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Siponimod and CYP2C9

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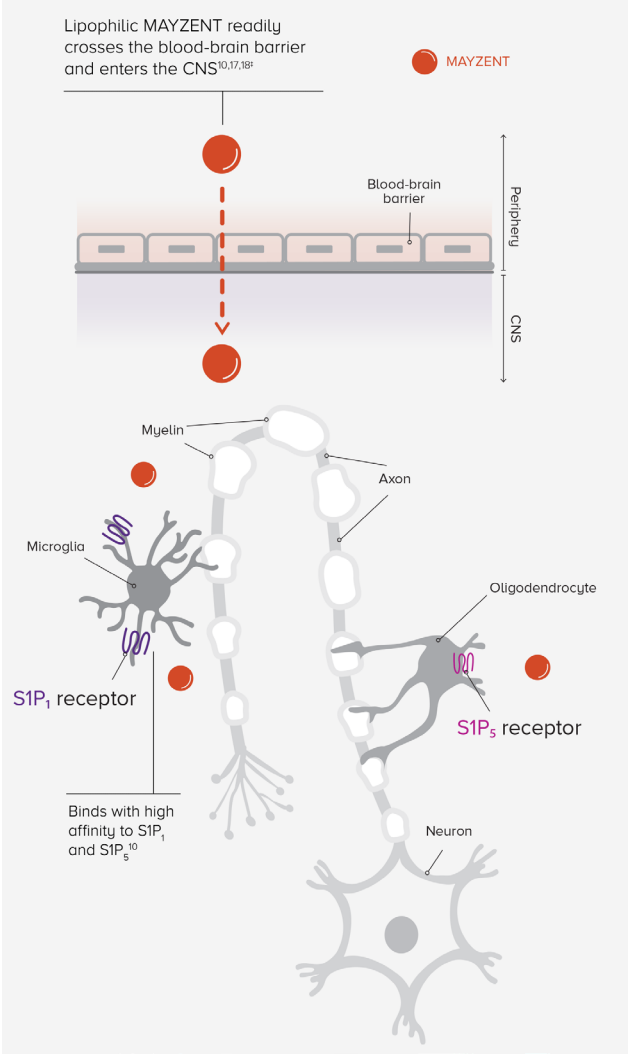
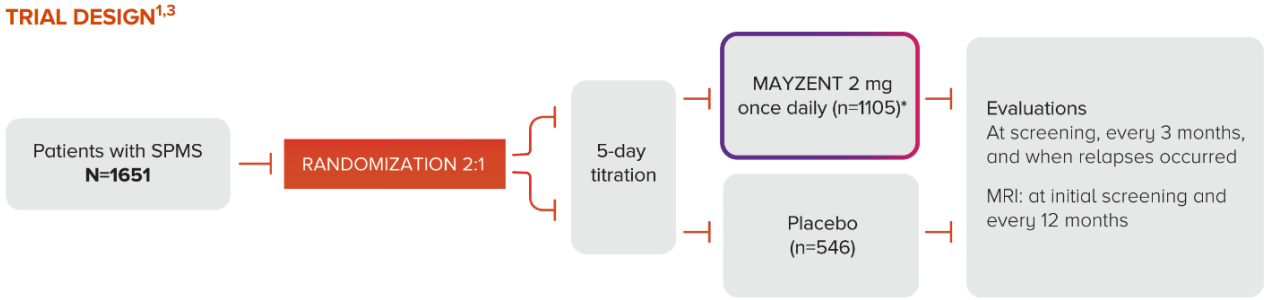
Siponimod Overview

First oral disease modifying drug available for secondary, progressive multiple sclerosis

MoA: Prevents the migration of lymphocytes to active areas of inflammation by binding to the sphingosine-1-phosphate receptor



Siponimod



Siponimod, developed by Novartis, was approved in the US in March 2019 for progressive MS

This followed a 3 year Phase 3 trial (EXPAND) of ~1,650 people which showed a significant delay to disease progression

Now also approved in Australia, Canada, UK, and Europe

5 day initiation titration to maintenance dose of 2mg orally per day

Contra-indications from the SPC

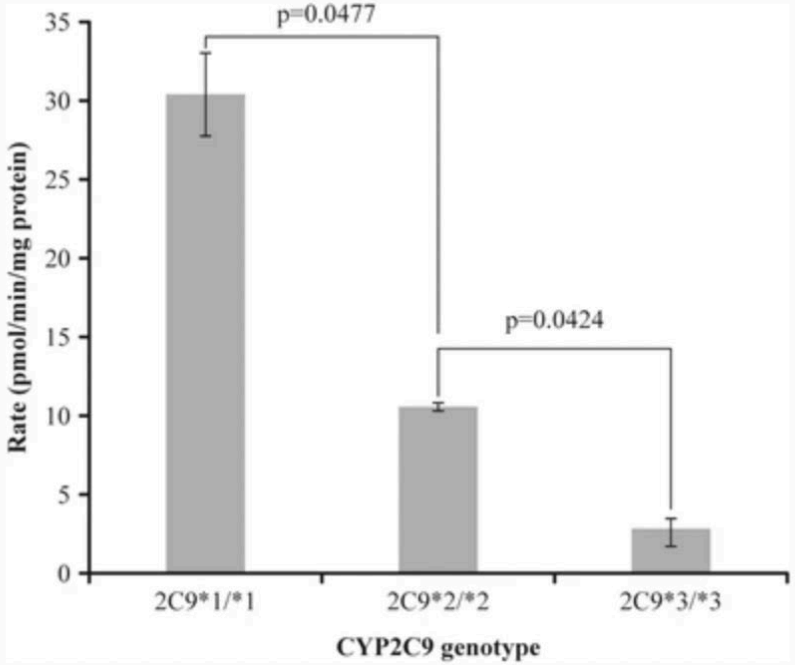
4.3 Contraindications

- Hypersensitivity to the active substance, or to peanut, soya or any of the excipients listed in section 6.1.
- Immunodeficiency syndrome.
- History of progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- Active malignancies.
- Severe liver impairment (Child-Pugh class C).
- Patients who in the previous 6 months had a 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 (see section 4.4).
- Patients with a history of second-degree Mobitz type II atrioventricular (AV) block, third-degree AV block, sino-atrial heart block or sick-sinus syndrome, if they do not wear a

- Patients homozygous for CYP2C9*3 (CYP2C9*3*3) genotype (poor metaboliser).

- During pregnancy and in women of childbearing potential not using effective contraception (see sections 4.4 and 4.6).

Siponimod Metabolism



Comparison of [^{14}C]siponimod metabolism rates in human liver microsomes

Eliminated by CYP2C9
Reduced/absent CYP2C9 activity predicted to result in high plasma levels
Increased risk of toxicity - bradyarrhythmias, hypertension, increased hepatic enzymes, increased risk of infection, nausea, headache

Yin et al. European Journal of Clinical Pharmacology 2018;74:455–464

Pharmacokinetic studies

CYP2C9 genotype	Frequency in Caucasians	Estimated CL/F (L/h)	% of CYP2C9*1*1 CL/F	% exposure increase versus CYP2C9*1*1
Extensive metabolisers				
CYP2C9*1*1	62-65	3.1-3.3	100	-
CYP2C9*1*2	20-24	3.1-3.3	99-100	-
Intermediate metabolisers				
CYP2C9*2*2	1-2	2.5-2.6	80	25
CYP2C9*1*3	9-12	1.9-2.1	62-65	61
Poor metabolisers				
CYP2C9*2*3	1.4-1.7	1.6-1.8	52-55	91
CYP2C9*3*3	0.3-0.4	0.9	26	284

Dosage Guidance based on genotype

FDA and EMEA

- *1/*1 - maintenance dose 2mg per day
- *1/*2, *2/*2 - maintenance dose 2mg per day
- *1/*3, *2/*3 - maintenance dose 1mg per day
- *3/*3 - contraindicated

PGx Guidance

PharmGKB →

	LEVEL	VARIANT	GENE	DRUGS	PHENOTYPE CATEGORIES
Details	Level 1A	CYP2C9*1, CYP2C9*2, CYP2C9*3	CYP2C9	siponimod	Metabolism/PK

FDA →

- Approval in 2019, with post-market requirements related to the genotyping

505(o)(3)(E)(ii) and could result in enforcement action.

We remind you of your postmarketing commitments:

3591-6 Establish an in-vitro diagnostic device to guide the use of siponimod in patients with relapsing forms of multiple sclerosis. The device should detect, at a minimum, the presence of the *2 and *3 alleles in cytochrome P450 2C9 (CYP2C9). The device should detect patients homozygous for the CYP2C9 *3/*3 genotype with statistical confidence.

with relapsing forms of multiple sclerosis. The device should detect, at a minimum, the presence of the *2 and *3 alleles in cytochrome P450 2C9

DPWG Guidelines

- Consistent with FDA and EMEA guidance but supplemented by:

CYP2C9 IM other[a]	siponimod	Theoretically, the risk of adverse effects in increased, as the genetic variation results in higher plasma concentrations of siponimod.	Use 50% of the normal maintenance dose. Reconsider the choice and the potential benefit of siponimod if the patient is also using a moderate CYP3A4 inducer, such as modafinil. For the comparable genetic variation *1/*3, the moderate CYP3A4 inducer results in a reduction in the exposure of siponimod by 49%, according to a pharmacokinetic model.
CYP2C9 PM other [a]	siponimod	Siponimod is contraindicated in patients with the comparable genetic variation *3/*3. Theoretically, the risk of adverse effects is greatly increased, as the genetic variation results in much higher plasma concentrations of siponimod.	Avoid siponimod.

So what are the outstanding challenges?

MS is more common in Black than White individuals
Also often associated with more severe disease - therefore siponimod a relevant therapeutic choice

CYP2C9 variant allele frequencies differ among different populations

CYP2C9 Allele	Black Allele Frequency	Americas Allele Frequency	Middle Eastern Allele Frequency	White (European + North American) Allele Frequency	East Asian Allele Frequency
*1	86.70	88.920	76.910	80.01	96.570
*2	2.30	6.625	13.211	12.60	0.064
*3	1.17	3.254	9.312	7.08	3.365
*5	1.28	0.500	0.067	0.00	0.000
*6	0.77	0.150	0.000	0.00	0.000
*8	6.66	0.338	0.500	0.14	0.000
*11	1.39	0.213	0.000	0.17	0.003

E.G. *8 is more common than *2 and *3 combined in black population

Multiple LoF and reduced function alleles not considered in prescribing advice - creating inequities
Evidence that these additional alleles are relevant metabolism of warfarin - acknowledge that substrate specific effects

Liu et al The Journal of Clinical Pharmacology 2020;60:429–431

Summary

- Should CPIC consider a guideline that considers all relevant *CYP2C9* alleles and impact on siponimod dosage?
- Is the data around CYP2C9*2/*2 robust and consistent with that for other variant alleles?