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Draft Guidance on Siponimod Fumaric Acid

February 2023

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Active Ingredient: Siponimod fumaric acid

Dosage Form; Route: Tablet; oral

Recommended Studies: Two in vivo bioequivalence studies with pharmacokinetic endpoints

1. Type of study: Fasting
Design: Single-dose, two- treatment, two-period crossover in vivo
Strength: EQ 2 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: Exclude subjects with CYP2C9*3 allele, such as CYP2C9*1/*3, CYP2C9*2/*3, and CYP2C9*3/*3. Females of reproductive potential should use effective contraception during the study and ten days after the study. Do not use live attenuated vaccines during the study and for four weeks after the last dose of siponimod. Monitor for 6 hours after the first dose for signs and symptoms of bradycardia with hourly pulse and blood pressure measurement. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of siponimod. Alternatively, a parallel study design may be considered.
2. Type of study: Fed
Design: Single-dose, two- treatment, two-period crossover in vivo
Strength: EQ 2 mg Base
Subjects: Healthy males and non-pregnant, non-lactating females
Additional comments: See comments above.

Analyte to measure: Siponimod in plasma

Bioequivalence based on (90% CI): Siponimod

Waiver request of in vivo testing: EQ 0.25 mg Base and EQ 1 mg Base strengths based on (i) acceptable bioequivalence studies on the EQ 2 mg Base strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across strengths

Dissolution test method and sampling times: The dissolution information for this drug product can be found in the FDA's Dissolution Methods database, <http://www.accessdata.fda.gov/scripts/cder/dissolution/>. Conduct comparative dissolution testing on 12 dosage units each of all strengths of the test and reference products. Specifications will be determined upon evaluation of the Abbreviated New Drug Application (ANDA).

Revision History: Recommended March 2021; Revised February 2023

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