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Draft Guidance on Metoclopramide Hydrochloride

May 2021

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This guidance, which interprets the Agency's regulations on bioequivalence at 21 CFR part 320, provides product-specific recommendations on, among other things, the design of bioequivalence studies to support abbreviated new drug applications (ANDAs) for the referenced drug product. FDA is publishing this guidance to further facilitate generic drug product availability and to assist the generic pharmaceutical industry with identifying the most appropriate methodology for developing drugs and generating evidence needed to support ANDA approval for generic versions of this product.

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This is a new draft product-specific guidance for industry on generic metoclopramide hydrochloride.

Active Ingredient: Metoclopramide hydrochloride

Dosage Form; Route: Spray, metered; nasal

Strength: EQ 15 mg Base/Spray

Recommended Studies: Two options: in vitro or in vivo studies

FDA recommends the following in vitro or in vivo studies to establish bioequivalence (BE) of the test (T) and reference (R) nasal sprays containing metoclopramide hydrochloride.

In Vitro BE Option

If the T formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the R formulation, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an abbreviated new drug application (ANDA) (as demonstrated by comparative analyses further described below), BE of the T metoclopramide hydrochloride metered nasal spray product to the R metoclopramide hydrochloride metered nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that prospective applicants conduct the following in vitro BE studies on samples from each of three or more batches of the T product and three or more batches of the R product, with no fewer than 10 units from each batch. FDA recommends that three primary stability batches be also used to demonstrate in vitro BE. The three batches of the T product should be manufactured from, at minimum, three different batches of the drug substance, three different batches of critical excipients, and three different batches of the device components (e.g., pump and actuator) proposed for the final device configuration of the commercial product. The T product should consist of the final device constituent part and final drug constituent formulation intended to be marketed. The following in vitro BE tests are recommended:

1. Single actuation content
2. Droplet size distribution by laser diffraction
3. Drug in small particles/droplets
4. Spray pattern
5. Plume geometry
6. Priming and repriming

Additional comments: Refer to the product-specific guidance on *Fluticasone Propionate Nasal Spray Metered* for recommendations on design and equivalence criteria for the aforementioned in vitro BE studies, and general recommendations on the conduct of the in vitro BE studies and data submission.

In Vivo BE Option

If the T product is not Q1 and Q2 the same as the R formulation and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for an ANDA (as demonstrated by comparative analyses further described below), the following PK study is recommended to establish BE between the T and R product:

Type of study: Fasting
Design: Single-dose, two-way crossover
Strength: EQ15 mg Base/Spray (dose: 15 mg, administer as one spray in one nostril)
Subjects: Adult males and non-pregnant, non-lactating females, general population

[1] Q1 (qualitative sameness) means that the T product uses the same inactive ingredient(s) as the R product.
[2] Q2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the T product are within ±5% of those used in the R product.

Additional comments: Subjects should adhere to the R drug product labeling for administration. Subjects should not engage in activities requiring complete mental alertness, operate hazardous machinery, drive a motor vehicle or ride a bicycle after taking nasal metoclopramide spray until they have completely returned to their level of baseline functioning. Subjects should not use alcohol or and other CNS depressants after administration of a dose of nasal metoclopramide spray until they have completely returned to their level of baseline functioning. Exclude subjects with history of extrapyramidal symptoms, movement disorders, depression, pheochromocytoma, hypertension, cirrhosis, and congestive heart failure. Exclude subjects taking antipsychotics (both typical and atypical), strong CYP2D6 inhibitors, and monoamine oxidase inhibitors. Exclude subjects with hypersensitivity to metoclopramide.

Analyte to measure: Metoclopramide in plasma

Equivalence based on: AUC and C_{max} for metoclopramide. The 90% confidence interval for the geometric mean T/R ratios of C_{max} and AUC should fall within the limits of 80.00 - 125.00%.

Additional Information

Device:

Prospective applicants should refer to FDA's guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*, which, when finalized, will provide the Agency's current thinking on the identification and assessment of any differences in the design of the user interface for a proposed generic drug-device combination product when compared to its RLD.

FDA recommends that prospective applicants consider the following characteristics of the R product when designing the T product:

- Number of doses in the R product
- External operating principles and external critical design attributes of the R product
- Size and shape of the R product

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