Patient leaflet in accordance with the Pharmacists' Regulations (Preparations) - 1986

This medicine is dispensed with a doctor's prescription only

Mayzent 0.25 mg
Mayzent 2 mg

Film-coated tablets

Active ingredient

siponimod 0.25 mg (as siponimod fumaric acid) in each film-coated tablet

siponimod 2 mg (as siponimod fumaric acid) in each film-coated tablet

Inactive ingredients and allergens in this medicine: See section 2 under 'Important information about some of this medicine's ingredients' and section 6 'Additional information'.

Read the entire leaflet carefully before you start using this medicine. This leaflet contains concise information about this medicine. If you have any further questions, consult your doctor or pharmacist.
This medicine has been prescribed to treat you. Do not pass it on to others. It may harm them, even if it seems to you that their medical condition is similar to yours.

In addition to the patient leaflet, Mayzent also has a Patient/Caregiver Guide and a Pregnancy Reminder Card.
These guides contain important safety information that you should know of before you start and during your treatment with Mayzent and which you should follow. Read the Patient/Caregiver Guide and the Pregnancy Reminder Card as well as the patient leaflet before you start taking this medicine. Keep the guides in case you need to read them again.

1. What is this medicine intended for?

Mayzent is intended for the treatment of adults with relapsing forms of multiple sclerosis (MS) including relapsing-remitting disease (RRMS), and active secondary progressive disease (SPMS).

Therapeutic group: immunosuppressants, selective immunosuppressants.

Active disease in secondary progressive multiple sclerosis is when there are relapses or when magnetic resonance imaging (MRI) results show signs of inflammation.

Mayzent helps to protect the central nervous system (CNS) from attacks by the body's own immune system. It does this by:

- making some white blood cells (called lymphocytes) less able to move freely within the body.
- stopping the white blood cells (lymphocytes) from reaching the brain and spinal cord.

This reduces nerve damage caused by SPMS and as a result Mayzent helps to slow down the effects of the disease activity (such as worsening disability, brain lesions, and relapses).

2. Before using this medicine

Do not use this medicine if:

- you are sensitive (allergic) to siponimod, peanuts, soya or any of the other ingredients in this medicine (see 'Important information about some of this medicine's ingredients' as well as section 6 'Additional information').
- you have an immunodeficiency syndrome.
- you have ever had progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- you have an active cancer.
- you have severe liver problems.
- in the last 6 months, you have had a heart attack, unstable angina, stroke or certain types of heart failure.
- you have certain types of irregular or abnormal heartbeat (arrhythmia) and you do not have a pacemaker.
- If your blood tests show that your body cannot break down this medicine well enough, do not take it (see 'Tests and follow-up').
- you are pregnant or could become pregnant and are not using effective contraception.

Special warnings about using this medicine

Before treatment with Mayzent, tell your doctor if:

- you have an infection or if your immune system does not work properly (for example due to a disease or to medicines that suppress the immune system; see also 'Drug interactions').
- you have never had chickenpox and have not been vaccinated against it. You may be at a high risk of complications if you develop chickenpox during Mayzent treatment. Your doctor may want to vaccinate you against chickenpox before you start treatment.
- you are planning to have any vaccinations. Your doctor will advise you on this (see 'Drug interactions').
- you have ever had, or have, difficulties with your vision (in particular a condition called macular edema) or an infection or inflammation of the eye (uveitis). Your doctor may want you to have eye examinations before you start treatment and regularly while you are on treatment. Mayzent can cause a swelling in the macula (the area of the eye that enables you to see shapes, colors and details) known as macular edema. Your chance of developing macular edema is higher if you have had it before or if you have ever had an inflammation of the eye (uveitis).
- you have diabetes. The chance of developing macular edema (see above) is higher in patients with diabetes.
- you have ever had any of the following conditions (even if you are receiving treatment for them): severe heart disease, irregular or abnormal heartbeat (arrhythmia), stroke or other disease related to the blood vessels in the brain, a slow heart rate, fainting, disturbance of heart rhythm (indicated by abnormal ECG [electrocardiogram] results).
- you have severe breathing problems when sleeping (sleep apnea).
- you have high blood pressure that cannot be controlled by medicines. Your blood pressure will need to be checked regularly.
- you have ever had liver problems. Your doctor may want to perform blood tests to check your liver function before prescribing Mayzent.
- you could become pregnant, because using siponimod during pregnancy can harm the unborn baby. Before you start treatment, your doctor will explain the risks and ask you to do a pregnancy test to ensure that you are not pregnant. You must use effective contraception during treatment and up to 10 days after stopping treatment (see 'Pregnancy, breastfeeding and fertility').

If any of the above applies to you, tell your doctor **before** taking Mayzent.

Look out for the following while taking Mayzent
If you get any of the following while taking Mayzent, **tell your doctor immediately** because it could be serious:

- if you have an infection. Mayzent lowers the number of white blood cells in your blood. White blood cells fight infection, so you may get infections more easily while you are taking Mayzent (and up to 3 to 4 weeks after you stop taking it). These infections could be serious and possibly even life-threatening.
- if you think your MS is getting worse or if you notice any new or unusual symptoms. A very rare brain infection called progressive multifocal leukoencephalopathy (PML) can cause symptoms similar to SPMS. PML can occur in patients taking medicines like Mayzent and other medicines used for treating MS.
- if you have fever, feel like you have flu or have a headache together with a stiff neck, sensitivity to light, nausea or confusion. These may be symptoms of encephalitis and/or meningitis caused by a viral or fungal infection (such as cryptococcal meningitis).
- if you have changes in your vision, for example if the center of your vision becomes blurred or has shadows, a blind spot develops in the center of your vision, or you have problems seeing colors or fine detail. These could be symptoms of macular edema. You may not notice any symptoms in the early stages of macular edema, and it can cause the same visual symptoms as an MS attack (optic neuritis). Your doctor may want you to have an eye examination 3 or 4 months after starting treatment and possibly again later. If macular edema is confirmed, your doctor may advise you to stop Mayzent treatment.
- if you have symptoms such as sudden onset of severe headache, confusion, seizures and vision changes. These may be symptoms of a condition called posterior reversible encephalopathy syndrome (PRES).
- if you have symptoms such as unexplained nausea, vomiting, abdominal pain, tiredness, yellowing of the skin or whites of the eyes or abnormally dark urine. These may be symptoms of liver problems.
- if you notice skin nodules (e.g., shiny, pearly nodules), patches or open sores that do not heal within weeks.

Slow heart rate (bradycardia) and irregular heartbeat
During the first days of treatment, Mayzent can cause the heart rate to slow down (bradycardia). You may not feel anything or you may feel dizzy or tired. It may also cause your heartbeat to become irregular at the beginning of treatment.
If anything indicates that you may be at higher risk of experiencing these effects, your doctor may decide to monitor your condition more closely at the start of treatment, refer you first to a heart specialist (cardiologist), or choose not to give you Mayzent.

Skin cancer
Cases of skin cancer have been reported in MS patients treated with Mayzent. Talk to your doctor straight away if you notice any skin nodules (e.g., shiny pearly nodules), patches or open sores that do not heal within weeks.
Symptoms of skin cancer may include abnormal growth or changes of skin tissue (e.g., unusual moles) with a change in color, shape or size over time. Before you start taking Mayzent, a skin examination is required to check whether you have any skin nodules. Your doctor will also carry out regular skin examinations during your treatment with Mayzent. If you develop problems with your skin, your doctor may refer you to a dermatologist, who after consultation may decide that it is important to see you on a regular basis.

Exposure to the sun and protection against the sun
Mayzent weakens your immune system. This may increase your risk of developing skin cancer. You should limit your exposure to the sun and UV rays by:

- wearing appropriate protective clothing.

- regularly applying sunscreen with a high degree of UV protection.

Worsening of MS after stopping Mayzent treatment
Do not stop taking Mayzent or change your dose without talking to your doctor first.
Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Mayzent (see 'If you stop taking this medicine' in section 3).

Elderly patients (65 years of age and above)
Mayzent had not been studied in patients aged 65 years and above. Talk to your doctor if you have any concerns.

Children and adolescents
This medicine is not intended for children and adolescents below 18 years of age. There are no data available on safety and efficacy of use of this medicine in children and adolescents below 18 years of age.

Tests and follow-up
How quickly this medicine is broken down (metabolized) in the body varies from patient to patient and different people therefore require different doses. Your doctor will perform a blood test before you start treatment to determine which dose is best for you. In rare cases, the test result may indicate that Mayzent is not right for you.

Your blood may also be tested before the start of treatment and periodically during treatment to check the white blood cell count. Your doctor may need to stop or reduce your Mayzent dose if the white blood cell count is too low.

Before the start of treatment your blood will also be tested to check how well your liver is working.

Drug interactions
If you are taking or have recently taken other medicines, including nonprescription medications and dietary supplements, tell your doctor or pharmacist. Particularly if you are taking:
- medicines for an irregular heartbeat, such as amiodarone, procainamide, quinidine or sotalol. Your doctor may decide not to prescribe Mayzent because it could intensify the effect on irregular heartbeat.
- medicines that slow down the heartbeat, such as diltiazem or verapamil (which belong to a group of medicines called calcium channel blockers), digoxin or ivabradine. Your doctor may refer you to a heart specialist, as your medicines may need to be changed because Mayzent may also slow down your heartbeat in the first days of treatment. If you are taking a beta-blocker, such as atenolol or propranolol, your doctor may ask you to temporarily stop your beta-blocker treatment until you have reached your full daily dose of Mayzent.
- medicines that affect the immune system, such as chemotherapy, immunosuppressants or other medicines to treat MS. Your doctor may ask you to stop taking these medicines to avoid an increased effect on the immune system.
- vaccines. If you need to have a vaccination, talk to your doctor first. During and for up to 4 weeks after stopping treatment with Mayzent, you should not be given certain types of vaccines (called live attenuated vaccines) as they could trigger the infection that they were supposed to prevent (see 'Before treatment with Mayzent, tell your doctor if' in section 2).
- fluconazole and certain other medicines can increase the levels of Mayzent in the blood and taking them in combination with Mayzent is not recommended. Your doctor will advise you on this.
- carbamazepine and certain other medicines can lower the levels of Mayzent in your blood and can therefore stop it from working properly. Your doctor will advise you on this.

- modafinil and certain other medicines can lower the levels of Mayzent in the blood of certain patients and can therefore stop it from working properly. Your doctor will advise you on this if this is relevant for you.
- phototherapy with UV radiation or PUVA photochemotherapy. UV therapy during Mayzent treatment may increase your risk of developing skin cancer.

Pregnancy, breastfeeding, and fertility
If you are pregnant or breastfeeding, may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
Pregnancy
Do not use Mayzent during pregnancy, if you are trying to become pregnant, or if you are a woman of childbearing age and you are not using effective contraception. If Mayzent is used during pregnancy, there is a risk of harm to the unborn baby. If you are a woman of childbearing age, your doctor will inform you about this risk before you start treatment with Mayzent and will ask you to do a pregnancy test in order to ensure that you are not pregnant. You must use effective contraception while taking Mayzent and for at least 10 days after you stop taking it to avoid becoming pregnant. Ask your doctor about reliable methods of contraception.

If you do become pregnant while taking Mayzent, tell your doctor straight away. Your doctor will decide to stop treatment (see 'If you stop taking this medicine' in section 3). Specialized pre-natal monitoring will be performed.
Breastfeeding
Do not breastfeed while you are taking Mayzent. It is not known if Mayzent and its main breakdown products pass into breast milk.
Fertility
The impact of Mayzent on fertility in humans has not been studied.

Driving and using machines
Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. Mayzent has no effect or a negligible effect on your ability to drive and use machines when you are treated with your regular dose. At the start of treatment you may occasionally feel dizzy. On your first day of treatment with Mayzent, therefore, you should not drive and should not use machines.

Important information about some of this medicine's ingredients
Mayzent contains lactose and soya lecithin
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
If you are sensitive (allergic) to peanuts or soya, do not use this medicine.

3. How to use this medicine?
Treatment with Mayzent will be overseen by a doctor who is experienced in the treatment of MS.
Always use this medicine according to your doctor's instructions.
Check with your doctor or pharmacist if you are not sure about your dose or about how to take this medicine.

Only your doctor will determine your dose and how you should take this medicine. The usual recommended dosage is:

Starting treatment
You will be given a starter pack called a titration pack, with which your dose will be gradually increased over 5 days. Follow the instructions on the pack (see also the 'Titration pack' table).

The purpose of the titration phase is to reduce the risk of side effects on your heart at the start of treatment.
Your doctor will monitor you closely at the start of treatment if you are at risk of your heartbeat becoming slower or irregular.

Titration pack

Day	Dose	Number of Mayzent 0.25 mg tablets to take
Day 1	0.25 mg	1 tablet
Day 2	0.25 mg	1 tablet
Day 3	0.5 mg	2 tablets
Day 4	0.75 mg	3 tablets
Day 5	1.25 mg	5 tablets

On day 6, you will switch to your regular treatment dose.
On the first 6 days of treatment, it is recommended that you take the tablets in the morning with or without food.

Treatment dose
The recommended dose is 2 mg once daily (one tablet of 2 mg Mayzent) with or without food.

Your doctor may instruct you to take only 1 mg once daily (four 0.25 mg Mayzent tablets) if the blood test performed before the start of treatment showed that your body breaks down Mayzent more slowly (see 'Tests and follow-up' in section 2). If slow breakdown applies to you, note that it is nevertheless safe for you to take five 0.25 mg Mayzent tablets on day 5 of the titration period as indicated above.

Do not exceed the recommended dose.

How to take this medicine
Mayzent is for oral use only. Take the tablet with water.
There is no information about crushing/splitting/chewing the tablets.

If you have accidentally taken a higher dose
If you have accidentally taken too many Mayzent tablets, or if you take your first tablet from the treatment pack instead of the starter pack (titration pack) by mistake, contact your doctor straight away. Your doctor may decide to keep you under observation.
If a child has accidentally swallowed some medicine, immediately see a doctor or go to a hospital emergency room and bring the medicine package with you.

If you forget to take the medicine
During the first 6 days of treatment, if you have forgotten to take your dose on one day, contact your doctor before you take the next dose.
Your doctor will prescribe a new titration pack. You will have to restart your treatment at day 1.
If you miss a dose when you are on the regular treatment dose (day 7 onwards), take the missed dose as soon as you remember.

If it is almost time for your next dose, skip the missed dose and continue as usual. Do not take a double dose to make up for a forgotten dose.

If you forget to take Mayzent for 4 or more days in a row, contact your doctor before you take the next dose. Your doctor will prescribe a new titration pack and you will have to restart treatment at day 1.

Adhere to the treatment as recommended by your doctor.
Even if your health improves, do not stop taking this medicine without consulting your doctor.

If you stop taking this medicine
Do not stop taking Mayzent or change your dose without talking to your doctor first.
Mayzent will stay in your body for up to 10 days after you stop treatment. Your white blood cell (lymphocyte) count may remain low for up to 3 to 4 weeks after you stop taking Mayzent. The side effects described in this leaflet may still occur during this period (see the section 'Side effects').

If you have to restart Mayzent more than 4 days after you stopped taking it, your doctor will prescribe a new titration pack and you will have to restart treatment at day 1.
Tell your doctor straight away if you think your MS worsens after you have stopped treatment with Mayzent.

Do not take medicines in the dark! Check the label and dose <u>every time</u> you take medicine. Wear glasses if you need them.
If you have any further questions about using this medicine, consult your doctor or pharmacist.

4. <u>Side effects</u>
Like with all medicines, using Mayzent may cause side effects in some users. Do not be alarmed by this list of side effects; you may not experience any of them.

Some side effects could be serious
Common side effects (affect 1-10 in 100 users):
- rash with small fluid-filled blisters, appearing on reddened skin (symptoms of a viral infection called herpes zoster that can be severe)
- a type of skin cancer called basal cell carcinoma (BCC) which often appears as a pearly nodule, though it can also take other forms
- fever, sore throat and/or mouth ulcers due to infection (lymphopenia [reduced number of lymphocytes in your blood])
- convulsions, fits
- visual disturbances such as a shadow or a blind spot in the center of vision, blurred vision, problems seeing colors or details (symptoms of macular edema, which is a swelling in the macular area of the retina at the back of the eye)
- irregular heartbeat (atrioventricular block)
- slow heartbeat (bradycardia)

Uncommon side effects (affect 1-10 in 1,000 users):
- a type of skin cancer called squamous cell carcinoma which may present as a firm red nodule, a sore with a crust, or a new sore on an existing scar

If you get any of these side effects, **tell your doctor straight away**.

Side effects of unknown frequency (the frequency of these effects has not been established yet)
- cryptococcal infections (a type of fungal infection), including cryptococcal meningitis with symptoms such as headache together with stiff neck, sensitivity to light, nausea or confusion

Additional side effects
Additional side effects include those listed below. If any of these side effects become severe**, tell your doctor or pharmacist**.

Very common side effects (affect more than 1 in 10 users)
- headache
- high blood pressure (hypertension), sometimes with symptoms such as headache and dizziness
- blood test results showing increased liver enzyme levels

Common side effects (affect 1-10 in 100 users):
- new moles
- dizziness
- involuntary shaking of the body (tremor)
- diarrhea
- nausea
- pain in hands or feet
- swollen hands, ankles, legs or feet (peripheral edema)
- weakness, exhaustion
- lung function test results showing decreased function

If you experience any side effect, if any side effect gets worse, or if you experience a side effect not mentioned in this leaflet, consult your doctor.

You can report side effects to the Ministry of Health by following the link 'Reporting Side Effects of Drug Treatment' on the Ministry of Health home page (www.health.gov.il) which links to an online form for reporting side effects. You can also use this link: https://sideeffects.health.gov.il.

5. How to store the medicine?

Prevent poisoning! To prevent poisoning, keep this, and all other medicines, in a closed place, out of the reach and sight of children and/or infants. Do not induce vomiting unless explicitly instructed to do so by a doctor.

Do not use the medicine after the expiry date (exp. date) which is stated on the package. The expiry date refers to the last day of that month.

Storage conditions:
Store below 25°C. Do not use this medicine if you notice that the pack is damaged or shows signs of tampering.
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Additional information

In addition to the active ingredient, this medicine also contains:

Mayzent 0.25 mg and 2 mg tablet core:
lactose monohydrate, cellulose microcrystalline/microcrystalline cellulose, crospovidone (type A), glycerol dibehenate/glyceryl behenate, silica colloidal anhydrous/colloidal silica dixide.

Mayzent 0.25 mg tablet coating:
polyvinyl alcohol-part hydrolyzed, titanium dioxide (E171), talc, lecithin (soya) (E322), xanthan gum, iron oxide red (E172), black iron oxide (E172).

Mayzent 2 mg tablet coating:
polyvinyl alcohol-part hydrolyzed, titanium dioxide (E171), talc, lecithin (soya) (E322), xanthan gum, iron oxide yellow (E172), iron oxide red (E172).

What the medicine looks like and contents of the pack

Mayzent 0.25 mg - pale red, round, bevel-edged film-coated tablets with no score line and with the company logo on one side and "T" on the other side.

Mayzent 0.25 mg film-coated tablets are available in the following packages:

- Titration pack (as wallet) containing 12 tablets
- Pack of 120 tablets

Mayzent 2 mg - pale yellow, round, bevel-edged film-coated tablets with no score line and with the company logo on one side and "II" on the other side.

Mayzent 2 mg film-coated tablets are available in packs of 28 tablets.

Registration holder and importer name and address:
Novartis Israel Ltd., P.O.B 7126, Tel Aviv.

Revised in September 2022 according to MOH guidelines.

Registration number of the medicine in the Ministry of Health's National Drug Registry:

Mayzent 0.25 mg: 165-54-36195

Mayzent 2 mg: 165-55-36196