NOVARTIS

דצמבר 2025

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

הנדון:

Mayzent 0.25 mg, film-coated tablets	מייזנט 0.25 מ״ג, טבליות מצופות
Mayzent 1 mg, film-coated tablets	מייזנט 1 מ״ג, טבליות מצופות
Mayzent 2 mg, film-coated tablets	מייזנט 2 מ״ג, טבליות מצופות

אנו מבקשים להודיע על עדכון העלונים לרופא ולצרכן של התכשיר מייזנט.

התכשיר רשום בישראל להתוויה הבאה:

Mayzent is indicated for the treatment of relapsing forms of multiple sclerosis (MS), to include relapsing-remitting disease, and active secondary progressive disease, in adults.

המרכיב הפעיל: siponimod (as fumaric acid).

להלן פירוט השינויים המהותיים בלבד:

בעלון לרופא:

4.5 Interaction with other medicinal products and other forms of interaction

Potential of other medicinal products to affect siponimod pharmacokinetics

Cytochrome P450 (CYP2C9) is the major metabolising enzyme for siponimod, accounting for 79.5% of metabolism in extensive metabolisers with the CYP2C9*1*1 genotype. Residual elimination of siponimod is ascribed to various other cytochromes, each of which is responsible for a minor fraction of elimination. ~~Siponimod is metabolised primarily by cytochrome P450 2C9 (CYP2C9) (79.3%) and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%). CYP2C9 is a polymorphic enzyme and the drug-drug interaction (DDI) effect in the presence of CYP3A or CYP2C9 inhibitors or inducers is predicted to be dependent on the CYP2C9 genotype.~~

CYP2C9 ~~and CYP3A4~~ inhibitors
Concomitant use of siponimod and medicinal products that cause moderate or strong CYP2C9 inhibition is not recommended because a clinically relevant increase of siponimod exposure by 2- or 4-fold is anticipated, respectively.
~~Because of a significant increase in exposure to siponimod, concomitant use of siponimod and medicinal products that cause moderate CYP2C9 and moderate or strong CYP3A4 inhibition is not recommended. This concomitant drug regimen can consist of a moderate CYP2C9/CYP3A4 dual inhibitor (e.g. fluconazole) or a moderate CYP2C9 inhibitor in combination with a separate moderate or strong CYP3A4 inhibitor.~~

The co-administration of fluconazole (moderate CYP2C9/ CYP3A4 dual inhibitor) 200 mg daily at steady state and a single dose of siponimod 4 mg in healthy volunteers with a CYP2C9*1*1 genotype led to a 2-fold increase in the area under the curve (AUC) of siponimod. According to evaluation of the drug interaction potential using physiologically based pharmacokinetic (PBPK) modelling, a maximum of a 2.2-fold increase in the AUC ~~of siponimod~~ is predicted ~~across genotypes~~ with any type of ~~CYP3A4 and~~ moderate CYP2C9 inhibitors~~s~~ depending on the CYP2C9 genotype. ~~except for patients with a CYP2C9*2*2 genotype. In CYP2C9*2*2 patients, a 2.7-fold increase in the AUC of siponimod is expected in the presence of moderate CYP2C9/CYP3A4 inhibitors.~~

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CYP2C9 and CYP3A4 inducers

Siponimod may be combined with most types of CYP2C9 and CYP3A4 inducers. However, because of an expected reduction in siponimod exposure, the appropriateness and possible benefit of the treatment should be considered when siponimod is combined:

- with dual strong CYP3A4/moderate CYP2C9 ~~dual~~ inducers (e.g. rifampicin, carbamazepine) ~~or a moderate CYP2C9 inducer in combination with a separate strong CYP3A4 inducer~~ in all patients, regardless of genotype. Co-administration of 2 mg siponimod and 600 mg rifampicin decreased siponimod $AUC_{tau,ss}$ and $C_{max,ss}$ by 57% and 45%, respectively, in CYP2C9*1*1 subjects.
- with moderate CYP3A4 inducers (e.g. efavirenz, modafinil) ~~or strong CYP3A4 inducers in~~ for patients with a CYP2C9*1*3 or *2*3 genotype. The most pronounced reduction of siponimod exposure by 35% ($AUC_{tau,ss}$) and 39% ($C_{max,ss}$) is predicted after co-administration of 1 mg siponimod daily and 600 mg efavirenz daily in patients with CYP2C9*1*3 genotype compared to those with CYP2C9*1*1 genotype receiving their recommended dose of 2 mg siponimod without concomitant medication. No clinical data for siponimod combined with moderate CYP3A4 inducers are available.

~~A significant reduction of siponimod exposure (by up to 76% and 51%, respectively) is expected under these conditions according to evaluation of the drug interaction potential using PBPK modelling. 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.~~

5.2 Pharmacokinetic properties

Biotransformation

Siponimod is extensively metabolised, mainly by polymorphic CYP2C9 (79.5% for extensive- metaboliser CYP2C9*1*1) and its overall contribution to siponimod elimination depends on its genotype and enzyme activity. Residual elimination of siponimod is ascribed to various other cytochromes, including CYP3A4 (6.4%), which are considered to be minor across all CYP2C9 genotypes ~~cytochrome P450 2C9 (CYP2C9) (79.3%), and to a lesser extent by cytochrome P450 3A4 (CYP3A4) (18.5%)~~.

…

~~CYP2C9 is polymorphic and the genotype influences the fractional contributions of the two oxidative metabolism pathways to overall elimination. PBPK 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 (see section 4.5).~~

Drug-drug interaction (DDI)

The impact of moderate CYP2C9 inhibitors on siponimod exposure was observed and predicted to be up to 2-fold for AUC and 1.6-fold for C_{max} across all CYP2C9 genotypes at the maintenance dose. DDI predictions for strong CYP2C9 inhibitors resulted in an approximately 4-fold exposure increase compared to CYP2C9*1*1. The concomitant use of moderate or strong CYP2C9 inhibitors is therefore not recommended (see section 4.5).

The co-administration of clarithromycin (strong CYP3A4 inhibitor) 500 mg daily at steady state and a single dose of siponimod 0.25 mg in healthy volunteers with the CYP2C9*1*3 genotype led to a 1.09-fold increase in the AUC of siponimod that was not clinically relevant.

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בעלון לצרכן:

2. לפני השימוש בתרופה

אינטראקציות/תגובות בין תרופתיות

- ~~פלוקונאזול ותרופות מסוימות אחרות יכולות~~ מעכבים חזקים של האנזים CYP2C9 צפויים להעלות את הרמות של מייזנט בדם ולא מומלץ ליטול אותם בשילוב עם מייזנט. הרופא שלך ייעץ לך על כך.

העלונים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות, וניתן לקבלם מודפסים על-ידי פניה לבעל הרישום.

בברכה,
נוברטיס ישראל בע"מ

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