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Draft Guidance on Terlipressin Acetate

February 2024

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Active Ingredient: Terlipressin acetate

Dosage Form: Powder

Route: Intravenous

Strength: EQ 0.85 mg Base/vial

Recommended Study: Request for 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), a generic terlipressin acetate intravenous powder product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (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]

[1] Q1 (Qualitative sameness) means that the test 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 test products are within ±5% of those used in the RLD product.
[3] 21CFR 314.94(a)(9)(iii).

In addition to ensuring active pharmaceutical ingredient sameness (i.e., same primary sequence), the following comparative analyses of the proposed generic terlipressin and the RLD product should be provided on at least three batches each of the proposed generic and the RLD aged under various conditions.[4]

1. Active ingredient related impurity profile comparison: new impurities found in the proposed generic product but not in the RLD and impurities found at a significantly higher level in the proposed generic product than in the RLD, should be identified.[5]
2. Comparison of aggregation profile and any secondary structure.

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[4] Samples should be aged under conditions consistent with the worst-case label storage conditions.

[5] Immunogenicity assessment may be requested in situations where the comparative impurity or aggregation profile indicates the presence of an unusual new impurity or aggregation state, or a markedly elevated level of an impurity or aggregation state in the proposed generic product relative to the RLD. The need for such an immunogenicity assessment will be determined during abbreviated new drug application assessment.