Mayzent® *(MAY-zint)*  
Generic name: siponimod (sih-PON-i-mod)

**What is Mayzent®?**  
Mayzent® is an oral medication that easily enters the bloodstream. It binds to a protein called sphingosine 1-phosphate receptor (S1PR).

The S1PR is a protein found on the surface of many cells. There are five types of S1PR located on different types of cells in the body, and Mayzent® blocks two of these types. One of the types of S1PR that Mayzent® blocks is found on lymphocytes. Lymphocytes are believed to be responsible for the immune attack on the nervous system that causes multiple sclerosis. Lymphocytes circulate around the body in the blood. They eventually lodge in a lymph node which they must navigate through to exit back into the bloodstream. In the lymph node, potential targets are presented to lymphocytes. These lymphocytes can be activated by these targets and can attack the targets once they reenter the bloodstream. If lymphocytes are directed against inappropriate targets, like the body’s own proteins, they are killed in the lymph node. The S1PR is key to directing the navigation of lymphocytes through the lymph node. When S1PR is bound by Mayzent®, lymphocytes stay in the lymph node longer resulting in more opportunities to be eliminated if they are directed against inappropriate targets. Since lymphocytes do not live very long, many also die in the lymph nodes resulting in fewer in the bloodstream. This results in a decrease in blood levels of lymphocytes that contribute to the immune attack on the nervous system in multiple sclerosis.

Oligodendrocytes are the cells that make myelin in the nervous system. Oligodendrocyte precursors are cells that are capable of reproducing and making more mature oligodendrocytes. These cells also have S1PR receptors that Mayzent® binds. This causes these cells to reproduce. Thus, Mayzent® may have a role in promoting repair of myelin. This possible role for Mayzent® has not been proven in humans.

Mayzent® slows the course of multiple sclerosis when used regularly over long periods of time. It does not improve existing symptoms and is not used to treat acute MS attacks.
Starting on Mayzent®

To obtain Mayzent®

1. A blood test must be obtained to determine liver enzyme genotypes. This test measures which liver enzymes a person has. This is needed to determine whether it is safe to take Mayzent® and the correct dose. The blood must be drawn by LabCorp, which is the only laboratory providing this test nationally. There is a LabCorp blood draw station in our building.

2. A start form must be completed and faxed to the Alongside MS™ program. This program, operated by Novartis, the manufacturer of Mayzent®, will start the process of obtaining the medication. Pharmacotherapy clinic staff can assist with completion of these forms and getting insurance approval. It takes 1-2 weeks to get insurance approval. Sometimes, insurance denials and appeals may take longer.

3. Insurance often pays only part of the cost of Mayzent®. The contract between the patient and the insurance company specifies the amount of deductibles and copayments.
   a. The deductible is the amount patients must pay each year before their insurance starts covering costs.
   b. The copayment is the amount patients must pay for each medical bill.

For medications, the copayment is often a percent of the medication’s cost. Pharmacotherapy clinic staff can assist in getting the manufacturer or foundations to decrease the cost of deductibles and copayments.

4. The medication is not stocked in your pharmacy. It must be shipped overnight from a distributor to either your home or your pharmacy (depending on insurance requirements). Pharmacotherapy clinic staff can assist in the shipping process.

There are also several tests that must be obtained prior to starting the medication. We usually obtain these at the same time as the liver enzyme genotype testing (see #1 above). These are:

- Blood tests for basic liver, kidney and blood functions
- Blood tests to assure adequate immunity to chickenpox (varicella). If the immunity to chickenpox is not adequate, then patients are vaccinated. We then wait at least 30 days before sending another blood test for immunity to chickenpox. Mayzent® can be started when immunity is adequate.
- A baseline eye examination.
- An electrocardiogram (ECGs, EKGs, heart tracings)
- A test of pulmonary function is performed if patients have prior lung disease.
- A baseline MRI is usually obtained prior to or shortly after starting a new disease-modifying treatment.

After the medication is approved by your insurance, it will be shipped to your home or pharmacy (depending on your insurance preference). Most patients will start taking the medication at home. Occasional patients with heart disease will require medical monitoring for 6 hours after receiving their first dose.
**Safety Monitoring**
- Blood pressure checks during medical appointments
- Eye examination 3-4 months after starting medication

**How should Mayzent® be taken?**
When first starting Mayzent®, it should be started at a low dose and titrated upwards over 5 days. The titration minimizes effects on the pulse. There are 2 doses of Mayzent® which are determined by the results of the liver enzyme genotype blood test. Your healthcare provider will tell you which dose to use.

1. For most people the titration and dose will be:

<table>
<thead>
<tr>
<th>Titration</th>
<th>Titration dose</th>
<th>Titration regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 2</td>
<td>0.25 mg</td>
<td>1 x 0.25 mg</td>
</tr>
<tr>
<td>Day 3</td>
<td>0.50 mg</td>
<td>2 x 0.25 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.75 mg</td>
<td>3 x 0.25 mg</td>
</tr>
<tr>
<td>Day 5</td>
<td>1.25 mg</td>
<td>5 x 0.25 mg</td>
</tr>
</tbody>
</table>

Starting on Day 6, take **2 mg orally once daily** as a maintenance dose.

2. For some patients with certain types of liver enzyme genotypes, a lower dose will be needed. Your healthcare provider will tell you to use this lower titration and dose:

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<td>2 x 0.25 mg</td>
</tr>
<tr>
<td>Day 4</td>
<td>0.75 mg</td>
<td>3 x 0.25 mg</td>
</tr>
</tbody>
</table>

Starting on Day 5, take **1 mg orally once daily** as a maintenance dose.

**What if a dose is missed?**
Take the next dose if you are 8 hours late or less. If you are more than 8 hours late on the dose, then skip that dose and take your Mayzent® at your regular time the following day.

- If 1 or more doses are missed during the initial dose titration, the titration needs to be restarted.
- If 1 or more doses are missed after the initial dose titration, take it as soon as you remember.
- If Mayzent® is stopped for 4 days in a row, the titration needs to be restarted.

**How should Mayzent® be stored?**
- Unopened containers should be stored in a refrigerator between 2°C to 8°C.
• Opened starter packs or blister cards should be stored at room temperature (20°C to 25°C) up to 1 week after opening the blister.
• Opened bottles should be stored at room temperature (20°C to 25°C) up to 1 month after opening the bottle.

**How supplied:** The 0.25 mg tablets are supplied in a bottle of 28 tablets and the 2 mg tablets are supplied in a bottle of 30 tablets. Depending on insurance requirements, 4 or 12 weeks are usually shipped to patients each time.

**What are the common side effects?**

- **Slow heart rate:** Mayzent® can slow the heart rate after the first dose. This is the reason that the dose is titrated up. It is also the reason that the titration must be repeated if patients miss too many doses (see above).

- **Macular edema:** Macular edema is swelling of the retina in the back of the eye. This is seen in 1.8% of people receiving Mayzent® and 0.2% of those receiving placebo. It generally occurs within the first few months of starting the medication. Most people with macular edema have no symptoms, but about 1/3 notice blurring of vision. Other symptoms include shadows or a blind spot in the center of vision, sensitivity to light or tinted vision. Macular edema usually goes away without treatment.

An ophthalmology examination is done before starting Mayzent® and 3–4 months later. This examination usually includes a special test called an ocular coherence tomography (OCT). This test is painless, takes a few minutes per eye, and uses a light beam to measure the thickness of the retina.

- **Lymphocyte counts:** Lymphocytes are a type of white blood cell. The levels of lymphocytes in the blood may be markedly decreased. However, the risk of infections does not correlate to the level of lymphocytes seen with Mayzent®. Low lymphocyte counts are expected with the medication and are not a cause for alarm. In general, monitoring of lymphocytes is not recommended with this medication.

- **Infection (see also rare side effects below):** In general, there is not an increase in infections with Mayzent®. Bronchitis, sinusitis, upper respiratory infection are slightly increased. Care is taken to assure that patients receiving Mayzent® are immune to chicken pox since it can cause serious infections in adults who are not immune to the virus. Immunity to chicken pox can fade after several years, so having a history of chickenpox does not assure immunity. This requires a blood test prior to starting Mayzent®, and those with inadequate immunity to this virus are vaccinated for chickenpox before starting the medication.
What are the rare side effects?

- Liver function: Changes in liver function have been found in other medications in this family. These changes did not cause any symptoms and they returned to normal if the medication was stopped. In those cases where the medication was not stopped, the liver function still returned to normal.

Liver function is measured by a blood test before starting Mayzent®. Liver function should be checked during treatment if symptoms of liver damage occur such as jaundice (skin or white of eyes turn yellow), persistent dark urine, prolonged nausea or vomiting, stomach pain, loss of appetite or unexplained fatigue.

- Pulmonary function: Other medications in this family may cause a slight fall in pulmonary function. In a measure of how much air a patient could blow out in one second, those treated with other members of this family decreased 3.1% compared to 2% for placebo over 2 years. In a measure of oxygen absorption, those treated with other members of this family decreased 3.8% compared to 2.7% for placebo. There was no difference between groups in breathing symptoms.

Pulmonary function tests are obtained prior to starting the medication in patients with suspected lung disease. These tests may be obtained during treatment if patients develop lung symptoms.

- Blood pressure: In those taking other medications in this family, blood pressure increased slightly. Systolic pressure (the top number on a blood pressure reading) increased an average of 3 mmHg. Diastolic pressure (the bottom number on a blood pressure reading) increased an average of 2 mmHg. This effect was seen by 2 months on the medication. Blood pressures are measured during regular clinic visits.

- Diarrhea: With other medications in this family, diarrhea which was seen at least once in a 2-year period in 11.8% of those on medication and 7.4% of those on placebo.

- Severe worsening of MS upon stopping other medications in this family may occur in the first few months after stopping the medication. This is so rare that how often it occurs cannot be calculated. Starting another MS medication before this rebound occurs is believed to lessen this risk.

- Progressive multifocal leukoencephalopathy (PML): PML is a virus infection of the brain and is described in more detail on our website. The risk of PML with Mayzent® is assumed to be similar to other medications in this family, occurring in approximately 1 in 12,000 patients. For those on the medication longer than 2 years, PML is expected to occur in approximately 1 in 5,000. For comparison, the risk of getting struck by lightning...
Cryptococcus is a type of fungus that can cause a number of infections. The risk of Cryptococcus infections with Mayzent® is assumed to be similar to other medications in this family, occurring in 1 in 6,250 patients. For comparison, the risk of getting struck by lightning in the US is approximately 1 in 12,000.

Skin cancers, particularly basal cell carcinoma have been seen with other medications in this family. This is seen in 2% of people treated with these medications compared to 1% in those treated with placebo.

Lymphomas have been reported with other medications in this family, but they are so rare that how often they occur cannot be calculated.

Company Support:
The Alongside MS™ Program 1-877-629-9368 provides financial assistance, insurance assistance, information about Mayzent® and multiple sclerosis.

www.Mayzent.com