CLINICAL UPDATE

Brand Name	Mayzent®
Generic Name	siponimod fumaric acid
Drug Manufacturer	Novartis Pharmaceuticals Corporation.

Clinical Update

TYPE OF CLINICAL UPDATE

New strength

FDA APPROVAL DATE

March 01, 2022

LAUNCH DATE

March 22, 2022

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 1 - New Molecular Entity; New Drug Application (NDA): 209884

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Mayzent® is a sphingosine 1-phosphate (S1P) receptor modulator indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults.

MECHANISMS OF ACTION

Siponimod is an S1P receptor modulator. Siponimod binds with high affinity to S1P receptors 1 and 5. Siponimod blocks the capacity of lymphocytes to egress from lymph nodes, reducing the number of lymphocytes in peripheral blood. The mechanism by which siponimod exerts therapeutic effects in multiple sclerosis is unknown but may involve reduction of lymphocyte migration into the central nervous system.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 0.25 mg, 1 mg, and 2 mg

DOSE & ADMINISTRATION

Recommended Dosage in Patients with CYP2C9 Genotypes *1/*1, *1/*2, or *2/*2-

- Initiate treatment using a titration regimen. Give 0.25 mg orally once on days 1 and 2;

- 0.5 mg orally (two 0.25 mg tablets) once on day 3;
- 0.75 mg orally (three 0.25 mg tablets) once on day 4;
- 1.25 mg orally (five 0.25 mg tablets) once on day 5;
- Begin maintenance dose of 2 mg orally once daily on day 6;
- First dose monitoring is recommended in patients with bradycardia (heart rate less than 55 beats per minute), first or second degree (Mobitz type 1) AV block, or a history of myocardial infarction or heart failure. If 1 titration is missed for more than 24 hours, reinitiate with day 1 of the titration regimen. If maintenance treatment is interrupted for 4 or more consecutive days, reinitiate treatment with the titration regimen and complete first dose monitoring when needed.

Table 1 Dose Titration Regimen to Reach MAYZENT 2 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg
Day 5	1.25 mg	5 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

Recommended Dosage in Patients with CYP2C9 Genotypes *1/*3 or *2/*3-

- Initiate treatment using a titration regimen. Give 0.25 mg orally once on days 1 and 2;
- 0.5 mg orally (two 0.25 mg tablets) once on day 3;
- 0.75 mg orally (three 0.25 mg tablets) once on day 4;
- Begin maintenance dose of 1 mg orally once daily on day 5;
- First dose monitoring is recommended in patients with bradycardia (heart rate less than 55 beats per minute), first or second degree (Mobitz type 1) AV block, or a history of myocardial infarction or heart failure. If 1 titration is missed for more than 24 hours, reinitiate with day 1 of the titration regimen. If maintenance treatment is interrupted for 4 or more consecutive days, reinitiate treatment with the titration regimen and complete first dose monitoring when needed.

Table 2 Dose Titration Regimen to Reach MAYZENT 1 mg Maintenance Dosage

Titration	Titration Dose	Titration Regimen
Day 1	0.25 mg	1 x 0.25 mg
Day 2	0.25 mg	1 x 0.25 mg
Day 3	0.50 mg	2 x 0.25 mg
Day 4	0.75 mg	3 x 0.25 mg

If one titration dose is missed for more than 24 hours, treatment needs to be reinitiated with Day 1 of the titration regimen.

EFFICACY

The efficacy of Mayzent® was demonstrated in Study 1, a randomized, double-blind, parallel-group, placebo-controlled, time-to-event study in patients with secondary progressive multiple sclerosis (SPMS) who had evidence of disability progression in the prior 2 years, no evidence of relapse in 3 months prior to study enrollment, and an Expanded Disability Status Scale (EDSS) score of 3.0-6.5 at study entry (NCT 01665144).

Patients were randomized to receive either once daily Mayzent® 2 mg or placebo, beginning with a dose titration. Evaluations were performed at screening, every 3 months during the study, and at the time of a suspected 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), defined as at least a 1- point increase from baseline in EDSS (0.5-point increase for patients with baseline EDSS of 5.5 or higher) sustained for 3 months. A prespecified hierarchical analysis consisted of the primary endpoint and 2 secondary endpoints, the time to 3- month confirmed worsening of at least 20% from baseline on the timed 25-foot walk test and the change from baseline in T2 lesion volume. Additional endpoints included annualized relapse rate

(relapses/year) and MRI measures of inflammatory disease activity. Study duration was variable for individual patients (median study duration was 21 months, range 1 day to 37 months).

Table 3: Clinical and MRI Results from Study 1

	MAYZENT	PLACEBO
Clinical Outcomes		
Proportion of patients with confirmed disability progression[a]	26%	32%
Relative risk reduction	21% ($p = 0.0134$)[d]	
Absolute risk reduction	6%	
Proportion of patients with confirmed worsening in timed 25-foot walk	40%	41%
	p = NS	
Annualized relapse rate[b]	0.071	0.160
Relative reduction (%)	55% ($p < 0.01$)[c]	
Absolute reduction	0.089	
	$p < 0.01$[c]	
MRI Endpoints		
Change from baseline in T2 lesion volume (mm^3) (95% CI)[c]	184 (54; 314)	879 (712; 1047)
	$p < 0.01$[c]	

Abbreviation: MRI, magnetic resonance imaging; NS, not statistically significant.

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

[a] Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5. Progression confirmed at 3 months. Cox proportional hazard model.

[b] Defined as the average number of confirmed relapses per year (estimated from negative binomial regression model for recurrent events).

[c] Adjusted mean averaged over Months 12 and 24.

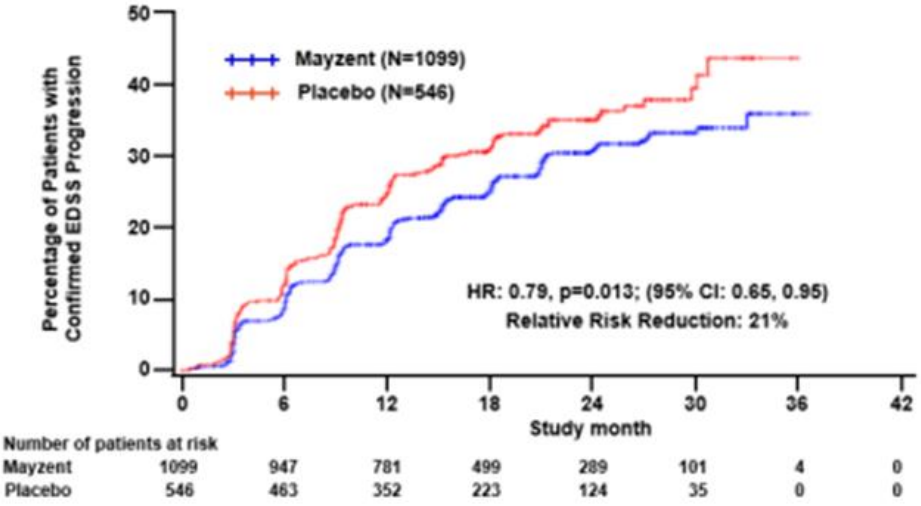
[d] Statistically significant.

[e] Nominal p value, not corrected for multiple comparisons.

Study 1 randomized 1651 patients to either Mayzent® 2 mg (N = 1105) or placebo (N = 546); 82% of Mayzent®-treated patients and 78% of placebo-treated patients completed the study. Median age was 49.0 years, 95% of patients were white, and 60% female. The median disease duration was 16.0 years, and median EDSS score at baseline was 6.0 (56% of patients had ≥ 6.0 EDSS at baseline); 36% of patients had one or more relapses in the 2 years prior to study entry; 22% of those patients with available imaging had one or more gadolinium-enhancing lesions on their baseline MRI scan; 78% of patients had been previously treated with an MS therapy.

Results are Mayzent® was superior to placebo in reducing the risk of confirmed disability progression, based on a time-to-event analysis (hazard ratio 0.79, p < 0.0134). Mayzent® did not significantly delay the time to 20% deterioration in the timed 25-foot walk, compared to placebo. Patients treated with Mayzent® had a 55% relative reduction in annualized relapse rate, compared to patients on placebo (nominal p-value < 0.0001). The absolute reduction in the annualized relapse rate was 0.089. Although Mayzent® had a significant effect on disability progression compared to placebo in patients with active SPMS (e.g., SPMS patients with an MS relapse in the 2 years prior to the study), the effect of Mayzent® in patients with non-active SPMS was not statistically significant.

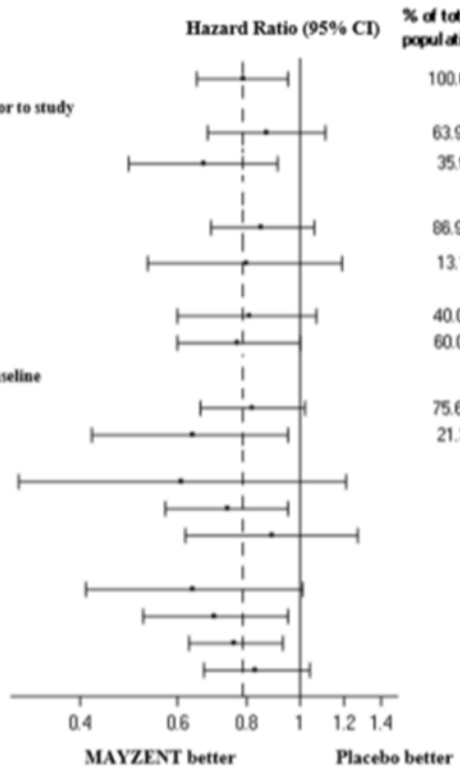
Figure 1 **Time to Confirmed Disability Progression Based on EDSS (Study 1)**



Number of patients at risk

Mayzent	1099	947	781	499	289	101	4	0
Placebo	546	463	352	223	124	35	0	0

Figure 2 **Time to Confirmed Disability Progression Based on EDSS (Study 1), Subgroup Analysis**



Subgroup	% of total population	MAYZENT n/N (%)	Placebo n/N (%)	HR (95% CI)
Overall	100.0	288/1099 (26.2)	173/546 (31.7)	0.79 (0.65, 0.95)
Superimposed relapses within 2 years prior to study				
- No	63.9	190/ 708 (26.8)	101/343 (29.4)	0.87 (0.68, 1.11)
- Yes	35.9	98/ 388 (25.3)	72/202 (35.6)	0.67 (0.49, 0.91)
Superimposed relapses during study				
- No	86.9	237/ 986 (24.0)	122/444 (27.5)	0.85 (0.69, 1.06)
- Yes	13.1	51/ 113 (45.1)	51/102 (50.0)	0.80 (0.53, 1.19)
Sex				
- Male	40.0	129/ 435 (29.7)	75/223 (33.6)	0.81 (0.60, 1.07)
- Female	60.0	159/ 664 (23.9)	98/323 (30.3)	0.77 (0.60, 1.00)
Number of Gd-enhancing T1 lesions at baseline				
- 0	75.6	219/ 828 (26.4)	128/415 (30.8)	0.82 (0.66, 1.02)
- ≥ 1	21.3	61/ 236 (25.8)	40/114 (35.1)	0.64 (0.42, 0.95)
Baseline age*				
- 20 years				0.61 (0.31, 1.21)
- 40 years				0.74 (0.57, 0.95)
- 60 years				0.89 (0.62, 1.27)
EDSS at baseline*				
- 3.0				0.64 (0.41, 1.01)
- 4.0				0.70 (0.52, 0.95)
- 5.0				0.76 (0.63, 0.93)
- 6.0				0.83 (0.67, 1.04)

*HR and 95% CI presented are model-based estimates for a range of values of age and Expanded Disability Status Scale (EDSS).