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Draft Guidance on Givosiran Sodium

May 2023

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Active Ingredient: Givosiran sodium

Dosage Form; Route: Solution; Subcutaneous

Strength: EQ 189 mg Base/mL

Recommended Studies: Comparative characterization studies to support active pharmaceutical ingredient (API) sameness and request for waiver of in vivo bioequivalence study requirements

This guidance provides recommendations for developing generic givosiran sodium subcutaneous solution containing givosiran sodium as the API. It includes recommendations for demonstrating API sameness and for requesting waiver of in vivo bioequivalence study requirements.

In addition, generic applicants are advised to contact the FDA for questions related to generic development of givosiran sodium including comparability of product- and process-related impurities in the test product and strategies to address immunogenicity and inflammation risk assessment.

Recommendations to Support API Sameness:

For characterization to support sameness between the test API and the API from the reference listed drug (RLD), FDA recommends that potential applicants develop and use appropriately validated orthogonal analytical methods to perform side-by-side comparative testing of the test API and the API from the RLD product. A minimum of three batches of the test API and three batches of the API from the RLD should be characterized to assess API sameness and robustness in the manufacturing process. The API sameness can be established by evaluating the equivalence in the following:

1. Primary sequence, chemical structure, and composition

The givosiran drug substance duplex is formed by Watson-Crick base pairing of the sense and the antisense single strand intermediates. The primary sequence of the sense and antisense strands in the test givosiran API can be controlled through each elongation cycle in the API synthesis. Sequence, chemical structure and diastereomeric composition related to the phosphorothioate linkages as well as the P=S to P=O ratios of both single strands should be investigated and confirmed with a broad range of orthogonal analytical methods. Reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled.[1]

The test API sequence, chemical structure and composition including strand composition, duplex vs residual single strands, diastereomeric composition, and P=S to P=O ratios should be compared to those of the API from the RLD using a broad range of orthogonal analytical methods with sufficient sensitivity, discriminating, and resolving power, that could include but are not limited to the following:

a. Mass spectrometry (MS), including tandem mass spectrometry (MS/MS)
b. Nuclear magnetic resonance (NMR) spectroscopy
c. Liquid chromatography (LC)
d. Flame atomic absorption spectroscopy (FAAS)
e. Duplex melting temperature (Tm)

2. Physicochemical properties

Comparative physicochemical characterizations of the test and RLD products should be performed using methods that could include but are not limited to the following:

a. Circular dichroism (CD) spectroscopy
b. Fourier transform infrared spectroscopy (FTIR)
c. Differential scanning calorimetry (DSC)
d. Size exclusion chromatography (SEC)
e. Sedimentation velocity analytical ultracentrifugation (SV-AUC)

If the sameness between the test and reference products can be adequately demonstrated using validated alternative analytical methods, applicants may submit comparative data for test and reference products along with appropriate justification as part of their product characterization within their abbreviated new drug application. In such case, comprehensive method validation data should be submitted to demonstrate the adequacy (e.g., sensitivity, resolution, and discriminative power) of the selected methods in demonstrating the sameness between the test and reference product.

[1] If resolution of all diastereomers of both strands could not be achieved by the analytical methods, the Rp/Sp configuration ratio at each phosphorothioate nucleotide linkage following respective elongation cycle should be measured using appropriate methods.

Waiver of in vivo bioequivalence study requirements:

To qualify from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), a generic givosiran sodium subcutaneous solution product should be qualitatively (Q1)[2] and quantitatively (Q2)[3] the same as the RLD.
An applicant may seek approval of a drug product that differ from the RLD in preservative, buffer, or antioxidant if the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.[4]

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[2] Q1 (Qualitative sameness) means that the test product uses the same inactive ingredient(s) as the RLD product.
[3] Q2 (Quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the RLD product.
[4] 21CFR 314.94(a)(9)(iii)