NOVARTIS

KIENDRA® 0.25 MG

KIENDRA® 2 MG

siponimod

PROFESSIONAL INFORMATION

Document status: Final

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NOVARTIS

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

KIENDRA 0.25 mg film-coated tablets

KIENDRA 2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KIENDRA 0.25 mg film-coated tablet contains 0,278 mg siponimod fumaric acid equivalent to 0,25 mg siponimod. Contains sugar: 62,2 mg lactose (as monohydrate) per tablet.

KIENDRA 2 mg film-coated tablet contains 2,224 mg siponimod fumaric acid equivalent to 2 mg siponimod. Contains sugar: 60,3 mg lactose (as monohydrate) per tablet.

For the full list of excipients see Section 6.1

3. PHARMACEUTICAL FORM

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.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

KIENDRA is indicated for the treatment of adult patients with secondary progressive multiple sclerosis (SPMS) who have a progressive increase in disability (of at least 6 months duration) in the absence of relapses or independent of relapses.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Patient selection

Before initiation of treatment with KIENDRA the CYP2C9 genotype of the patient should be determined. KIENDRA should not be used in patients with a CYP2C9*3*3 genotype (see section 4.4 Pharmacogenomics).

For recommendations related to switching treatment from other disease modifying therapies to KIENDRA, see section 4.4 Prior treatment with immunosuppressive or immune-modulating therapies.

Treatment initiation

Treatment has to be initiated with a starter pack that lasts for 5 days (see section 5.1 Pharmacodynamic Properties). The dose titration starts with 0.25 mg once daily on day 1 and 2, followed by once daily doses of 0.5 mg on day 3 (two tablets of 0.25 mg), 0.75 mg on day 4 (three tablets of 0.25 mg), and 1.25 mg on day 5 (five tablets of 0.25 mg), to reach the maintenance dose of 2 mg* KIENDRA starting on day 6.

Table 1 Dose titration regimen to reach siponimod maintenance dosage

Titration	Titration dose	Titration regimen	Pack
Day 1	0.25 mg	1 x 0.25 mg	
Day 2	0.25 mg	1 x 0.25 mg	
Day 3	0.5 mg	2 x 0.25 mg	STARTER
Day 4	0.75 mg	3 x 0.25 mg	
Day 5	1.25 mg	5 x 0.25 mg	
Day 6	2 mg*	1 x 2 mg*	MAINTENANCE
*The recommended maintenance dose is 1 mg daily for patients with CYP2C9 *2*3 or *1*3 genotype. See "Special population – Pharmacogenomics" below.			

During the first 6 days of treatment initiation the recommended daily dose should be taken once daily in the morning with or without food.

If a titration dose is missed on one day during the first 6 days of treatment, treatment needs to be re-initiated with a new starter pack.

General target population

The recommended maintenance dose of KIENDRA is 2 mg taken once daily with or without food. For patients with a CYP2C9 *1*3 or *2*3 genotype see below (Special populations – Pharmacogenomics).

Re-initiation of maintenance therapy after treatment interruption

If KIENDRA maintenance treatment is interrupted for 4 or more consecutive daily doses, treatment has to be re-initiated with a new starter pack (see Treatment initiation above). Treatment interruptions for up to 3 missed consecutive daily doses do not require re-titration and treatment should be continued at the maintenance dose level.

Special populations

Pharmacogenomics

KIENDRA should not be used in patients with a CYP2C9*3*3 genotype (see sections 4.4 Pharmacogenomics.

The recommended maintenance dose of KIENDRA in patients with a CYP2C9 *2*3 or *1*3 genotype is 1 mg once daily (see sections 4.4). For treatment initiation in these patients the same starter pack should be used (see Treatment initiation).

Renal impairment

No KIENDRA dose adjustments are needed in patients with renal impairment.

Hepatic impairment

No KIENDRA dose adjustments are needed in patients with hepatic impairment.

Paediatric patients (below 18 years)

No studies have been performed in paediatric patients.

Elderly patients (65 years or above)

No KIENDRA dose adjustment is needed in patients aged 65 years and over.

Method of administration

KIENDRA tablets should be taken orally and swallowed whole with water, with or without food.

4.3 CONTRAINDICATIONS

- Hypersensitivity to siponimod or any of the ingredients in the KIENDRA.
- Patients with a CYP2C9*3*3 genotype, see section 4.4.
- Live attenuated bacterial or viral vaccine use while taking KIENDRA, see section 4.4.
- Active or latent tuberculosis.
- HIV patients with CD4 counts below 400 cells per mL.
- Severe active infection is a contraindication to commencing KIENDRA, see section 4.4.
- Presence of macular oedema, see section 4.4.
- Symptomatic bradycardia, see section 4.4.
- Concomitant use with beta-blockers, digoxin & amiodarone before the heart/pulse rate have been stabilised.
- Patients, who in the last 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 Class III/IV heart failure.
- KIENDRA should not be used in patients with heart block (Second degree Mobitz type II or higher AV block, sick-sinus–syndrome, or sino-atrial heart block, if they do not have a pacemaker).
- Anti-neoplastic, immune-modulating or immunosuppressive therapies, see section 4.4.
- Uncontrolled seizures or epilepsy, see section 4.4.
- Pregnancy and lactation, see section 4.6.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Infections

A core pharmacodynamic effect of KIENDRA is a dose dependent reduction of peripheral lymphocyte count to 20 to 30 % of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues.

The immune system effects of KIENDRA may increase the risk of infections.

Before initiating treatment with KIENDRA, a recent complete blood count (CBC) (i.e. within last 6 months or after discontinuation of prior therapy) should be available.

Initiation of treatment with KIENDRA should be delayed in patients with severe active infection until resolution. Because residual pharmacodynamic effects, such as lowering effects on peripheral lymphocyte count, may persist for up to 3 to 4 weeks after discontinuation of KIENDRA, vigilance for infection should be continued throughout this period (see below: Stopping KIENDRA therapy).

Patients receiving KIENDRA should be instructed to report symptoms of infections to their medical practitioner. Effective diagnostic and therapeutic strategies should be employed in patients with symptoms of infection while on therapy. Suspension of treatment with KIENDRA, should be considered if a patient develops a serious infection.

Cryptococcal meningitis (CM) has been reported during KIENDRA use. Medical practitioners should be vigilant for clinical symptoms or signs of CM. Patients with such symptoms and signs should undergo prompt diagnostic evaluation. KIENDRA treatment should be suspended until CM has been excluded. If CM is diagnosed, appropriate treatment should be initiated.

No cases of progressive multifocal leukoencephalopathy (PML) have been reported for KIENDRA, however, cases of PML have been reported for another S1P receptor modulator. Medical practitioners should be vigilant for clinical symptoms or MRI findings that may be suggestive of PML. If PML is suspected, KIENDRA treatment should be suspended until PML has been excluded.

Cases of herpes viral infection, including cases of meningitis or meningoencephalitis caused by varicella zoster virus, have been reported with KIENDRA. Patients without a health care professional confirmed history of varicella (chickenpox) or without documentation of a full course of vaccination against varicella zoster virus (VZV) should be tested for antibodies to VZV before initiating KIENDRA (see subsection Vaccination).

Cases of progressive multifocal leukoencephalopathy (PML) have been reported for S1P receptor modulators, including KIENDRA, and other therapies for MS (see section 4.8).

Initiation of treatment with KIENDRA should be delayed in patients with severe active infection (e.g. active TB and HIV patients with CD4 counts below 400 copies cells per mL) until resolution.

Anti-neoplastic, immune-modulating or immunosuppressive therapies (including corticosteroids) should be co-administered with caution due to the risk of additive immune system effects during such therapy (see section 4.4).

Vaccination

A full course of vaccination for antibody-negative patients with varicella vaccine is recommended prior to commencing treatment with KIENDRA, following which initiation of treatment with KIENDRA should be postponed for 1 month to allow the full effect of vaccination to occur (see section 4.8).

Live attenuated vaccines

The use of live attenuated vaccines should be avoided while patients are taking KIENDRA and for 4 weeks after stopping KIENDRA treatment (see section 4.5).

Non-Live attenuated vaccines

Non-live attenuated vaccines may be less effective if administered during KIENDRA treatment. The decision whether to continue or pause the treatment with KIENDRA should be based on the benefit-risk assessment of the individual patient (section 4.4 subheading “Stopping therapy” and section 4.5)

Macular oedema

Macular oedema (see section 4.8) with or without visual symptoms may occur during treatment with KIENDRA. The majority of cases occurred within the first 3 to 4 months of therapy. An ophthalmic evaluation is therefore recommended 3 to 4 months after treatment initiation. As cases of macular oedema have also occurred on longer term treatment, patients should report visual disturbances at any time while on KIENDRA therapy and an evaluation of the fundus, including the macula, is recommended.

Patients with a history of diabetes mellitus, uveitis and underlying/co-existing retinal diseases are at increased risk of macular oedema. It is recommended that patients with diabetes mellitus, uveitis or a history of retinal disorders undergo an ophthalmic evaluation prior to initiating KIENDRA therapy and have follow-up evaluations while receiving KIENDRA therapy.

Continuation of KIENDRA therapy in patients with macular oedema has not been evaluated. Patients with macular oedema should not start KIENDRA treatment and patients who develop macular oedema should stop KIENDRA.

KIENDRA therapy should not be initiated in patients with macular oedema until resolution.

Bradydysrhythmia

Heart rate

Since initiation of KIENDRA treatment results in a transient decrease in heart rate, an up-titration scheme to reach the maintenance dose of KIENDRA on day 6 is applied at treatment start (see section 4.2).

After the first titration dose, the heart rate decrease starts within an hour and the day 1 decline is maximal at approximately 3 to 4 hours. With continued up-titration, further heart rate decreases are seen on subsequent days with maximal decrease from day 1-baseline reached on day 5 to 6. The highest daily post-dose decrease in absolute hourly mean heart rate is observed on day 1 with the pulse declining on average 5 to 6 beats per minute (bpm). Post-dose declines on the following days are less pronounced. With continued dosing, heart rate starts increasing after day 6 and reaches placebo levels within 10 days after treatment initiation.

Atrioventricular Conduction

Patients who develop AV conduction problems and/or symptomatic bradycardia should be admitted to an appropriate health care facility with equipment to manage their condition. Initiation of KIENDRA treatment has been associated with atrioventricular conduction delays that follow a similar temporal pattern as the observed decrease in heart rate during dose titration. The atrioventricular conduction delays manifested in most of the cases as first-degree atrioventricular (AV) blocks (prolonged PR interval on electrocardiogram). Second-degree AV blocks, usually Mobitz type I (Wenckebach), have been observed in less than 1.7 % of patients in clinical trials at the time of treatment initiation with KIENDRA. The conduction abnormalities typically were asymptomatic, resolved within 24 hours and did not require discontinuation of KIENDRA treatment.

Treatment initiation recommendations in patients with certain preexisting cardiac conditions

As a precautionary measure, initiation of treatment in patients with:

- sinus bradycardia (heart rate (HR) <55 bpm),
- first or second-degree [Mobitz type I] atrioventricular block (AV block),
- or a history of myocardial infarction or heart failure, if not contraindicated,

is required to be done in a health care facility or institution which has cardiac monitoring facilities and resuscitation facilities. The patient should remain under observation for 6 hours or until the heart rate has stabilised. Obtaining an electrocardiogram (ECG) prior to dosing, and at the end of the observation period is recommended. Once first-dose observation is complete in these patients, ensure that they continue to titrate to the recommended maintenance dose.

Should post-dose bradydysrhythmia or conduction related symptoms occur or if ECG 6 hours post-dose show new onset second degree or higher AV block or QTc ≥ 500 msec, appropriate management should be initiated and observation should be continued until the symptoms/findings have resolved. If pharmacological treatment is required, monitoring should be continued overnight and 6-hour monitoring should be repeated after the second dose.

Due to the risk of serious cardiac rhythm disturbances, KIENDRA should not be used in patients with second-degree Mobitz type II or higher AV block, sick-sinus syndrome, or sino-atrial heart block. Since significant bradycardia may be poorly tolerated in patients with history of cardiac arrest, cerebrovascular disease, uncontrolled hypertension or severe untreated sleep apnoea, KIENDRA should not be used in these patients. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy.

Use of KIENDRA in patients with a history of recurrent syncope or symptomatic bradycardia should be based on an overall benefit-risk assessment. If treatment is considered, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring.

A thorough QT study demonstrated no significant direct QT prolonging effect of KIENDRA and KIENDRA is not associated with a dysrhythmogenic potential related to QT prolongation. Initiation of KIENDRA treatment may result in decreased heart rate and indirect prolongation of the QT interval during the titration phase. KIENDRA was not studied in patients with significant QT prolongation (QTc > 500 msec) or who were treated with QT prolonging medicines. If treatment with KIENDRA is considered in patients with pre-existing significant QT prolongation or who are treated with QT prolonging medicines with known dysrhythmogenic properties, advice from a cardiologist should be sought prior to initiation of treatment in order to determine the most appropriate monitoring strategy during treatment initiation.

KIENDRA has not been studied in patients with dysrhythmias requiring treatment with Class Ia (e.g. quinidine, procainamide) or Class III anti-dysrhythmic medicines (e.g. amiodarone, sotalol). Class Ia and Class III medicines have been associated with cases of Torsades de Pointes in patients with bradycardia. Since initiation of KIENDRA treatment results in decreased heart rate, KIENDRA should not be used concomitantly with these medicines during treatment initiation.

Experience with KIENDRA is limited in patients receiving concurrent therapy with heartrate lowering calcium channel blockers (such as verapamil or diltiazem), or other medicines that may decrease heart rate (e.g. ivabradine or digoxin). Concomitant use of these medicines during KIENDRA initiation may be associated with severe bradycardia and heart block. Because of the potential additive effect on heart rate, treatment with KIENDRA should generally not be initiated in patients who are concurrently treated with these medicines.

If concomitant treatment with KIENDRA of the above-mentioned medicines is considered during initiation of treatment with KIENDRA, advice from a cardiologist should be sought regarding the switch to non-heart rate lowering medicines or appropriate monitoring for treatment initiation.

Bradydysrhythmic effects are more pronounced when KIENDRA is added to beta-blocker therapy. For patients receiving a stable dose of beta-blocker, the resting heart rate should be considered before introducing KIENDRA treatment. If the resting heart rate is > 50 bpm under chronic beta-blocker treatment, KIENDRA can be introduced. If resting heart rate is ≤ 50 bpm, then beta-blocker treatment should be interrupted until the baseline heart rate is > 50 bpm. Treatment with KIENDRA can then be initiated and treatment with beta-blocker can be re-initiated after KIENDRA has been up-titrated to the target maintenance dose.

Missed dose during treatment initiation and re-initiation of therapy following treatment interruption

If a titration dose is missed on one day during the first 6 days of treatment or if 4 or more consecutive daily doses are missed during maintenance therapy, the same initial dose titration and monitoring recommendations should apply (see above “Treatment initiation recommendations” and section 4.2 posology and method of administration).

Liver function

Recent (i.e. within last 6 months) transaminase and bilirubin levels should be available before initiation of treatment with KIENDRA. In the phase 3 clinical study, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) three times upper limit of normal (ULN) were observed in 5.6 % of patients treated with KIENDRA 2 mg compared to 1.5% of patients receiving placebo (see section 4.8

undesirable effects). In clinical trials, KIENDRA was discontinued if the elevation exceeded a 3-fold increase and the patient showed symptoms related to hepatic function.

Patients who develop symptoms suggestive of hepatic dysfunction, such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, rash with eosinophilia or jaundice and/or dark urine during treatment, should have liver enzymes checked and KIENDRA should be discontinued if significant liver injury is confirmed.

Although there are no data to establish that patients with preexisting liver disease are at increased risk to develop elevated liver function test (LFT) values when taking KIENDRA, caution should be exercised when using KIENDRA in patients with a history of significant liver disease.

Cutaneous neoplasms

Cases of basal cell carcinoma have been reported in patients treated with KIENDRA, particularly during longer exposure (see section 4.8). Cases of other skin malignancies, including melanoma, have also been reported in patients treated with KIENDRA and in patients on another S1P modulator. Periodic skin examination is recommended for all patients, particularly those with risk factors for skin cancer and patients with suspicious skin lesions. Patients treated with KIENDRA should be cautioned against exposure to sunlight without protection. These patients should not receive concomitant phototherapy with UV-B radiation or PUVA-photochemotherapy.

Blood pressure effect

Blood pressure should be monitored during treatment with KIENDRA and managed appropriately.

Unexpected neurological or psychiatric symptoms/signs

Cases of posterior reversible encephalopathy syndrome (PRES) have been reported for sphingosine 1-phosphate (S1P) receptor modulator medicines. Should a patient on KIENDRA treatment develop any unexpected neurological or psychiatric symptoms/signs (e.g. cognitive deficits, behavioural changes, cortical visual disturbances or any other neurological cortical symptoms/signs or any symptom/sign suggestive of an increase of intracranial pressure) or accelerated neurological deterioration, the medical practitioner should promptly schedule a complete physical and neurological examination and should consider a magnetic resonance imaging (MRI).

Prior treatment with immunosuppressive or immune-modulating therapies

When switching from other disease modifying therapies, the half-life and mode of action of the other therapy must be considered to avoid an additive immune effect whilst at the same time minimising risk of disease reactivation.

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with KIENDRA after alemtuzumab is not recommended.

Pharmacogenomics

Before initiation of treatment with KIENDRA, patients should be genotyped for CYP2C9 to determine the CYP2C9 metaboliser status. Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.3 to 0.4 % of Caucasians and less in others) should not be treated with KIENDRA. Use of KIENDRA in these patients results in substantially elevated siponimod plasma levels.

The recommended maintenance dose of KIENDRA is 1 mg daily in patients with CYP2C9 *2*3 or *1*3 genotype to avoid an increased exposure to siponimod (see sections 4.2).

Stopping therapy

Severe exacerbation of disease, including disease rebound, has been reported after discontinuation of a S1P receptor modulator. The possibility of severe exacerbation of disease should be considered after stopping KIENDRA treatment.

Patients should be observed for a severe increase in disability upon KIENDRA discontinuation and appropriate treatment should be instituted, as required.

After stopping KIENDRA therapy siponimod remains in the blood for up to 10 days. Starting other therapies during this interval will result in concomitant exposure to siponimod.

Lymphocyte counts typically return to the normal range in the vast majority (90 %) of SPMS patients within 10 days of stopping therapy. However, residual pharmacodynamics effects, such as lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose. Use of immunosuppressants within this period may lead to an additive effect on the immune system and therefore caution should be applied 3 to 4 weeks after the last dose.

Excipients

The tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take KIENDRA.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Pharmacodynamic interactions

Anti-neoplastic, immune-modulating or immunosuppressive therapies

KIENDRA has not been studied in combination with anti-neoplastic, immune-modulating or immunosuppressive therapies. Caution should be used during concomitant administration due to the risk of additive immune effects during such therapy and in the weeks following stopping administration of any of these medicines (see section 4.4).

When switching from other disease modifying therapies, 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 minimising risk of disease reactivation.

Due to the characteristics and duration of alemtuzumab immune suppressive effects described in its product information, initiating treatment with KIENDRA after alemtuzumab is not recommended

KIENDRA can generally be started immediately after discontinuation of beta interferon or glatiramer acetate.

Anti-dysrhythmic medicines, QT prolonging medicines, medicines that may decrease heart rate

During treatment initiation KIENDRA should not be concomitantly used in patients receiving Class Ia (e.g. quinidine, procainamide), Class III anti-dysrhythmic medicines (e.g. amiodarone, sotalol), QT prolonging medicines with known dysrythmogenic properties, heart rate lowering calcium channel blockers (such as verapamil or diltiazem) or other medicines which may decrease heart rate (e.g. ivabradine or digoxin) because of the potential additive effects on heart rate. If treatment with KIENDRA is considered, advice from a cardiologist should be sought (see sections 4.3 and 4.4 Treatment initiation recommendations).

Beta-blockers

Caution should be applied when KIENDRA is initiated in patients receiving beta-blockers due to the additive effects on lowering heart rate (see sections 4.3 and 4.4 Treatment initiation recommendations). Beta-blocker treatment can be initiated in patients receiving stable doses of KIENDRA.

The negative chronotropic effect of co-administration of siponimod and propranolol was evaluated in a dedicated PD/safety study. The addition of propranolol on top of siponimod PK/PD steady-state had less pronounced negative chronotropic effects (less than additive) in comparison to addition of siponimod on top of propranolol PK/PD steady state (additive HR effect).

Vaccination

Live attenuated vaccines

The use of live attenuated vaccines may carry the risk of infection and should therefore be avoided during KIENDRA treatment and for up to 4 weeks after treatment with KIENDRA (see section 4.4 - Vaccination).

Non-Live attenuated vaccines

Potential effects of siponimod on the immune response/immunogenicity of selected non-live attenuated vaccines were investigated in a dedicated study with two representative vaccines, a PPV-23 vaccine (T cell-independent vaccine) and a quadrivalent influenza vaccine (T cell-dependent vaccine). The study demonstrated that concomitant KIENDRA treatment does not compromise the efficacy of a PPV-23 vaccination and therefore no KIENDRA treatment pause is necessary. The efficacy of the influenza vaccination is not compromised if KIENDRA treatment is paused 1 week prior and until 4 weeks after vaccination. Shorter treatment pause from 10 days prior to 14 days after vaccination and concomitant KIENDRA treatment showed only modest impact on influenza vaccination efficacy with responder rates approximately 15 % to 30 % lower than on placebo (see section 4.4 - Vaccination).

Pharmacokinetic interactions

Potential of other medicines to affect siponimod pharmacokinetics (PK) (siponimod as a substrate)

Siponimod is primarily metabolised by cytochrome P450 CYP2C9 (79.3 %) and to a lesser extent by CYP3A4 (18.5 %). CYP2C9 is a polymorphic enzyme and the medicine-medicine interaction effect in presence of CYP3A or CYP2C9 perpetrator medicines is predicted to be dependent on the CYP2C9 genotype.

CYP2C9 and CYP3A4 inhibitors

Caution should be applied with concomitant use of KIENDRA with drugs that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition due to a clinically relevant increase in exposure to siponimod. This concomitant drug regimen can consist of moderate CYP2C9/CYP3A4 inhibitors (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor.

KIENDRA should be used with caution in patients with CYP2C9*2*2 genotype. Dosage adjustment to 1 mg daily may be considered in these patients as an approximately 2.7-fold increase of siponimod exposure is expected.

CYP2C9 and CYP3A4 inducers

Caution should be applied with concomitant use of KIENDRA with medicine that cause moderate CYP2C9 and strong CYP3A4 induction because of a clinically relevant decrease in siponimod exposure. This concomitant drug regimen can consist of moderate CYP2C9/strong CYP3A4 dual inducers (e.g., rifampin or carbamazepine) or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer. Caution is also needed with concomitant use of KIENDRA with moderate (e.g. modafinil) or strong CYP3A4 inducers for patients with CYP2C9*1/*3 and*2/*3 genotype.

Strong CYP3A4/moderate CYP2C9 inducers (e.g. carbamazepine) and moderate CYP3A4 inducers (e.g. modafinil) are expected to significantly reduce siponimod exposure by up to 76 % and up to 51 % respectively according to clinical medicine-medicine interaction studies and in silico evaluation of the medicine interaction potential.

Potential of siponimod to affect the PK or PD of oral contraceptives

Co-administration with siponimod did not reveal clinically relevant effects on the PK and PD of the combined ethinylestradiol and levonorgestrel oral contraceptive. Therefore the efficacy of the investigated oral contraceptive was maintained under siponimod treatment. No interaction studies have been performed with oral contraceptives containing other progestogens, however an effect of siponimod on the efficacy of oral contraceptives is not expected.

Laboratory tests

Since siponimod 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 KIENDRA.

Laboratory tests requiring the use of circulating mononuclear cells require large blood volumes due to reduction in the number of circulating lymphocytes.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy

KIENDRA is contraindicated during pregnancy or for use in women of child-bearing potential, (see section 4.3).

Based on animal data and its mechanism of action KIENDRA may cause foetal harm when administered to a pregnant woman. Reproductive and developmental studies in pregnant rats and rabbits have demonstrated siponimod induced embryotoxicity and foetotoxicity in rats and rabbits and teratogenicity in rats. Increased incidences of post-implantation loss and foetal abnormalities (external, urogenital and skeletal) in rats and of embryo-foetal deaths, abortions and foetal variations (skeletal and visceral) in rabbits were observed following prenatal exposure to siponimod starting at a dose 2 times the exposure in humans at the highest recommended dose of 2 mg/day.

Pregnant women should be advised of a potential risk to the foetus if KIENDRA is used during pregnancy or if the patient becomes pregnant while taking this medicine.

The use of KIENDRA in women who have child-bearing potential should only be considered when effective contraception (methods that result in less than 1 % pregnancy rates) are being used during KIENDRA therapy and for at least ten days after stopping treatment with KIENDRA.

Breastfeeding

Women taking KIENDRA must not breastfeed their infants. See section 4.3

Animal data

In lactating rats dosed with a single oral dose of 10 mg/kg, siponimod and its metabolites passed into the milk.

Infertility

There are no data regarding the effect of KIENDRA on fertility in humans.

Siponimod had no effect on male reproductive organs in rats and monkeys or fertility parameters in rats.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

KIENDRA has no or negligible influence on the ability to drive and use machines. However, dizziness may occasionally occur when initiating therapy with KIENDRA. Therefore, patients should not drive or use machines during the first day of treatment initiation with KIENDRA (see section 4.4).

4.8 UNDESIRABLE EFFECTS

Summary of the safety profile

A total of 1,737 multiple sclerosis (MS) patients have been treated with siponimod in doses of at least 2 mg daily. These were included in study A2304, a phase 3, multicenter, randomised, double-blind, placebo-controlled study in patients with SPMS and study A2201, a phase 2, double-blind, randomised, multicenter, adaptive dose-ranging, placebo-controlled study in patients with relapsing-remitting MS (RRMS). Study A2304 randomised 1,651 SPMS patients 2:1 to receive either KIENDRA 2 mg once daily or placebo. Median treatment duration was 18 months (range 0 to 37 months). Study A2201 randomised a total of 297 RRMS patients to receive KIENDRA at once daily doses ranging from 0.25 mg to 10 mg or placebo for up to 6 months.

In study A2304 a higher percentage of siponimod than placebo patients completed the double-blinded part of the study medicine treatment (66.7 % and 59.0 %, respectively). The most common reasons for discontinuations in the siponimod and placebo groups were subject/guardian decisions (10.3 % siponimod vs. 13.0 % placebo), disease progression (9.1 % for siponimod vs. 14.8 % for placebo) and

adverse events (8.5 % siponimod vs. 5.1 % placebo). The most common adverse medicine reactions in the siponimod 2 mg group (incidence ≥ 10 %) in study A2304 were headache and hypertension.

Tabulated summary of adverse medicine reactions from clinical trials

Adverse medicine reactions from clinical trials have been defined primarily on the basis of the experience in study A2304 (Table 7-2) and are listed by MedDRA system organ class. Within each system organ class, the adverse medicine reactions are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category for each adverse medicine reaction is based on the following convention (CIOMS III): very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

Table 2.1 List of adverse reactions

Adverse medicine reactions		**Frequency category**
Infections and infestations	Herpes zoster*	common
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Melanocytic naevus*	common
	Basal cell carcinoma**	common
	Squamous cell carcinoma	uncommon
	Malignant melanoma	uncommon

Blood and lymphatic system disorders	Lymphopenia*	common
Nervous system disorders	Headache*	very common
	Dizziness	common
	Seizure*	common
	Tremor*	common
Eye disorders	Macular oedema*	common
Cardiac disorders	Bradycardia*	common
	Atrioventricular block*(1st & 2nd degree)	common
Vascular disorders	Hypertension*	very common
Gastrointestinal disorders	Nausea	common
	Diarrhoea	common
Musculoskeletal and connective tissue disorders	Pain in extremity*	common
General disorders and administration site conditions	Oedema peripheral*	common
	Asthenia	common
Investigations	Liver function test increased*	very common
	Pulmonary function test decreased*	common

^Core phase - Controlled pool

**Grouping of preferred terms (PTs) were considered for ADR frequency determination*

***Adverse drug reactions from open-label extension part of the phase 3 study A2304*

Adverse drug reactions from open-label extension part of clinical trials or from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with KIENDRA via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency which is therefore categorised as not known. Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, ADRs are presented in order of decreasing seriousness.

Table 2.2 Adverse drug reactions from open-label extension part of clinical trials or from spontaneous reports and literature (frequency not known)

Infections and infestations
Progressive multifocal leukoencephalopathy; cryptococcal meningitis; herpes viral infection including cases of meningitis or meningoencephalitis caused by varicella zoster virus (see section 4.4).

Description of selected medicine reactions

Infections

In the phase 3 clinical trial in patients with SPMS the overall rate of infections was comparable between the patients on siponimod and those on placebo (49.0 % vs. 49.1 % respectively). However, an increase in the rate of herpes zoster infections was reported on siponimod (2.5 %) compared to placebo (0.7 %).

Macular oedema

Macular oedema was more frequently reported in patients receiving siponimod (1.8 %) than placebo (0.2 %). Although the majority of cases occurred within 3 to 4 months of commencing siponimod, cases were also reported in patients treated with siponimod for more than 6 to 12 months (see section 4.4 special warnings and precautions). Some patients presented with blurred vision or decreased visual

acuity, but others were asymptomatic and diagnosed on routine ophthalmic examination. The macular oedema generally improved or resolved spontaneously after KIENDRA discontinuation. The risk of recurrence after re-challenge has not been evaluated. KIENDRA should not be restarted thereafter.

Bradydysrhthmia

Initiation of siponimod treatment results in a decrease in heart rate and may also be associated with atrio-ventricular conduction delays (see section 4.4).

Liver function tests

Increased hepatic enzymes (mostly ALT elevation) have been reported in MS patients treated with siponimod. In the phase 3 trial in patients with SPMS, liver function test increase were more frequently observed in 11.3 % of patients on siponimod than in those on placebo (3.1 %), mainly due to liver transaminase (ALT/AST/GGT) elevations. The majority of elevations occurred within 6 months of starting treatment. ALT levels returned to normal within approximately 1 month after discontinuation of siponimod (see section 4.4).

Blood pressure

Hypertension was more frequently reported in 12.6 % of patients on siponimod than on placebo (9.0 %) in the phase 3 clinical trial in patients with SPMS. Treatment with siponimod resulted in an increase of systolic and diastolic blood pressure starting early after treatment initiation, reaching maximum effect after approximately 6 months of treatment (systolic 3 mmHg, diastolic 1.2 mmHg) and staying stable thereafter. The effect persisted with continued treatment.

Seizures

Cases of seizures were reported in 1.7 % of patients treated with siponimod compared to 0.4 % on placebo in the phase 3 clinical trial in patients with SPMS. It is not known whether these events were related to the effects of MS, to siponimod, or to a combination of both.

Respiratory effects

Minor reductions in forced expiratory volume in 1 second (FEV_1) and in the diffusing capacity of the lung for carbon monoxide (DLCO) values were observed with siponimod treatment. At month 3 and month 6 of treatment in the phase 3 clinical trial in patients with SPMS, mean changes from baseline in the siponimod group were -0.1 L at each time point, with no change in the placebo group. On chronic treatment, this reduction did not translate into clinically significant adverse events and was not associated with an increase in reports of cough or dyspnoea.

Reporting of suspected adverse reactions

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.

4.9 OVERDOSE

There is no specific antidote or treatment for KIENDRA overdoses. Treatment should be supportive and symptomatic treatment.

It is important to observe for signs and symptoms of bradycardia, which should include overnight monitoring. Regular measurements of pulse rate and blood pressure are required and electrocardiograms should be performed (see sections 4.2 and 4.4). This is especially important if the

overdose constitutes first dose exposure to KIENDRA or occurs during the dose titration phase of KIENDRA.

Neither dialysis nor plasma exchange would result in meaningful removal of siponimod from the body.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Selective immunosuppressants,

ATC code: L04AE03

5.1 PHARMACODYNAMIC PROPERTIES

Siponimod is a sphingosine-1-phosphate (S1P) receptor modulator. Siponimod binds selectively on two out of five G-protein-coupled receptors (GPCRs) for S1P, namely $S1P_1$ and $S1P_5$. By acting as a functional antagonist on $S1P_1$ receptors on lymphocytes, siponimod prevents egress from lymph nodes. This reduces the recirculation of T-cells into the central nervous system (CNS) to limit central inflammation. Siponimod spares effector memory T-cells in peripheral tissues and blood and does not impair lymphocyte activation.

Siponimod readily crosses the blood brain barrier.

In animal studies direct effects have been demonstrated for siponimod on neural cells, via $S1P_1$ on astrocytes and $S1P_5$ on oligodendrocytes. In a mouse model of experimental autoimmune encephalomyelitis a direct neuroprotective effect, independent from effects on lymphocytes, was also demonstrated for siponimod applied centrally (via intracerebroventricular infusions).

Immune system

Siponimod induces a dose-dependent reduction of the peripheral blood lymphocyte count within 6 hours of the first dose, due to the reversible sequestration of lymphocytes in lymphoid tissues.

With continued daily dosing, the lymphocyte count continues to decrease, reaching a nadir median (90 % CI) lymphocyte count of approximately 0.560 (0.271 to 1.08) cells/nL in a typical CYP2C9*1*1 or *1*2, non-Japanese SPMS patient, corresponding to 20 to 30 % of baseline. Low lymphocyte counts are maintained with chronic daily dosing.

Before initiating treatment, a recent complete blood count (CBC) (i.e. within last 6 months or after discontinuation of prior therapy) should be available. Absolute lymphocyte counts <0.2 x 10^9/L, if confirmed, should lead to dose reduction to 1 mg, because in clinical studies siponimod dose was reduced in patients with absolute lymphocyte counts <0.2 x 10^9/L. Confirmed absolute lymphocyte counts <0.2 x 10^9/L in a patient already receiving siponimod 1 mg should lead to interruption of siponimod therapy until the level reaches 0.6 x 109/L when re-initiation of siponimod can be considered.

Lymphocyte counts typically return to the normal range in the vast majority (90 %) of SPMS patients within 10 days of stopping therapy. After stopping siponimod treatment residual lowering effects on peripheral lymphocyte count may persist for up to 3 to 4 weeks after the last dose.

Cardiac electrophysiology

Heart rate and rhythm

Siponimod causes a transient reduction in heart rate and atrioventricular conduction upon treatment initiation (see section 4.8). The maximum decline in heart rate is seen in the first 6 hours post-dose.

Autonomic responses of the heart, including diurnal variation of heart rate and response to physical exercise, are not affected by siponimod treatment.

A transient, dose-dependent decrease in heart rate was observed during the initial dosing phase of siponimod, that plateaued at doses ≥5 mg and bradyarrhythmic events (AV blocks and sinus pauses) were detected at a higher incidence under siponimod treatment compared to placebo.

No second degree AV blocks of Mobitz type II or higher degree were observed. Most AV blocks and sinus pauses occurred above the therapeutic dose of 2 mg with notably higher incidence under non titrated conditions compared to dose titration conditions.

The decrease in heart rate induced by siponimod can be reversed by atropine or isoprenaline.

Potential to prolong the QT interval

The effects of therapeutic (2 mg) and supratherapeutic (10 mg) doses of siponimod on cardiac repolarisation were investigated in a thorough QT study. The results did not suggest an arrhythmogenic potential related to QT prolongation with siponimod. Siponimod increased the mean placebo-corrected baseline-adjusted mean QTcF (ΔΔQTcF) by more than 5 ms with a maximum mean effect of 7.8 ms (2 mg) and 7.2 ms (10 mg), respectively at 3 h post-dose. The upper bound of the one-sided 95 % CI for the ΔΔQTcF at all time points remained below 10 ms. Categorical analysis revealed no treatment-emergent QTc values above 480 ms, no QTc increases from baseline of more than 60 ms and no corrected or uncorrected QT/QTc value exceeded 500 ms.

Pulmonary function

Siponimod treatment with single doses or multiple doses for 28 days is not associated with clinically relevant increases in airway resistance as measured by forced expiratory volume in 1 second (FEV1)

and forced expiratory flow (FEF) during expiration of 25 to 75 % of the forced vital capacity (FEF25-75). A slight trend of reduced FEV1 was detected at non-therapeutic single doses (>10 mg). Multiple doses of siponimod were associated with mild to moderate changes in FEV1 and FEF25-75 % which were not dose and daytime dependent and were not associated with any clinical signs of increased airway resistance.

Concomitant treatment of siponimod with propranolol resulted in minimal decrease of FEV1 in comparison to propranolol alone. The changes with the individual medicines or with the combination were within the physiological variability of FEV1 and not clinically significant.

Clinical studies

Study A2304 (EXPAND) in SPMS

Study A2304 was a randomised, double-blind, placebo-controlled, event and follow-up duration driven, phase 3 study in patients with SPMS who had documented evidence of progression in the prior 2 years in the absence or independent of relapses, no evidence of relapse in 3 months prior to study enrolment and with Expanded Disability Status Scale (EDSS) score of 3.0 to 6.5 at study entry.

Patients were randomised 2:1 to receive either once daily siponimod 2 mg or placebo. Evaluations were performed at screening and every 3 months and at the time of relapse. MRI evaluations were performed at screening and every 12 months.

The primary endpoint of the study was the time to 3-month confirmed disability progression (CDP) determined as at least a 1-point increase from baseline in EDSS (0.5 point increase for patients with baseline EDSS of 5.5 or more) sustained for 3 months. Key secondary endpoints were time to 3-month confirmed worsening of at least 20 % from baseline in the timed 25-foot walk test (T25FW) and change

from baseline in T2 lesion volume. Additional secondary endpoints included time to 6-month CDP, percent brain volume change, measures of inflammatory disease activity.

Study duration was variable for individual patients (median study duration was 21 months, range 1 day to 37 months).

Median age was 49.0 years, median disease duration was 16.0 years and median EDSS score was 6.0 at baseline; 63.9 % of patients had no relapses in the 2 years prior to study entry and 78 % had no gadolinium (Gd)-enhancing lesions on their baseline MRI scan; 78.3 % of patients had been previously treated with a therapy for their MS.

Time to onset of 3-month confirmed disability progression (primary endpoint) was significantly delayed for siponimod with a 21.2 % risk reduction compared to placebo (hazard ratio (HR) 0.79, p<0.0134).

The results for this study are summarised in Table 3 and Figure -1.

Table 3 Overview of results from efficacy endpoints

Efficacy Parameter	**Statistic**	**Estimate (95 % CI)**	**p-value**
Clinical			
Time to 3-month CDP (primary endpoint)	Hazard ratio (1)	0.79 (0.65,0.95)	0.0134
Time to 6-month CDP	Hazard ratio (1)	0.74 (0.60, 0.92)	0.0058
Annualized relapse rate (ARR), confirmed relapses	ARR ratio (3)	0.45 (0.34, 0.59)	<0.0001
Change from baseline in Symbol Digit Modality Test	Treatment difference (4)	1.38 (0.58, 2.18)	0.0007

Efficacy Parameter	Statistic	Estimate (95 % CI)	p-value
MRI			
Change from baseline in T2 lesion volume (mm^3)	Treatment difference (2)	-695 (-877, -513)	<0.0001
Percent brain volume change relative to baseline	Treatment difference (2)	0.15 (0.07,0.23)	0.0002
Number of Gd-enhancing T1 weighted lesions	Rate ratio (5)	0.14 (0.10, 0.19)	<0.0001
Number of new/enlarging T2 lesions	Rate ratio (6)	0.19 (0.16, 0.24)	<0.0001

All analyses are based on the full analysis set (FAS), which includes all randomised subjects who took at least one dose of study medication. p values are two-sided.

(1) Hazard ratio (siponimod/placebo), Cox proportional hazard model

(2) Treatment difference in the average over mean changes at Months 12 and 24, repeated measures model

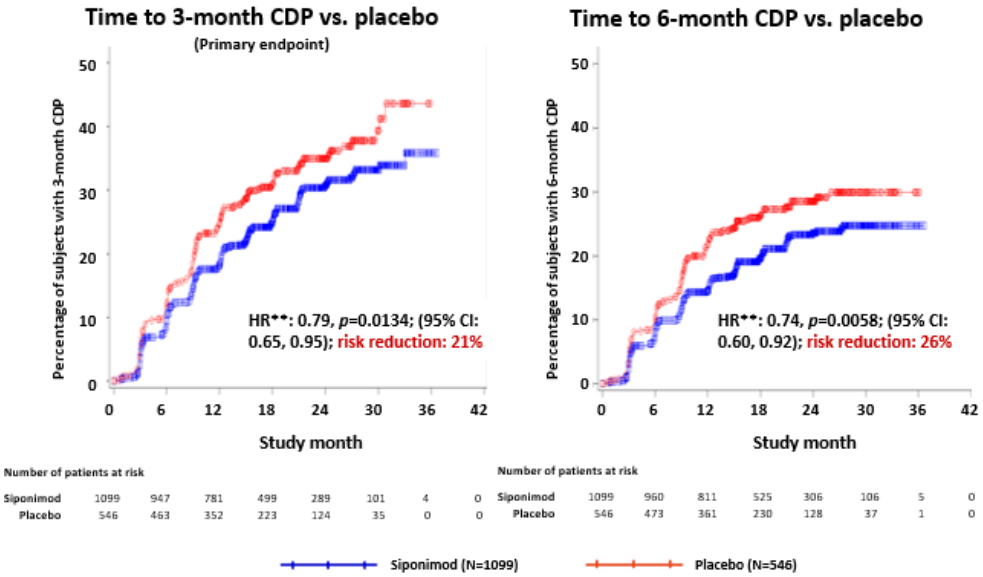
(3) ARR ratio (siponimod/placebo), negative binomial model

(4) Treatment difference in the average over all visits, repeated measures model

(5) Rate ratio (siponimod/placebo) up to and including Month 24, negative binomial model

(6) Rate ratio (siponimod/placebo) per scan, average over Months 12 and 24, negative binomial model

Figure 1 Patients with 3-month and 6-month CDP based on EDSS-Kaplan-Meier curves (FAS)



Siponimod did not significantly delay time to 3-month confirmed ≥20 % deterioration in the T25FW (a numerical 6.2 % risk reduction was observed).

Results from the study showed a consistent risk reduction in the time to 3-month CDP with siponimod in subgroups defined based on gender, age, prior multiple sclerosis therapy, pre-study relapse activity, baseline MRI disease activity and disability levels at baseline.

5.2 PHARMACOKINETICS

Absorption

The time (T_{max}) to reach maximum plasma concentrations (C_{max}) after multiple oral administration of siponimod was about 4 hours (range 2 to12 hours). Siponimod absorption is extensive (≥70 %, based on the amount of radioactivity excreted in urine and the amount of metabolites in faeces extrapolated to infinity). The absolute oral bioavailability of siponimod is approximately 84 %. For 2 mg siponimod given once daily over 10 days, a mean C_{max} of 30.4 ng/mL and mean AUC_{tau} of 558 h*ng/mL were observed on day 10. Steady state was reached after approximately 6 days of multiple once daily administration of siponimod.

Food effect

Food intake had no effect on the systemic exposure of siponimod (C_{max} and AUC). Therefore KIENDRA may be taken without regard to meals (see section 4 Dosage regimen and administration).

Distribution

Siponimod is distributed to body tissues with a moderate mean volume of distribution of 124 L. Siponimod fraction found in plasma is 68 % in humans. Animal studies show that siponimod readily crosses the blood-brain-barrier. Protein binding of siponimod is >99.9 % in healthy subjects and in hepatic and renal impaired patients.

Biotransformation/metabolism

Siponimod is extensively metabolised, mainly via CYP2C9 (79.3 %), followed by CYP3A4 (18.5 %).

The pharmacological activity of the main metabolites M3 and M17 is not expected to contribute to the clinical effect and the safety of siponimod in humans.

Elimination

An apparent systemic clearance (CL/F) of 3.11 L/h was estimated in MS patients. The apparent elimination half-life is approximately 30 hours.

Siponimod is eliminated from the systemic circulation mainly due to metabolism, and subsequent biliary/fecal excretion. Unchanged siponimod was not detected in urine.

Linearity/non-linearity

Siponimod concentration increases in an apparent dose proportional manner after multiple once daily doses of siponimod 0.3 mg to 20 mg.

Steady-state-plasma concentrations are reached after approximately 6 days of once daily dosing and steady-state levels are approximately 2 to 3-fold greater than the initial dose. An up-titration regimen is used to stepwise reach the clinical therapeutic dose of siponimod of 2 mg after 6 days and 4 additional days of dosing are required to reach the steady-state-plasma concentrations.

***In vitro* and *in vivo* evaluation of medicine interaction potential**

Siponimod (and metabolites M3, M17) as a causative medicine of interaction

In vitro investigations indicated that siponimod and its major systemic metabolites M3 and M17 do not show any clinically relevant medicine-medicine interaction potential at the therapeutic dose of 2 mg once daily for all investigated CYP enzymes and transporters, and do not necessitate clinical investigation.

Siponimod as a medicine of interaction

CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. Physiologically based pharmacokinetic modelling indicates a differential CYP2C9 genotype-dependent inhibition and induction of CYP3A4 pathways. With decreased CYP2C9 metabolic activity in the respective genotypes, a larger effect of the CYP3A4 perpetrators on siponimod exposure is anticipated.

Co-administration of siponimod with CYP2C9 and CYP3A4 inhibitors

The co-administration of fluconazole (moderate CYP2C9/CYP3A4 inhibitor) 200 mg daily at steady-state and a single dose of siponimod 4 mg in CYP2C9*1*1 healthy volunteers led to a two-fold increase in the AUC of siponimod. Mean siponimod terminal half-life was increased by 50 %.

Co-administration of siponimod with CYP2C9 and CYP3A4 inducers

Strong CYP3A4/moderate 2C9 inducers (e.g. carbamazepine) and moderate CYP3A4 inducers (e.g. modafinil) significantly reduced siponimod AUC by up to 76 % and up to 51 %, respectively, according to clinical interaction studies and in silico evaluation of the medicine interaction potential. The co-administration of siponimod 2 mg daily in the presence of 600 mg daily doses of rifampin (strong CYP3A4 and moderate CYP2C9 inducer) decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57 % and 45 %, respectively in CY2C9*1*1 subjects.

Special populations

Elderly patients (65 years or above)

Results from population pharmacokinetics suggest that dose adjustment would not be necessary in elderly patients. However, to date clinical experience in patients aged above 65 years is limited.

Gender

Gender has no influence on siponimod pharmacokinetics.

Renal impairment

No siponimod dose adjustments are needed in patients with mild, moderate or severe renal impairment. Mean siponimod half-life and C_{max} (total and unbound) were comparable between subject with severe

renal impairment and healthy subjects. Total and unbound AUCs were only slightly increased (by 23 to 33 %), compared to healthy subjects. The effects of end-stage renal disease or haemodialysis on the pharmacokinetics of siponimod has not been studied. Due to the high plasma protein binding (>99.9 %) of siponimod, haemodialysis is not expected to alter the total and unbound siponimod concentration and no dose adjustments are anticipated based on these considerations.

Hepatic impairment

No dose adjustments for siponimod are needed in patients with hepatic impairment. The unbound siponimod pharmacokinetics AUC is 15 % and 50 % higher in subjects with moderate and severe hepatic impairment, respectively, in comparison with healthy subjects for the 0.25 mg single dose studied. The mean half-life of siponimod was unchanged in hepatic impairment.

Pharmacogenomics

The CYP2C9 genotype has a significant impact on siponimod metabolism. Patients homozygous for CYP2C9*3 (CYP2C9*3*3 genotype: approximately 0.3 to 0.4 % of Caucasians and less in others) are contraindicated with siponimod (see section 4.3). Use of siponimod in these patients results in substantially elevated siponimod plasma levels. The recommended maintenance dose of siponimod is 1 mg daily in patients with CYP2C9 *2*3 or *1*3- genotype to avoid an increased exposure to siponimod (see section 4.2).

There are other less frequent occurring polymorphisms for CYP2C9. The pharmacokinetics of siponimod have not been evaluated in such subjects. Some polymorphisms such as *5, *6, *8 and *11 are associated with decreased or loss of enzyme function. It is estimated that CYP2C9 *5, *6, *8 and *11 alleles have a combined frequency of approximately 10 % in populations with African ancestry, 2 % in Latinos/Hispanics and < 0.4 % in Caucasians and Asians.

After a single dose of 0.25 mg siponimod, AUC_{inf} and AUC_{last} was approximately 2- and 4-fold higher in subjects with the CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively, while there was only a minor increase of C_{max} by 21 % and 16 %, respectively, compared to extensive metabolisers (CYP2C9*1*1). The mean half-life was prolonged in CYP2C9*2*3 and CYP2C9*3*3 carriers (51 and 126 h).

An apparent systemic clearance (CL/F) of about 3.11 L/h was estimated in CYP2C9 extensive metaboliser (CYP2C9*1*1 and CYP2C9*1*2) SPMS patients after multiple oral administrations of siponimod. CL/F is 2.5, 1.9, 1.6, and 0.9 L/h in subjects with the CYP2C9*2*2, CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively. The resultant increase in siponimod AUC was 25, 61, 91, 285 % in subjects with the CYP2C9*2*2, CYP2C9*1*3, CYP2C9*2*3 and CYP2C9*3*3 genotypes, respectively, as compared to those with the CYP2C9*1*1 genotype. As the apparent clearance estimated for subjects with the CYP2C9*1*2 genotype was comparable to that for subjects of the CYP2C9*1*1 genotype, similar siponimod exposure is expected for both genotypes.

6. LIST OF PHARMACEUTICAL PARTICULARS

6.1 EXCIPIENTS:

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.

6.3 SHELF-LIFE

36 months

6.4 SPECIAL PRECAUTIONS FOR STORAGE

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.

6.5 NATURE AND CONTENTS OF THE CONTAINER:

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.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Novartis South Africa (Pty) Ltd.

Magwa Crescent West

Waterfall City, Jukskei View

NOVARTIS

Johannesburg, 2090

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8. REGISTRATION NUMBERS:

KIENDRA® 0.25 mg: 54/34/0653

KIENDRA® 2 mg: 54/34/0654

9. DATE OF FIRST AUTHORISATION:

08 April 2021

10. DATE OF REVISION OF TEXT

05 February 2026