Contains Nonbinding Recommendations

Draft Guidance on Esketamine Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic.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

Active Ingredient: Esketamine hydrochloride

Dosage Form; Route: Spray; nasal

Strength: EQ 28 mg Base

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 esketamine hydrochloride.

In Vitro Option

If the test (T) formulation is qualitatively (Q1)[1] and quantitatively (Q2)[2] the same as the reference (R) formulation, and the nasal spray device (e.g., pump and actuator design) of the T product is appropriate for approval in an abbreviated new drug application (ANDA) (as demonstrated by comparative analyses further described below), BE of the T esketamine hydrochloride nasal spray product to the R esketamine hydrochloride nasal spray product can be established solely through in vitro performance tests in lieu of a pharmacokinetic (PK) BE study. FDA recommends that 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

[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.

5. Plume geometry

Additional Comments: Refer to the product-specific guidance for *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 Option

If the T formulation 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 approval in 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: EQ 28 mg Base
Dose: 28 mg esketamine (2 sprays, 1 spray in each nostril)
Subjects: Adult males and non-pregnant, non-lactating females, general population.
Additional Comments: Exclude subjects with a blood pressure >140/90 mmHg. Exclude subjects with for whom an increase in blood pressure or intracranial pressure poses a serious risk (e.g., aneurysmal vascular disease, arteriovenous malformation, history of intracerebral hemorrhage). Subjects should adhere to the R drug product labeling for administration and risk management including the Risk Evaluation Mitigation Strategy (REMS) program. All pertinent elements of the REMS must be incorporated into the protocol and informed consent in the study. Monitor subjects for at least two hours after esketamine intranasal administration. Subjects should not to engage in potentially hazardous activities, such as driving a motor vehicle or operating machinery, until the next day after a restful sleep. Females of reproductive potential should use effective contraception during the study and for at least 1 week after the last dose of esketamine.

Analyte to measure: Esketamine in plasma

Equivalence based on: AUC and C_{max} for esketamine. The 90% confidence intervals 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 the FDA guidance for industry entitled, *Comparative Analyses and Related Comparative Use Human Factors Studies*, 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:

- Single-use, two-spray containing device
- External operating principles and external critical design attributes of the R product
- Size and shape of the R product
- Dose indicator