Contains Nonbinding Recommendations

Draft - Not for Implementation

Draft Guidance on Ponesimod

November 2022

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

Active Ingredient: Ponesimod

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: 2 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: Exclude subjects with abnormal complete blood count or liver function tests. Exclude subjects with electrocardiogram abnormalities (e.g., bradycardia [or heart rate <50 beat per minute] or atrioventricular conduction abnormalities). Monitor for four hours after dosing for signs and symptoms of bradycardia with hourly pulse and blood pressure measurements. Female subjects of reproductive potential should use non-hormonal contraception during the study and continue to use effective contraception for two weeks after the last dose. Subjects should be informed not to use live attenuated vaccines at least 1 month prior, during, and for up to 2 weeks after the study. Ensure an adequate washout period between treatments in the crossover study due to the long elimination half-life of ponesimod. Alternatively, a parallel study design may be considered.

2. Type of study: Fed
   Design: Single-dose, two-treatment, two-period crossover in vivo
   Strength: 2 mg
   Subjects: Healthy males and non-pregnant, non-lactating females
   Additional comments: See comments above.

Analyte to measure: Ponesimod in plasma

Bioequivalence based on (90% CI): Ponesimod

Waiver request of in vivo testing: 3 mg, 4 mg, 5 mg, 6 mg 7 mg, 8 mg, 9 mg, 10 mg and 20 mg strengths based on (i) acceptable bioequivalence studies on the 2 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all 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 of all strengths of the test and reference products. Specifications will be determined upon evaluation of the Abbreviated New Drug Application (ANDA).

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