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Draft – Not for Implementation

Draft Guidance on Risperidone

November 2024

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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: Risperidone

Dosage Form: Suspension, extended release

Route: Subcutaneous

Strengths: 50 mg/0.14 mL (50 mg/0.14 mL),
75 mg/0.21 mL (75 mg/0.21 mL),
100 mg/0.28 mL (100 mg/0.28 mL),
125 mg/0.35 mL (125 mg/0.35 mL),
150 mg/0.42 mL (150 mg/0.42 mL),
200 mg/0.56 mL (200 mg/0.56 mL),
250 mg/0.70 mL (250 mg/0.70 mL)

Recommended Study: One in vivo bioequivalence study with pharmacokinetic endpoints

1. Design: Parallel or crossover, steady state
   Strengths: 50 mg/0.14 mL, 75 mg/0.21 mL, 100 mg/0.28 mL, 125 mg/0.35 mL, 150 mg/0.42 mL, 200 mg/0.56 mL, 250 mg/0.70 mL
   Subjects: Male and non-pregnant female patients with schizophrenia who are already receiving a stable regimen of risperidone extended-release suspension via subcutaneous route. Patients who are already receiving any dosage regimen of risperidone extended-release suspension every month or every 2 months would be eligible to participate in the study by continuing their established maintenance dose.
   Additional comments:
   a. FDA does not recommend studies be conducted using healthy subjects or patients on a different antipsychotic treatment.

b. Patients who are receiving oral risperidone may be eligible to participate the study by switching to the appropriate strength of risperidone extended-release suspension following product labeling. The decision for switching a patient from oral risperidone should be made by a healthcare professional based upon their knowledge and experience with the patient, and assessment of the benefits and risks. The transitioning should not be considered solely for the purpose of satisfying enrollment criteria for the bioequivalence study.
c. Trough concentration data should be analyzed using appropriate statistical method to demonstrate that the steady state of test and reference product has been reached for each individual.

Analyte to measure: Risperidone in plasma

Bioequivalence based on (90% CI): Risperidone

In the evaluation of bioequivalence of the multiple dose study, the following pharmacokinetic data should be submitted for risperidone:

- Individual and mean blood drug concentration levels in a dosing interval after steady state is reached
- Individual and mean trough levels (C_{min} ss)
- Individual and mean peak levels (C_{max} ss)
- Calculation of individual and mean steady-state AUC_{τ} (AUC_{τ} is AUC during a dosing interval at steady-state)
- Individual and mean percent fluctuation [=100 * (C_{max} ss – C_{min} ss)/$C_{average}$ ss]
- Individual and mean time to peak concentration

The 90% confidence interval for the ratio of the geometric means of the pharmacokinetic parameters (AUC and C_{max}) should be within 80% - 125%. Fluctuation for the test product should be evaluated for comparability with the fluctuation of the reference product.

Waiver request of in vivo testing: Any strength that is not studied in vivo based on (i) acceptable bioequivalence study on the strength(s) tested in vivo, and (ii) evidence supporting identical formulation composition 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 each of all strengths of the test and reference products. Specifications will be determined upon review of the abbreviated new drug application (ANDA).

Additional information:

Formulation:
The proposed parenteral drug product should be qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference listed drug (RLD) for all strengths. To support Q1 sameness, provide comparative characterization data on the mixture of methoxy-poly(ethylene glycol)-co-poly(D,L-lactide) and poly(D,L-lactide)-co-poly(ethylene glycol)-co-poly(D,L-lactide) extracted from both the test and the reference products. The characterization on the extracted polymer mixture should include, but not limited to, polymer composition, molecular weight and weight distribution, glass transition temperature and the ratio between the lactic acid units and ethylene oxide units. Additional data on the polymer characterization may be requested during the scientific assessment of the ANDA. Sufficient validation data for the methods used for comparative characterization of the polymer mixture should be provided in the ANDA.

Device:
The RLD is presented as a kit containing a pre-filled syringe with drug and a copackaged needle with safety shield. The syringe and needle are the device constituent parts.

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 test device including:

- Single-dose, single-use, prefilled syringe format
- Needle gauge and length
- Needle safety system

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]

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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.

[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 product are within ±5% of those used in the RLD product.