# Sclemod®

## Fingolimod

**FORMS AND PRESENTATION**

Sclemod®: Capsules: Box of 28.

**COMPOSITION**

Sclemod®: Each capsule contains Fingolimod Hydrochloride eq. to Fingolimod 0.5mg.

Excipients: calcium hydrogen phosphate dihydrate, croscarmellose sodium, hydroxypropylcellulose, magnesium stearate, gelatin, titanium dioxide, yellow iron oxide.

**PHARMACOLOGICAL PROPERTIES**

***Pharmacodynamic properties***

Pharmacotherapeutic group: Immunosuppressants, selective immunosuppressants, ATC code: L04AA27.

Mechanism of action

Fingolimod is a sphingosine 1-phosphate receptor modulator. Fingolimod is metabolised by sphingosine kinase to the active metabolite fingolimod phosphate. Fingolimod phosphate binds at low nanomolar concentrations to sphingosine 1-phosphate (S1P) receptor 1 located on lymphocytes, and readily crosses the blood-brain barrier to bind to S1P receptor 1 located on neural cells in the central nervous system (CNS). By acting as a functional antagonist of S1P receptors on lymphocytes, fingolimod phosphate blocks the capacity of lymphocytes to egress from lymph nodes, causing a redistribution, rather than depletion, of lymphocytes. Animal studies have shown that this redistribution reduces the infiltration of pathogenic lymphocytes, including pro-inflammatory Th17 cells, into the CNS, where they would be involved in nerve inflammation and nervous tissue damage. Animal studies and in vitro experiments indicate that fingolimod may also act via interaction with S1P receptors on neural cells.

***Pharmacokinetic properties***

The pharmacologically active metabolite responsible for efficacy is fingolimod phosphate.

Absorption

Fingolimod absorption is slow (tmax of 12-16 hours) and extensive (≥85%). The apparent absolute oral bioavailability is 93% (95% confidence interval: 79-111%). Steady-state-blood concentrations are reached within 1 to 2 months following once-daily administration and steady-state levels are approximately 10-fold greater than with the initial dose.

Distribution

Fingolimod highly distributes in red blood cells, with the fraction in blood cells of 86%. Fingolimod phosphate has a smaller uptake in blood cells of <17%. Fingolimod and fingolimod phosphate are highly protein bound (>99%).

Fingolimod is extensively distributed to body tissues with a volume of distribution of about 1,200±260 litres.

Biotransformation

Fingolimod is transformed in humans by reversible stereoselective phosphorylation to the pharmacologically active (S)-enantiomer of fingolimod phosphate. Fingolimod is eliminated by oxidative biotransformation catalysed mainly via CYP4F2 and possibly other isoenzymes and subsequent fatty acid-like degradation to inactive metabolites. Formation of pharmacologically inactive non-polar ceramide analogues of fingolimod was also observed. The main enzyme involved in the metabolism of fingolimod is partially identified and may be either CYP4F2 or CYP3A4.

Elimination

Fingolimod blood clearance is 6.3±2.3 l/h, and the average apparent terminal half-life (t1/2) is 6-9 days. Blood levels of fingolimod and fingolimod phosphate decline in parallel in the terminal phase, leading to similar half-lives for both.

**INDICATIONS**

Sclemod® is indicated as single disease modifying therapy in highly active relapsing remitting multiple sclerosis for the following groups of adult patients and paediatric patients aged 10 years and older:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy. Or,
- Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

**CONTRAINDICATIONS**

- Immunodeficiency syndrome.
- Patients with increased risk for opportunistic infections, including immunocompromised patients (including those currently receiving immunosuppressive therapies or those immunocompromised by prior therapies).
- Severe active infections, active chronic infections (hepatitis, tuberculosis).
- Active malignancies.
- Severe liver impairment (Child-Pugh class C).
- Patients who in the previous 6 months had myocardial infarction (MI), unstable angina pectoris, stroke/transient ischaemic attack (TIA), decompensated heart failure (requiring inpatient treatment), or New York Heart Association (NYHA) class III/IV heart failure.
- Patients with severe cardiac arrhythmias requiring anti-arrhythmic treatment with class Ia or class III anti-arrhythmic medicinal products.
- Patients with second-degree Mobitz type II atrioventricular (AV) block or third-degree AV block, or sick-sinus syndrome, if they do not wear a pacemaker.
- Patients with a baseline QTc interval ≥ 500 msec.
- Hypersensitivity to the active substance or to any of the excipients listed.

**PRECAUTIONS**

Bradyarrhythmia

Initiation of fingolimod treatment results in a transient decrease in heart rate and may also be associated with atrioventricular conduction delays, including the occurrence of isolated reports of transient, spontaneously resolving complete AV block.

After the first dose, the decline in heart rate starts within one hour, and is maximal within 6 hours. This post-dose effect persists over the following days, although usually to a milder extent, and usually abates over the next weeks. With continued administration, the average heart rate returns towards baseline within one month. However individual patients may not return to baseline heart rate by the end of the first month. If necessary, the decrease in heart rate induced by fingolimod can be reversed by parenteral doses of atropine or isoprenaline.

All patients should be monitored for a period of 6 hours for signs and symptoms of bradycardia with hourly heart rate and blood pressure measurement. Continuous (real time) ECG monitoring during this 6 hour period is recommended.

The effects on heart rate and atrioventricular conduction may recur on re-introduction of fingolimod treatment depending on duration of the interruption and time since start of fingolimod treatment. The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:

- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

Due to the risk of serious rhythm disturbances or significant bradycardia, Fingolimod should not be used in patients with sino-atrial heart block, a history of symptomatic bradycardia, recurrent syncope or cardiac arrest, or in patients with significant QT prolongation (QTc>470 msec [adult female], QTc >460 msec [paediatric female] or >450 msec [adult and paediatric male]), uncontrolled hypertension or severe sleep apnoea.

Experience with fingolimod is limited in patients receiving concurrent therapy with beta blockers, heart-rate-lowering calcium channel blockers (such as verapamil or diltiazem), or other substances which may decrease heart rate (e.g. ivabradine, digoxin, anticholinesteratic agents or pilocarpine). Since the initiation of fingolimod treatment is also associated with slowing of the heart rate, concomitant use of these substances during fingolimod initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate treatment with fingolimod should not be initiated in patients who are concurrently treated with these substances.

QT interval

In a thorough QT interval study of doses of 1.25 or 2.5 mg fingolimod at steady-state, when a negative chronotropic effect of fingolimod was still present, fingolimod treatment resulted in a prolongation of QTcI, with the upper limit of the 90% CI ≤13.0 ms. There is no dose- or exposure-response relationship of fingolimod and QTcI prolongation. There is no consistent signal of increased incidence of QTcI outliers, either absolute or change from baseline, associated with fingolimod treatment.

Medicinal products that may prolong QTc interval are best avoided in patients with relevant risk factors, for example, hypokalaemia or congenital QT prolongation.

Immunosuppressive effects

Fingolimod has an immunosuppressive effect that predisposes patients to an infection risk, including opportunistic infections that can be fatal, and increases the risk of developing lymphomas and other malignancies, particularly those of the skin. Physicians should carefully monitor patients, especially those with concurrent conditions or known factors, such as previous immunosuppressive therapy. If this risk is suspected, discontinuation of treatment should be considered by the physician on a case-by-case basis.

Infections

Before initiating treatment with fingolimod, a recent complete blood count (CBC) (i.e. within 6 months or after discontinuation of prior therapy) should be available. Assessments of CBC are also recommended periodically during treatment, at month 3 and at least yearly thereafter, and in case of signs of infection.

Absolute lymphocyte count <0.2x10^9/l, if confirmed, should lead to treatment interruption until recovery, because in clinical studies, fingolimod treatment was interrupted in patients with absolute lymphocyte count <0.2x10^9/l.

Initiation of treatment with fingolimod should be delayed in patients with severe active infection until resolution.

Patients need to be assessed for their immunity to varicella (chickenpox) prior to fingolimod treatment. It is recommended that patients without a health care professional confirmed history of chickenpox or documentation of a full course of vaccination with varicella vaccine undergo antibody testing to varicella zoster virus (VZV) before initiating fingolimod therapy. A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with fingolimod. Initiation of treatment with fingolimod should be postponed for 1 month to allow full effect of vaccination to occur.

The immune system effects of fingolimod may increase the risk of infections, including opportunistic infections. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. During treatment, patients receiving fingolimod should be instructed to report promptly symptoms of infection to their physician.

Suspension of fingolimod should be considered if a patient develops a serious infection and consideration of benefit-risk should be undertaken prior to re-initiation of therapy.

Cases of cryptococcal meningitis (a fungal infection), sometimes fatal, have been reported in the post-marketing setting after approximately 2-3 years of treatment, although an exact relationship with the duration of treatment is unknown. If cryptococcal meningitis is diagnosed, fingolimod should be suspended and appropriate treatment should be initiated.

Progressive multifocal leukoencephalopathy (PML) has been reported under fingolimod treatment since marketing authorization. Additional PML cases have occurred in patients who had been treated previously with natalizumab, which has a known association with PML. PML can only occur in the presence of a JCV infection. Before initiating treatment with fingolimod, a baseline MRI should be available (usually within 3 months) as a reference. During routine MRI (in accordance with national and local recommendations), physicians should pay attention to PML suggestive lesions. MRI may be considered as part of increased vigilance in patients considered at increased risk of PML. If PML is suspected, MRI should be performed immediately for diagnostic purposes and treatment with fingolimod should be suspended until PML has been excluded.

Human papilloma virus (HPV) infection, including papilloma, dysplasia, warts and HPV-related cancer, has been reported under treatment with fingolimod in the post-marketing setting. Cancer screening, including Pap test, is recommended as per standard of care.

Elimination of fingolimod following discontinuation of therapy may take up to two months and vigilance for infection should therefore be continued throughout this period. Patients should be instructed to report symptoms of infection up to 2 months after discontinuation of fingolimod.

Macular oedema

Macular oedema with or without visual symptoms has been reported in 0.5% of patients treated with fingolimod 0.5 mg, occurring predominantly in the first 3-4 months of therapy. An ophthalmological evaluation is therefore recommended at 3-4 months after treatment initiation

It is recommended that multiple sclerosis patients with diabetes mellitus or a history of uveitis undergo an ophthalmological evaluation prior to initiating therapy and have follow-up evaluations while receiving therapy.

It is recommended that fingolimod be discontinued if a patient develops macular oedema.

Liver function

Increased hepatic enzymes, in particular alanine aminotransaminase (ALT) but also gamma glutamyltransferase (GGT) and aspartate transaminase (AST) have been reported in multiple sclerosis patients treated with fingolimod.

Fingolimod has not been studied in patients with severe pre-existing hepatic injury (Child-Pugh class C) and should not be used in these patients.

Due to the immunosuppressive properties of fingolimod, initiation of treatment should be delayed in patients with active viral hepatitis until resolution.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine, should have liver enzymes checked and fingolimod should be discontinued if significant liver injury is confirmed. Caution in the use of fingolimod should be exercised in patients with a history of significant liver disease.

Interference with serological testing

Since fingolimod reduces blood lymphocyte counts via re-distribution in secondary lymphoid organs, peripheral blood lymphocyte counts cannot be utilised to evaluate the lymphocyte subset status of a patient treated with Fingolimod. Laboratory tests involving the use of circulating mononuclear cells require larger blood volumes due to reduction in the number of circulating lymphocytes.

Blood pressure effects

Blood pressure should be regularly monitored during treatment with fingolimod.

Respiratory effects

Fingolimod should be used with caution in patients with severe respiratory disease, pulmonary fibrosis and chronic obstructive pulmonary disease.

Posterior reversible encephalopathy syndrome

Rare cases of posterior reversible encephalopathy syndrome (PRES) have been reported at the 0.5 mg dose in clinical trials and in the post-marketing setting. If PRES is suspected, fingolimod should be discontinued.

Prior treatment with immunosuppressive or immunomodulatory therapies

When switching patients from another disease modifying therapy to fingolimod, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the

same time minimizing the risk of disease reactivation. A CBC is recommended prior to initiating fingolimod to ensure that immune effects of the previous therapy (i.e. cytopenia) have resolved.
Fingolimod can generally be started immediately after discontinuation of interferon or glatiramer acetate.
For dimethyl fumarate, the washout period should be sufficient for CBC to recover before treatment with fingolimod is started.
Due to the long half-life of natalizumab, elimination usually takes up to 2-3 months following discontinuation. Teriflunomide is also eliminated slowly from the plasma. Without an accelerated elimination procedure, clearance of teriflunomide from plasma can take from several months up to 2 years. An accelerated elimination procedure as defined in the teriflunomide summary of product characteristics is recommended or alternatively washout period should not be shorter than 3.5 months. Caution regarding potential concomitant immune effects is required when switching patients from natalizumab or teriflunomide to fingolimod.
Initiating treatment with fingolimod after alemtuzumab is not recommended unless the benefits of such treatment clearly outweigh the risks for the individual patient.
A decision to use prolonged concomitant treatment with corticosteroids should be taken after careful consideration.

Co-administration with potent CYP450 inducers

The combination of fingolimod with potent CYP450 inducers should be used with caution. Concomitant administration with St John's wort is not recommended.

Cutaneous neoplasms

Basal cell carcinoma (BCC) and other cutaneous neoplasms, including malignant melanoma, squamous cell carcinoma, Kaposi's sarcoma and Merkel cell carcinoma, have been reported in patients receiving fingolimod. Vigilance for skin lesions is warranted and a medical evaluation of the skin is recommended at initiation, and then every 6 to 12 months taking into consideration clinical judgement. The patient should be referred to a dermatologist in case suspicious lesions are detected.
Patients treated with fingolimod should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B-radiation or PUVA-photochemotherapy.

Tumefactive lesions

Rare cases of tumefactive lesions associated with MS relapse were reported in the post-marketing setting. Discontinuation of fingolimod should be considered by the physician on a case-by-case basis taking into account individual benefits and risks.

Return of disease activity (rebound)

In the post-marketing setting, severe exacerbation of disease has been observed rarely in some patients stopping fingolimod.

Stopping therapy

If a decision is made to stop treatment with fingolimod a 6 week interval without therapy is needed, based on half-life, to clear fingolimod from the circulation. Lymphocyte counts progressively return to normal range within 1-2 months of stopping therapy in most patients although full recovery can take significantly longer in some patients. Starting other therapies during this interval will result in concomitant exposure to fingolimod. Use of immunosuppressants soon after the discontinuation of fingolimod may lead to an additive effect on the immune system and caution is therefore indicated.
Caution is also indicated when stopping fingolimod therapy due to the risk of a rebound. If discontinuation of fingolimod is deemed necessary, patients should be monitored during this time for relevant signs of a possible rebound.

Paediatric population

The safety profile in paediatric patients is similar to that in adults and the warnings and precautions for adults therefore also apply to paediatric patients.
In particular, the following should be noted when prescribing fingolimod to paediatric patients:
- Precautions should be followed at the time of the first dose. The same precautions as for the first dose are recommended when patients are switched from the 0.25 mg to the 0.5 mg daily dose.
- In the controlled paediatric trial D2311, cases of seizures, anxiety, depressed mood and depression have been reported with a higher incidence in patients treated with fingolimod compared to patients treated with interferon beta-1a. Caution is required in this subgroup population.
- Mild isolated bilirubin increases have been noted in paediatric patients on fingolimod.
- It is recommended that paediatric patients complete all immunisations in accordance with current immunisation guidelines before starting fingolimod therapy.
- There are very limited data available in children between 10–12 years old, less than 40 kg or at Tanner stage <2. Caution is required in these subgroups due to very limited knowledge available from the clinical study.
- Long-term safety data in the paediatric population are not available.

***Effects on ability to drive and use machines***

Dizziness or drowsiness may occasionally occur when initiating therapy with Sclemod®. On initiation of Sclemod® treatment it is recommended that patients be observed for a period of 6 hours.

**PREGNANCY AND LACTATION**

Pregnancy: While on treatment, women should not become pregnant and active contraception is recommended. If a woman becomes pregnant while taking Sclemod®, discontinuation of Sclemod® is recommended.
Breast-feeding: Fingolimod is excreted in milk of treated animals during lactation. Women receiving Sclemod® should not breastfeed.

**DRUG INTERACTIONS**

Anti-neoplastic, immunomodulatory or immunosuppressive therapies

Anti-neoplastic, immunomodulatory or immunosuppressive therapies should not be co-administered due to the risk of additive immune system effects.
Caution should also be exercised when switching patients from long-acting therapies with immune effects such as natalizumab, teriflunomide or mitoxantrone.

Vaccination

During and for up to two months after treatment with Sclemod® vaccination may be less effective. The use of live attenuated vaccines may carry a risk of infections and should therefore be avoided.

Bradycardia-inducing substances

Treatment with Sclemod® should not be initiated in patients receiving beta blockers, or other substances which may decrease heart rate, such as class Ia and III antiarrhythmics, calcium channel blockers (such as verapamil or diltiazem), ivabradine, digoxin, anticholinesteratic agents or pilocarpine because of the potential additive effects on heart rate. If treatment with Sclemod® is considered in such patients, advice from a cardiologist should be sought regarding the switch to non heart-rate lowering medicinal products or appropriate monitoring for treatment initiation, at least overnight monitoring is recommended, if the heart-rate-lowering medication cannot be stopped.

Pharmacokinetic interactions of other substances on fingolimod

Caution should be exercised with substances that may inhibit CYP3A4 (protease inhibitors, azole antifungals, some macrolides such as clarithromycin or telithromycin).
Co-administration of carbamazepine 600 mg twice daily at steady-state and a single dose of fingolimod 2 mg reduced the AUC of fingolimod and its metabolite by approximately 40%. Other strong CYP3A4 enzyme inducers, for example rifampicin, phenobarbital, phenytoin, efavirenz and St. John's Wort, may reduce the AUC of fingolimod and its metabolite at least to this extent. As this could potentially impair the efficacy, their co-administration should be used with caution. Concomitant administration with St. John's Wort is however not recommended.

Pharmacokinetic interactions of fingolimod on other substances

Fingolimod is unlikely to interact with substances mainly cleared by the CYP450 enzymes or by substrates of the main transporter proteins.
Fingolimod is not expected to alter the pharmacokinetics of medicinal products that are CYP3A4 substrates.
- Infections and infestations: Influenza, Sinusitis (very common); Herpes viral infections, Bronchitis, Tinea versicolor (common); Pneumonia (uncommon); Progressive multifocal leukoencephalopathy (PML), Cryptococcal infections (not known).
-Neoplasms benign, malignant and unspecified (incl cysts and polyps): Basal cell carcinoma (common); Malignant melanoma (uncommon); Lymphoma, Squamous cell carcinoma (rare); Kaposi's sarcoma (very rare); Merkel cell carcinoma (not known).
-Blood and lymphatic system disorders: Lymphopenia Leucopenia (common); Thrombocytopenia (uncommon); Peripheral oedema (Not known).
-Immune system disorders: Hypersensitivity reactions, including rash, urticaria and angioedema upon treatment initiation (not known).
-Psychiatric disorders: Depression (common); Depressed mood (uncommon).
-Nervous system disorders: Headache (Very common); Dizziness, Migraine (common); Seizure (uncommon); Posterior reversible encephalopathy syndrome (PRES) (rare).
-Eye disorders: Vision blurred (common); Macular oedema (uncommon).
-Cardiac disorders: Bradycardia, Atrioventricular block (common); T-wave inversion (very rare).
-Vascular disorders: Hypertension (common).
-Respiratory, thoracic and mediastinal disorders: Cough (very common); Dyspnoea (common).
-Gastrointestinal disorders: Diarrhoea (Very common); Nausea (uncommon).
-Skin and subcutaneous tissue disorders: Eczema, Alopecia. Pruritus (common).
-Musculoskeletal and connective tissue disorders: Back pain (Very common); Myalgia, Arthralgia (common).
-General disorders and administration site conditions: Asthenia (common).
-Investigations: Hepatic enzyme increased (increased ALT, Gamma glutamyltransferase, Aspartate transaminase) (very common); Blood triglycerides increased (common); Neutrophil count decreased (Uncommon).

**DOSAGE AND ADMINISTRATION**

The treatment should be initiated and supervised by a physician experienced in multiple sclerosis.
In adults, the recommended dose of Sclemod® is one 0.5 mg capsule taken orally once daily.
In paediatric patients (10 years of age and above), the recommended dose is dependent on body weight:
-Paediatric patients with body weight ≤40 kg: one 0.25 mg capsule taken orally once daily.
-Paediatric patients with body weight >40 kg: one 0.5 mg capsule taken orally once daily.
Paediatric patients who start on 0.25 mg capsules and subsequently reach a stable body weight above 40 kg should be switched to 0.5 mg capsules.
When switching from a 0.25 mg to a 0.5 mg daily dose, it is recommended to repeat the same first dose monitoring as for treatment initiation.
Sclemod® can be taken with or without food.
The capsules should always be swallowed intact, without opening them.
The same first dose monitoring as for treatment initiation is recommended when treatment is interrupted for:
- 1 day or more during the first 2 weeks of treatment.
- more than 7 days during weeks 3 and 4 of treatment.
- more than 2 weeks after one month of treatment.
If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

**Special populations**

Elderly population

Sclemod® should be used with caution in patients aged 65 years and over due to insufficient data on safety and efficacy.

Renal impairment

Based on clinical pharmacology studies, no dose adjustments are needed in patients with mild to severe renal impairment.

Hepatic impairment

Sclemod® must not be used in patients with severe hepatic impairment (Child-Pugh class C). Although no dose adjustments are needed in patients with mild or moderate hepatic impairment, caution should be exercised when initiating treatment in these patients.

Paediatric population

In children aged below 10 years: No data are available.
There are very limited data available in children between 10–12 years old.

**OVERDOSAGE**

If the overdose constitutes first exposure to Sclemod®, it is important to monitor patients with a continuous (real time) ECG and hourly measurement of heart rate and blood pressure, at least during the first 6 hours. Additionally, if after 6 hours the heart rate is <45 bpm in adults, <55 bpm in paediatric patients aged 12 years and above, or <60 bpm in paediatric patients aged 10 years to below 12 years, or if the ECG at 6 hours after the first dose shows second degree or higher AV block, or if it shows a QTc interval ≥500 msec, monitoring should be extended at least for overnight and until the findings have resolved. The occurrence at any time of third degree AV block should also lead to extended monitoring including overnight monitoring.
Neither dialysis nor plasma exchange results in removal of fingolimod from the body.

**STORAGE CONDITIONS**

Store below 30°C.
Store in the original package in order to protect from moisture.
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**Benta Lyon S.A.S. Saint Genis Laval, France**
**For Benta S.A.L., Lebanon**

BPI

**Prepared by:** Jessica Saliba

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