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Draft Guidance on Eplontersen Sodium

November 2024

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Active Ingredient:	Eplontersen sodium
Dosage Form:	Solution
Route:	Subcutaneous
Strength:	EQ 45 mg base/0.8 mL
Recommended Studies:	Comparative characterization studies to support active ingredient sameness and request for waiver of in vivo bioequivalence study requirements

Applicants are advised to contact the FDA for proposed strategies and questions related to generic development of eplontersen sodium including questions on immunogenicity and inflammation risk assessment, and comparability of impurities in the test (T) product.

Recommendations to support active ingredient sameness:

For characterization to support sameness between the T active ingredient and the active ingredient 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 T active ingredient and the active ingredient from the RLD product. A minimum of three batches of the T active ingredient and three batches of the active ingredient from the RLD should be characterized to assess active ingredient sameness and robustness in the manufacturing process. The active ingredient sameness can be established by evaluating the equivalence in the following:

1. Primary sequence, chemical structure and diastereomeric composition

The primary sequence of the oligonucleotide can be controlled through each elongation cycle in the active ingredient synthesis. Due to the stereochemistry at the phosphorus chiral center of the phosphorothioate linkage, eplontersen sodium contains many different diastereomers. To ensure the diastereomeric sameness of T active ingredient and the active ingredient from the RLD, reagents and reaction conditions that can impact the diastereomeric composition outcomes should be appropriately selected and adequately controlled. The R/S configuration ratio at each phosphorothioate linkage following each elongation cycle should be measured using appropriate methods. The T active ingredient sequence, chemical structure, PS to PO ratio, and diastereomeric composition should be compared to that of the active ingredient 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) or inductively coupled plasma-optical emission spectroscopy (ICP-OES)
e. Duplex melting temperature (Tm) to a complementary strand

Approaches for demonstrating the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis should be appropriately justified. Alternatively, the sensitivity, discriminating and resolving power of an analytical method for diastereomeric composition analysis may be demonstrated, for example, through negative control studies that introduce variations in the process and corresponding variations to the resulting diastereomeric composition, in conjunction with the corresponding analysis of the R/S configuration ratio at each phosphorothioate nucleotide linkage following each elongation cycle.

2. Physicochemical properties

Side-by-side comparative physicochemical characterizations of the T and RLD products should be performed to include aggregation or high order structures of the active ingredient in the drug product, 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 T and RLD can be adequately demonstrated using validated alternative analytical methods, applicants may submit comparative data for T and RLD along with appropriate justification as part of their product characterization within their abbreviated new drug application (ANDA). 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 T and RLD.

Waiver of in vivo bioequivalence study requirements:

To qualify for a waiver from submitting an in vivo bioequivalence study on the basis that bioequivalence is self-evident under 21 CFR 320.22(b), the T product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the RLD.

An applicant may seek approval of a drug product that differs 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.[3]

Additional information:

Device:
The RLD is presented in an autoinjector. The autoinjector is the device constituent part.

FDA recommends that prospective applicants examine the size and shape, the external critical design attributes, and the external operating principles of the RLD device when designing the T device including:

- Single-use, single-dose format
- Inspection window
- Needle gauge and length

User interface assessment:
An ANDA for this product should include complete comparative analyses so FDA can determine whether any differences in design for the user interface of the proposed generic product, as compared to the RLD, are acceptable and whether the product can be expected to have the same clinical effect and safety profile as the RLD when administered to patients under the conditions specified in the labeling. For additional information, refer to the most recent version of the FDA guidance for industry on *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.[a]

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

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[a] For the most recent version of a guidance, check the FDA guidance website at https://www.fda.gov/regulatory-information/search-fda-guidance-documents.