NOVARTIS

KIENDRA® 0.25 MG

KIENDRA® 2 MG

siponimod

PATIENT INFORMATION LEAFLET

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NOVARTIS

SCHEDULING STATUS: **S4**

PRODUCT NAME:

KIENDRA® 0.25 mg film-coated tablets

Contains sugar: 62,2 mg lactose (as monohydrate) per tablet.

KIENDRA® 2 mg film-coated tablets

Contains sugar: 60,3 mg lactose (as monohydrate) per tablet.

Siponimod

Read all of this leaflet carefully before you start taking KIENDRA

- **Keep this leaflet. You may need to read it again.**
- **If you have any further questions, please ask your doctor pharmacist, nurse or other health care providers.**
- **KIENDRA has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours.**

What is in this leaflet

1. What KIENDRA is and what it is used for

2. What you need to know before you take KIENDRA

3. How to take KIENDRA

4. Possible side effects

5. How to store KIENDRA

6. Contents of the pack and other information

1. WHAT KIENDRA IS AND WHAT IT IS USED FOR

KIENDRA contains an active substance called siponimod which belongs to a group of medicines called sphingosine-1-phosphate (S1P) receptor modulators. KIENDRA is used for the treatment of adult patients with secondary progressive multiple sclerosis.

How KIENDRA works

Siponimod binds selectively on two out of five receptors for a mediator substance called sphingosine-1-phosphate (S1P) that occurs naturally in the body, namely S1P1 and S1P5. Siponimod can affect the ability of some white blood cells to move freely within the body and in this, alter the way the body's immune system works. KIENDRA can stop the cells that cause inflammation from reaching the brain and can help to fight against attacks of the immune system. This reduces nerve damage caused by multiple sclerosis (MS).

If you have any questions about how KIENDRA works or why this medicine has been prescribed for you, ask your doctor, your pharmacist or your health care provider.

2. WHAT YOU NEED TO KNOW BEFORE YOU TAKE KIENDRA

Do not take KIENDRA:

- If you are hypersensitive (allergic) to siponimod or any of the other ingredients of KIENDRA listed in this leaflet.
- If you have the CYP2C9 *3*3 genotype.
- If you plan to receive a vaccine. You should not receive certain types of vaccines (called "live attenuated vaccines") during treatment with KIENDRA and up to 4 weeks after stopping treatment.

- If you have active or latent tuberculosis.
- If you have HIV with a CD4 count below 400 cells per mL.
- If you have severe active infection at start of treatment.
- If you have macular oedema.
- If you have an abnormally slow heart rate.
- If you have heart block (abnormal heartbeat) and you do not have a pacemaker.
- If, in the last 6 months, you have had a heart attack, angina, stroke or certain types of heart failure.
- If you are using medicines such as beta-blockers, digoxin or amiodarone and your heart rate has not yet stabilised.
- If you are being treated with anti-neoplastic, immune-modulating or immunosuppressive medicines.
- If you have uncontrolled seizures or epilepsy.
- If you are pregnant or breast-feeding.

Warnings and precautions:

Take special care with KIENDRA:

- Before initiation of treatment with KIENDRA your doctor will determine your genotype for the natural enzyme cytochrome P450 2C9 (CYP2C9), which exists in different variants.
- If you have the CYP2C9 *3*3 genotype (affecting less than 0.4 to 0.5 % of the population), you should not take KIENDRA.
- Before you start taking KIENDRA, you will have a blood test to check your white blood cells and to check your liver function unless your doctor has the results of a recent blood test.

- **if you have an infection.** Any infection that you already have may get worse. Infections could be serious and sometimes life-threatening.

- **if you have a lowered immune response** (due to a disease or medicines that suppress the immune system, see “Taking other medicines”). You may get infections more easily or an infection you already have may get worse. KIENDRA lowers the white blood cell count (particularly the lymphocyte count). White blood cells fight infection. While you are taking KIENDRA (and for up to 3 to 4 weeks after you stop taking it), you may get infections more easily.

- **if you have no history of chickenpox or have not been vaccinated against varicella zoster virus.** Your doctor will test your status of the antibody against this virus and may decide to vaccinate you if you do not have antibodies to this virus. In this case, you will start KIENDRA treatment one month after the full course of the vaccination is completed.

- **if you plan to receive a vaccine**. You should not receive certain types of vaccines (called “live attenuated vaccines”) during treatment with KIENDRA and for up to 4 weeks after stopping treatment with KIENDRA (see “Taking other medicines”). For the other vaccines, they can be less effective, and your doctor may want you to temporarily stop KIENDRA.

- **if you have or have had visual disturbances or other signs of swelling in the central vision area at the back of the eye (a condition known as macular oedema) if you have or have had inflammation or infection of the eye (uveitis) or diabetes.** Your doctor may want you to undergo an eye examination before you start KIENDRA and at regular intervals after the start of KIENDRA treatment. The macula is a small area of the retina at the back of the eye which enables you to see shapes, colors, and details clearly and sharply (central vision). KIENDRA may cause swelling in the macular and it usually happens during the first 3 to 4 months of KIENDRA treatment. Your chance of developing macular oedema is higher if you have diabetes or have had an inflammation of the eye called uveitis. Macular oedema can cause some of the same vision symptoms as an MS attack (optic neuritis). Be sure to tell your doctor about any changes in your vision. Your doctor may want you to undergo an eye examination 3 to 4 months after starting KIENDRA and later if the center of

your vision becomes blurred or has shadows, if you develop a blind spot in the center of your vision, or if you have problems seeing colors or fine detail.

- **if you have an irregular or abnormal heartbeat, if you have a severe heart disease, if you have uncontrolled high blood pressure, if you have a history of stroke or other diseases related to blood vessels in the brain, if when you sleep you are severely affected by interruptions of breathing** (sleep apnoea that is not treated), **if you are at risk for, or if you have heart rhythm disturbances** (called abnormal ECG heart tracing). Your doctor may decide not to use KIENDRA if you have or have had one of these conditions or may refer you first to a cardiologist.

- **if you are taking medicines for an irregular heartbeat** such as quinidine, procainamide, amiodarone or sotalol, your doctor may decide not to use KIENDRA (see “Taking other medicines”).

- **if you suffer from a slow heart rate**, **if at the start of treatment with KIENDRA you are taking medicines that slow your heart rate or if you have a history of sudden loss of consciousness (fainting).** Your doctor may decide not to use KIENDRA or may refer you first to a cardiologist to switch your treatment to medicines that do not slow your heart rate.

- At the beginning of treatment, KIENDRA can cause the heart rate to slow down. It cannot be excluded that KIENDRA can also cause indirectly an irregular heartbeat, during the titration phase (first 6 days of treatment when the dose is gradually increased). Slow heart rate usually returns to normal within 10 days after treatment initiation. Irregular heartbeat usually returns to normal in less than one day. If your heart rate slows down during the titration phase, you may not feel anything or you may feel dizzy or tired.

- **if you have liver problems.** KIENDRA may affect your liver function. You will probably not notice any symptoms but if you notice yellowing of your skin or the whites of your eyes, abnormally dark urine or unexplained nausea, vomiting and tiredness during your treatment, tell your doctor straight away. Your doctor may carry out blood tests to check your liver function and may consider stopping KIENDRA treatment if your liver problem is serious.

- **if you have high blood pressure.** Your blood pressure will need to be checked regularly.

Tell your doctor straight away, if you get any of the following symptoms or diseases **during your treatment** with KIENDRA, because it could be serious:

- if you believe your MS is getting worse (e.g. weakness or visual changes) or if you notice any new or unusual symptoms, because these may be the symptoms of a rare brain disorder caused by infection and called **progressive multifocal leukoencephalopathy** (PML).

- if you have fever, feel like you have a flu, or have a headache accompanied by stiff neck, sensitivity to light, nausea, and/or confusion as these may be symptoms of **meningitis** and/or encephalitis caused by a viral or fungal infection (such as cryptococcal meningitis).

- a type of skin cancer called basal cell carcinoma (BCC) and other cutaneous neoplasms such as squamous cell carcinoma or malignant melanoma, have been reported in MS patients treated with KIENDRA. Your doctor will carry out regular skin examinations during your treatment with KIENDRA.

  Symptoms of BCC may include skin nodules (e.g. shiny pearly nodules), patches or open sores that do not heal within weeks. Symptoms of other cutaneous neoplasms may include abnormal growth or changes of skin tissue (e.g. unusual moles) which may present as a change in color, shape or size over time.

  Long-term exposure to the sun and a weak immune system can affect the risk of developing BCC or other cutaneous neoplasms. You should limit your exposure to the sun and UV rays by wearing appropriate protective clothing and regularly applying sunscreen with a high degree of UV protection. Phototherapy with UV radiation or PUVA photochemotherapy should be avoided during KIENDRA treatment (it may increase your risk of developing skin cancer).

- if you have symptoms such as sudden onset of severe headache, confusion, seizures and vision changes, a condition called **posterior reversible encephalopathy syndrome** (PRES).

Tell your doctor straight away, if you get any of the following symptoms or diseases **after you have stopped your treatment** with KIENDRA because it could be serious:

- if you believe your MS is getting worse.

Children and adolescents (below 18 years)

KIENDRA has not been studied in patients below 18 years.

Older people (65 years or above)

You can use KIENDRA if you are aged 65 years or over at the same dose as younger adults.

Other medicines and KIENDRA

Always tell your health care provider if you are taking any other medicine. (This includes all complementary or traditional medicines).

- Medicines for an irregular heartbeat such as, quinidine, procainamide, amiodarone or sotalol. Your doctor may decide not to use KIENDRA if you take these medicines due to a possible added effect on irregular heartbeat.
- Medicines that slow down heartbeat such as verapamil or diltiazem (called calcium channel blockers), ivabradine or digoxin. Your doctor may decide to refer you to a cardiologist to change your medicines due to a possible added effect on slowing down heartbeat during the first days you start KIENDRA. For medicines such as atenolol or propranolol (called beta-blockers), if your heart rate at rest is above 50 beats per minute, your doctor will ask you to start treatment with KIENDRA without stopping your beta-blocker treatment. However, if your heart rate at rest is below 50 beats per minute, your doctor may ask you to stop your beta-blocker treatment first for the heart rate to

return above 50, then to start treatment with KIENDRA. In this case, it is only after you have reached the usual daily dose of KIENDRA that your doctor will ask you to restart your beta-blocker treatment.

- Medicines that suppress or modulate the immune system including other medicines used to treat MS such as beta-interferon, glatiramer acetate, natalizumab, mitoxantrone, dimethyl fumarate, teriflunomide, alemtuzumab or corticosteroids due to a possible added effect on the immune system.
- Vaccines. If you need to receive a vaccine, seek your doctor's advice first. During treatment and for up to 4 weeks after stopping treatment with KIENDRA, administration of some vaccines containing live virus (live attenuated vaccines) may result in infection. Other vaccines (non-live attenuated vaccines) may be less effective if administered while taking KIENDRA and your doctor may want you to temporarily stop KIENDRA (See Warnings and Precautions - Vaccines).

- If you have the CYP2C9 *1*3 or *2*3 genotype, treatment with medicines such as modafinil (moderate cytochrome P450 3A4 inducers) can lower the level of KIENDRA in your blood. Your doctor may give you further instruction or change your other medicines.

- If you have the CYP2C9 *2*2 genotype, treatment with medicines such as fluconazole (moderate CYP2C9 inhibitors or moderate CYP3A4 inhibitors) can increase the level of KIENDRA in your blood. Your doctor may give you further instruction, decide to reduce your daily dose to 1 mg KIENDRA or change your other medicines.
- Fluconazole and certain other medicines can increase the levels of siponimod (KIENDRA) in the blood and are not recommended to be taken in combination with KIENDRA. Your doctor will advise you on this.

- Carbamazepine and certain other medicines can lower the levels of siponimod (KIENDRA) 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 siponimod (KIENDRA) 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.

Tell your doctor or a pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Taking KIENDRA with food

You can take KIENDRA with or without food.

Pregnancy, breastfeeding and fertility

You should not take KIENDRA if you are pregnant or are planning to become pregnant. KIENDRA may cause harm to your baby.
Your doctor will discuss with you the potential risks of taking KIENDRA during pregnancy.

Breastfeeding

You should not breast-feed while you are taking KIENDRA. KIENDRA can pass into breast milk and there is a risk of serious side effects for a breast-fed baby. Talk with your doctor before breast-feeding while you take KIENDRA.

Females of child-bearing potential

You should avoid becoming pregnant while taking KIENDRA and for at least 10 days after you stop taking it. KIENDRA may harm your unborn baby. Female patients who might become pregnant should use effective birth control methods during treatment and for at least 10 days after stopping KIENDRA. Ask your doctor about options of effective birth control. See also above “Tell your doctor straight away...after you have stopped your treatment with KIENDRA ...”

If you become **pregnant or think you are pregnant, tell your doctor right away. You and your doctor will decide what is best for you and your baby.**

Driving and using machines

Your doctor will tell you whether your illness allows you to drive vehicles and use machines safely. KIENDRA is not expected to affect your ability to drive and use machines when you are on your regular treatment dose. At the start of treatment, you may occasionally feel dizzy. On your first day of treatment with KIENDRA, therefore, you should not drive or use machines.

KIENDRA contains lactose

KIENDRA contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking KIENDRA.

3. HOW TO TAKE KIENDRA

Do not share medicines prescribed for you with any other person.

Always take KIENDRA exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will tell you how long your treatment with KIENDRA will last. Do not stop treatment early. If you have the impression that the effect of KIENDRA is too strong or too weak, tell your doctor or pharmacist.

How much KIENDRA to take:

Treatment initiation with a starter pack:

Titration	Titration dose	Titration regimen
Day 1	0.25 mg	1 tablet of 0.25 mg KIENDRA
Day 2	0.25 mg	1 tablet of 0.25 mg KIENDRA
Day 3	0.5 mg	2 tablets of 0.25 mg KIENDRA
Day 4	0.75 mg	3 tablets of 0.25 mg KIENDRA
Day 5	1.25 mg	5 tablets of 0.25 mg KIENDRA

On day 6 switch to your prescribed treatment dose.

During the first 6 days of treatment the recommended daily dose should be taken once daily in the morning with or without food. If you missed a dose on one day during the first 6 days of treatment, the treatment should be re-started with a new starter pack.

The usual daily dose after the titration phase is 2 mg (one tablet of 2 mg siponimod).

For some patients that have a CYP2C9 *2*3 or CYP2C9 *1*3 genotype the usual daily dose is 1 mg once daily. The same treatment initiation schedule (with a starter pack) applies as well for these patients.

When to take KIENDRA

Taking KIENDRA at the same time each day will help you to remember when to take your medicine.

How to take KIENDRA

Take KIENDRA once a day, with half a glass of water. You can take KIENDRA with or without food.

How long to take KIENDRA

Continue taking KIENDRA every day for as long as your doctor tells you.

This is a long-term treatment, possibly lasting for months or years. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.

If you have questions about how long to take KIENDRA, talk to your doctor or your pharmacist or health care provider.

If you take more KIENDRA than you should.

If you have taken too much KIENDRA at one time, or if you have taken a first dose of KIENDRA by mistake, contact your doctor right away.

Your doctor may decide to observe you with heart rate and blood pressure measurements, to run electrocardiograms (ECGs) and he may decide to monitor you overnight.

If you forget to take KIENDRA

If you missed a dose on one day during the first 6 days of treatment, call your doctor before you take the next dose. Your doctor will need to prescribe a new starter pack. You will have to restart at Day 1 with a new starter pack.

Subsequently if you miss a dose, take it as soon as you remember, and then take the next tablet as usual (see also below: “If you stop taking KIENDRA”).

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 tablet. Instead, wait until it is time for your next tablet.

If you stop taking KIENDRA

Do not stop taking KIENDRA or change your dose without talking with your doctor.

If you stop taking KIENDRA for 4 or more consecutive daily doses, treatment has to be re-started with the starter pack.

After KIENDRA treatment is stopped, symptoms of MS can return and may become worse compared to before or during treatment. Tell your doctor if you have worsening of MS symptoms after stopping KIENDRA.

If you are a woman, see “Pregnancy and breast-feeding”.

KIENDRA will stay in your body for up to 10 days after you stop taking it. Your white blood cell count (lymphocyte count) may also remain low during this time and for up to 3 to 4 weeks and the side effects described in this leaflet may still occur.

4. POSSIBLE SIDE EFFECTS

KIENDRA can have side effects. Not all side effects reported for KIENDRA are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking KIENDRA, please consult your health care provider for advice.

Some side effects could be serious. If you experience any of these side effects, **stop taking the medicine and tell your doctor immediately or go to the casualty department at your nearest hospital:**

- Rash of small fluid-filled blisters, appearing on reddened skin, signs of viral infection that can be potentially severe (herpes zoster).

A type of skin cancer called basal cell carcinoma (BCC) which often appears as a pearly nodule, though it can also appear in other forms.

- A type of skin cancer called malignant melanoma which usually develops from an unusual mole. Possible signs of melanoma include moles which may change size, shape, elevation or colour over time, or new moles. The moles may itch, bleed or ulcerate.
- Fever, sore throat or mouth ulcers due to infections (lymphopenia).
- Convulsion, fits (seizures).
- Shadows or blind spot in the center of the vision, blurred vision, problems seeing colours or details (signs of swelling in the macular area of the retina at the back of the eye: macular oedema).
- Irregular heartbeat (atrioventricular block).
- Slow heartbeat (bradycardia).
- A rare brain infection called progressive multifocal leukoencephalopathy (PML). The symptoms of PML may be similar to MS (such as weakness or visual changes, memory loss, trouble thinking or difficulty walking).
- Cryptococcal infections (a type of fungal infection), or viral infections (caused by herpes or varicella zoster virus), including meningitis and/or encephalitis with symptoms such as headache accompanied by stiff neck, sensitivity, sensitivity to light, nausea and/or confusion.
- A type of skin cancer called squamous cell carcinoma which may appear as a firm red nodule, a sore with a crust, or a new sore on an existing scar.

These are all serious side effects. You may need urgent medical attention.

Tell your doctor if you notice any of the following

These side effects are frequent

- Headache.

- High blood pressure with sometimes signs such as headache and dizziness (hypertension).
- Abnormal liver function test results that give information about the health of the liver (liver function test increased): high level of an enzyme called alanine aminotransferase (ALT), high level of an enzyme called gamma-glutamyltransferase (GGT), high level of aspartate aminotransferase (AST).
- Moles or nevi that appear recently: small (less than 1 cm in diameter) macules papules or nodules of unified borders and colors ranging from blue/dark to brown, pink to skin colored (melanocytic naevus).
- Dizziness.
- Involuntary shaking of the body (tremor).
- Diarrhoea.
- Nausea.
- Pain in extremity.
- Swollen hands, ankles, legs or feet (oedema peripheral).
- Weakness (asthenia).
- Decreased results for the tests of lung function (pulmonary function test decreased).

If you notice any other side effects not mentioned in this leaflet, please inform your doctor or pharmacist.

Reporting of side effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X

SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website. By reporting side effects, you can help provide more information on the safety of KIENDRA.

5. HOW TO STORE KIENDRA

- Store all medicines out of reach of children.
- Store in a refrigerator between 2 ˚C to 8 ˚C before dispensing. Do not freeze. After dispensing: store below 25 °C for up to 3 months.
- Store in the original package.

6. CONTENTS OF THE PACK AND OTHER INFORMATION

The active substance(s) of KIENDRA is siponimod (as siponimod fumaric acid).

KIENDRA 0,25 mg film-coated tablet contains 0.278 mg siponimod fumaric acid equivalent to 0,25 mg siponimod.

KIENDRA 2 mg film-coated tablet contains 2.224 siponimod fumaric acid equivalent to 2 mg siponimod.

The other ingredients (excipients) of KIENDRA are:

- Tablet core

  Lactose monohydrate, microcrystalline cellulose, crospovidone, glyceryl dibehenate and silica, colloidal anhydrous.
  Each 0.25 mg tablet contains 62.2 mg lactose monohydrate.
  Each 2 mg tablet contains 60.3 mg lactose monohydrate.

- Tablet coating

  Polyvinyl alcohol, titanium dioxide, iron oxide, talc, lecithin, xanthan gum.

KIENDRA 0,25 mg film-coated tablets in blisters composed of PA/AL/PVC-AL blister packs. Pack sizes: 12 or 120 tablets per pack KIENDRA 2 mg film-coated tablets in blisters composed of PA/AL/PVC-AL blister packs. Pack sizes: 28 tablets per pack.

IDENTIFICATION OF KIENDRA

KIENDRA 0.25 mg: Pale red, round, biconvex, bevelled-edged film-coated tablet with Novartis logo on one side and T on other side.

KIENDRA 2 mg: Pale yellow, round, biconvex, bevelled-edged film-coated tablet with Novartis logo on one side and II on other side.

HOLDER OF CERTIFICATE OF REGISTRATION

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REGISTRATION NUMBER

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