficacy of Mayzent was established in a double-blind, time-to-event study in 1,651 patients with SPMS. Patients were randomized to receive either Mayzent 2 mg or placebo, beginning with a dose titration. The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP). Other key secondary endpoints included the confirmed worsening in timed 25-foot walk and the annualized relapse rate.

    — Mayzent was superior to placebo in reducing the risk of CDP, based on a time-to-event analysis (Hazard Ratio 0.79; $p < 0.0134$). Overall, 26% of patients had CDP with Mayzent vs. 32% with placebo.
    — Mayzent did not significantly delay the time to 20% deterioration in the timed 25-foot walk, vs. placebo.
    — Patients treated with Mayzent had a 55% relative reduction in annualized relapse rate, vs. patients on placebo ($p < 0.0001$). The annualized relapse rate was 0.071 for Mayzent vs. 0.160 for placebo.

- Mayzent is contraindicated in patients who have:

    — A CYP2C9*3/*3 genotype
    — In the last 6 months experienced myocardial infarction, unstable angina, stroke, transient ischemia attack, decompensated heart failure requiring hospitalization, or Class III or IV heart failure
    — Presence of Mobitz type II second-degree, third-degree AV block, or sick sinus syndrome, unless patient has a functioning pacemaker

- Additional warnings and precautions of Mayzent include infections, macular edema, bradyarrhythmia and atrioventricular conduction delays, respiratory effects, liver injury, increased blood pressure,

Continued . . .

fetal risk, posterior reversible encephalopathy syndrome, unintended additive immunosuppressive effects from prior treatment with immunosuppressive or immune-modulating therapies, severe increase in disability after stopping Mayzent, and immune system effects after stopping Mayzent.

- The most common adverse reactions (> 10%) with Mayzent use were headache, hypertension, and transaminase increases.

- Before initiation and treatment with Mayzent, patients should be tested for CYP2C9 variants to determine CYP2C9 genotype.

    - In patients with CYP2C9 genotypes *1/*1, *1/*2, or *2/*2, Mayzent should be initiated with a 5-day titration. After treatment titration, the recommended maintenance dosage of Mayzent is 2 mg taken orally once daily starting on day 6.
    - In patients with a CYP2C9 *1/*3 or *2/*3 genotype, Mayzent should be initiated with a 4-day titration. After treatment titration, the recommended maintenance dosage of Mayzent is 1 mg taken orally once daily starting on day 5.
    - Prior to treatment initiation with Mayzent, patients should receive an electrocardiogram to determine whether preexisting conduction abnormalities are present. In patients with certain preexisting conditions, advice from a cardiologist and first-dose monitoring is recommended.
    - Refer to the Mayzent drug label for additional dosing and administration details.

- Mayzent will be priced at $88,000 per year.

- Novartis plans to launch Mayzent in approximately one week. Mayzent will be available as 0.25 mg and 2 mg tablets.