SIPOMID® F. C. TABLET

SIPOMID®
SIPONIMOD

SIPOMID® (SIPONIMOD) F. C. TABLET FOR ORAL USE
Read this patient information carefully before you start taking Sipomid® because it answers some common questions about Sipomid®. This medication is prescribed for your current condition, therefore do not use it in similar cases and do not recommend it to others.
To report SUSPECTED ADVERSE REACTIONS, contact Noavaran Daroui Kimia Co. at +982166433514 or send email to medical@kimia-pharma.co
Read this patient information carefully before you start taking Sipomid® because it contains important information for you. This leaflet does not take the place of talking with your healthcare provider about your medical condition or treatment.

Composition
Each film coated tablet Sipomid® 0.25 mg contains: Siponimod (as fumaric acid) 0.25 mg.
Each film coated tablet Sipomid® 1 mg contains: Siponimod (as fumaric acid) 1 mg.
Each film coated tablet Sipomid® 2 mg contains: Siponimod (as fumaric acid) 2 mg.

Mechanism of action
Siponimod is an sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds with high affinity to S1P receptors 1 and 5.

Pharmacokinetic
Absorption
The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after oral administration was about 4 hours. The absolute oral bioavailability is approximately 84%.
Distribution
Sipomid® distributes to body tissues with a moderate mean volume of distribution of 124 L. Sipomid® readily crosses the blood-brain-barrier. Protein binding of Sipomid® is greater than 99.9% .
Metabolism
Sipomid® is extensively metabolized, mainly via CYP2C9 (79.3%), followed by CYP3A4 (18.5%).
Excretion
The apparent elimination half-life is approximately 30 hours. Sipomid® is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion.

Indication
Sipomid® is a sphingosine 1-phosphate (S1P) receptor modulator indicated 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.

It is not known if Sipomid® is safe and effective in children.

Dosage and Administration
- Assessments are required prior to initiating Sipomid®.
- Titration is required for treatment initiation.
- The recommended maintenance dosage is 2 mg.
- The recommended maintenance dosage in patients with a CYP2C9*1/*3 or *2/*3 genotype is 1 mg.
- First-dose monitoring is recommended for patients with sinus bradycardia, first- or second-degree [Mobitz type I] atrioventricular (AV) block, or a history of myocardial infarction or heart failure.

Side effects / Adverse reactions
It should be noted that these side effects do not occur in all patients. These are not all the possible side effects of Sipomid®. For more information, ask your healthcare provider or pharmacist.

Sipomid® may cause serious side effects including:

- **increased blood pressure.**
- **liver problems.** Your healthcare provider should do blood tests to check your liver before you start taking Sipomid®. Call your healthcare provider right away if you have any of the following symptoms of liver problems:
  - o nausea
  - o loss of appetite
  - o vomiting
  - o stomach pain
  - o dark urine
  - o tiredness
  - o your skin or the whites of your eyes turn yellow
- **breathing problems.** Call your healthcare provider right away if you have new or worsening breathing problems including shortness of breath.
- **swelling and narrowing of the blood vessels in your brain.** Symptoms of PRES (Posterior Reversible Encephalopathy Syndrome) usually get better when you stop taking Sipomid®. However, if left untreated, it may lead to a stroke. Call your healthcare provider right away if you have any of the following symptoms:
  - o sudden severe headache
  - o sudden loss of vision or other changes in your vision
  - o sudden confusion
  - o seizure
- **severe worsening of multiple sclerosis after stopping Sipomid®.** When Sipomid® 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 Sipomid® for any reason. Tell your healthcare provider if you have worsening symptoms of MS after stopping Sipomid®.
- **types of skin cancer called basal cell carcinoma (BCC), melanoma, and squamous cell carcinoma.** Tell your doctor if you have any changes in the appearance of your skin, including changes in a mole, a new darkened area on your skin, a sore that does not heal, or growths on your skin, such as a bump that may be shiny, pearly white, skincolored, or pink. Your doctor should check your skin for any changes during treatment with Sipomid®. Limit the amount of time you spend in sunlight and ultraviolet (UV) light. Wear protective clothing and use a sunscreen with a high sun protection factor.
- **slow heart rate (bradycardia or bradyarrhythmia) when you start taking Sipomid®.** You should have a test to check the electrical activity of your heart called an electrocardiogram (ECG) before you take your first dose of Sipomid®.
  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 Sipomid®, you need to restart the updosing. Call your healthcare provider if you miss a dose of Sipomid®.
- **infections.** Sipomid® can increase your risk of serious infections that can be life-threatening and cause death. Your healthcare provider should review a recent blood test of your white blood cells before you start taking Sipomid®. Call your healthcare provider right away if you have any of these symptoms of an infection during treatment with Sipomid® and for 3 to 4 weeks after your last dose of Sipomid®:
  - o fever
  - o vomiting
  - o tiredness
  - o body aches
  - o nausea
  - o chills
  - o 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)

- **macular edema.** Macular edema can cause some of the same vision symptoms as a multiple sclerosis (MS) attack (optic neuritis). If macular edema happens, it usually starts in the first 1 to 4 months after you start taking Sipomid®. Your risk of macular edema is higher if you have diabetes or have had an inflammation of your eye called uveitis. Call your healthcare provider right away if you have any of the following:
  - o blurriness or shadows in the center of your vision
  - o sensitivity to light
  - o a blind spot in the center of your vision
  - o unusually colored (tinted) vision

Tell your healthcare provider if you have any side effects that bother you or that do not go away.

The most common side effects

The most common side effects (incidence greater than 10%) in people who take Sipomid® include:
- o headache
- o high blood pressure (hypertension)
- o abnormal liver tests

Drug interactions
- **Vaccination:** During and for up to one month after discontinuation of treatment with Sipomid®, vaccinations may be less effective. Avoid live attenuated vaccines during and for up to 4 weeks after discontinuation of treatment with Sipomid®.
- **CYP2C9 and CYP3A4 Inhibitors:** Increase in Sipomid® exposure; concomitant use of Sipomid® with moderate CYP2C9 **and** moderate or strong CYP3A4 inhibitors is not recommended (e.g., fluconazole as a moderate CYP2C9/CYP3A4 dual inhibitor).
  Caution should be exercised for concomitant use of Sipomid® with moderate CYP2C9 inhibitors.
- **CYP2C9 and CYP3A4 Inducers:** Decrease in Sipomid® exposure; concomitant use of Sipomid® with moderate CYP2C9 **and** strong CYP3A4 inducers is not recommended for all patients (e.g., rifampin or carbamazepine as a moderate CYP2C9/strong CYP3A4 dual inducer). Caution should be exercised for concomitant use of Sipomid® with moderate CYP2C9 inducers.
- **Anti-arrhythmic medicinal products, QT-prolonging medicinal products, medicinal products that may decrease heart rate:** During treatment initiation, Sipomid® should not be concomitantly used in patients receiving class Ia (e.g. quinidine, procainamide) or class III (e.g. amiodarone, sotalol) anti-arrhythmic medicinal products, QT-prolonging medicinal products with known arrhythmogenic properties, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem) or other substances that may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate.
- **Beta blockers:** Caution should be exercised when Sipomid® is initiated in patients receiving beta blockers due to the additive effects on lowering heart rate. Beta-blocker treatment can be initiated in patients receiving stable doses of Sipomid®.
- **Anti-Neoplastic, Immune-Modulating, or Immunosuppressive Therapies:** Caution should be used during concomitant administration because of the risk of additive immune effects during such therapy and in the weeks following administration. Because of the characteristics and duration of alemtuzumab immune suppressive effects, initiating treatment with Sipomid® after alemtuzumab is not recommended. Sipomid® can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Warnings
Before taking Sipomid®, tell your healthcare provider about all of your medical conditions, including if you:
- have an irregular or abnormal heartbeat
- a history of stroke or other diseases related to blood vessels in the brain
- breathing problems, including during your sleep
- a fever or infection, or have a disease or taking medicines that lower your immune system. Tell your healthcare provider if you have had chickenpox or have received the vaccine for chickenpox. Your healthcare provider may do a blood test for chickenpox virus. You may need to get the full course of vaccine for chickenpox and then wait 1 month before you start taking Sipomid®.
- have slow heart rate
- have liver problems
- have diabetes
- have eye problems, especially an inflammation of the eye called uveitis
- had or now have a type of skin cancer called basal cell carcinoma (BCC), melanoma, or squamous cell carcinoma
- have high blood pressure
- are pregnant or plan to become pregnant. Sipomid® may harm your unborn baby.
- are breastfeeding or plan to breastfeed.

Do not take Sipomid® if you:
- have a CYP2C9*3/*3 genotype. Before starting treatment with Sipomid®, your CYP2C9 genotype should be determined by your healthcare provider.
- 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.

Tell your healthcare provider about all the medicines you take, including prescription medicines and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your healthcare 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.
- have recently received a live vaccine. You should avoid receiving **live** vaccines during treatment with Sipomid®. Sipomid® 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 Sipomid®.

Missed dose
- If you miss 1 dose (for more than 24 hours) or more doses of Sipomid® **during** the initial dose titration, you need to restart the medication with Day 1 of the titration regimen.
- If you miss a dose of Sipomid® **after** the initial dose-titration, take it as soon as you remember.
- If Sipomid® treatment is stopped for 4 days in a row **during** maintenance treatment, treatment has to be restarted with the titration.

Overdose
In the event of an overdosage, stop Sipomid®, call your healthcare provider or go to the nearest hospital emergency room right away.

Pregnancy and lactation
Sipomid® may harm your unborn baby. Talk to your healthcare provider right away if you become pregnant while taking Sipomid® or if you become pregnant within 10 days after you stop taking Sipomid®.
If you are a woman who can become pregnant, you should use effective birth control during your treatment with Sipomid® and for at least 10 days after you stop taking Sipomid®.
It is not known if Sipomid® passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you take Sipomid®.

Patient information
- The daily maintenance dose of Sipomid® is either 1 mg or 2 mg, depending on your CYP2C9 genotype. Ask your healthcare provider if you are not sure about your daily maintenance dose.
- Do not split, crush, or chew Sipomid® tablets; take tablets whole.
- Start your treatment with Sipomid® using the following titration schedule with your starter pack:

For the 1 mg daily maintenance dose :	Tablets a day
Day 1	1 × 0.25 mg tablet
Day 2	1 × 0.25 mg tablet
Day 3	2 × 0.25 mg tablet
Day 4	3 × 0.25 mg tablet
Day 5 and every day after	1 × 1 mg tablet

For the 2 mg daily maintenance dose:	Tablets a day
Day 1	1 × 0.25 mg tablet
Day 2	1 × 0.25 mg tablet
Day 3	2 × 0.25 mg tablet
Day 4	3 × 0.25 mg tablet
Day 5	5 × 0.25 mg tablet
Day 6 and every day after	1 × 2 mg tablet

- Take Sipomid® exactly as your healthcare provider tells you. Do not change your dose unless your healthcare provider tells you to.
- Take Sipomid® 1 time each day.
- Take Sipomid® with or without food.
- **Do not stop taking Sipomid® without talking with your healthcare provider first.**
- If you are allergic to peanut or soy products, do not use this medicine.

Storage
Unopened Containers
Sipomid® 0.25 mg, 1 mg, and 2 mg tablets may be stored at room temperature between 20°C to 25°C for up to 3 months. If you need to store Sipomid® tablets for more than 3 months, containers should remain unopened and stored in a refrigerator between (2°C to 8°C) until use.

Opened Containers
Sipomid® 0.25 mg, 1 mg, and 2 mg tablets may be stored at room temperature between 20°C to 25°C for up to 1 month. Do not refrigerate after opening.
Store in original container.

Keep Sipomid® and all medicines out of the reach of children.
Keep in the original container. Keep the desiccant in the bottle.

Packaging
Sipomid® 0.25 mg: Bottle of 7 and 12 F. C. Tablets as Starter Packs.
Sipomid® 1 mg: Bottle of 30 F. C. Tablets.
Sipomid® 2 mg: Bottle of 30 F. C. Tablets.

MANUFACTURED BY:
Noavaran Daroui Kimia Co., Tehran, Iran.
Telefax: +982166437014
www.kimia-pharma.co

References
https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/209884s007lbl.pdf
BNF 81 (British National Formulary) March 2021
https://www.ema.europa.eu/en/documents/product-information/mayzent-epar-product-information_en.pdf