Contains Nonbinding Recommendations

Draft Guidance on Fluticasone Propionate; Salmeterol Xinafoate

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Active ingredient: Fluticasone Propionate; Salmeterol Xinafoate

Form/Route: Powder/Inhalation

Recommended studies: In Vitro and In Vivo Studies

The following in vitro and in vivo studies are recommended to establish bioequivalence (BE) of the test (T) and reference (R) dry powder inhalers (DPIs) containing fluticasone propionate and salmeterol xinafoate.

In Vitro Studies

The following in vitro studies are recommended to be conducted for all strengths of the T and R products. For each strength, these in vitro studies should be conducted using at least three batches each of T and R products with no fewer than 10 units from each batch.

1. Type of study: Single actuation content (SAC)
   Design: The SAC test should be performed at the beginning (B), middle (M), and end (E) lifestages[1] of the product using flow rates of 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus B or another appropriate apparatus may be used to determine the SAC using a validated assay. The number of actuations per determination should be one. The volume of air drawn through the delivery system should be 2 L.

   Equivalence based on: Population bioequivalence (PBE) analysis of SAC. Please refer to the draft Budesonide Inhalation Suspension BE Guidance for additional information regarding PBE.[2]

2. Type of study: Aerodynamic particle size distribution (APSD)
   Design: The APSD test should be performed at the B and E lifestages of the product using flow rates of 28.3 L/min or 30 L/min, 60 L/min and 90 L/min. The USP <601> Apparatus 3, Apparatus 5, or another appropriate method may be used to determine APSD using a validated assay. The APSD determination of each unit should be performed with a minimum number of inhalations justified by the sensitivity of the validated assay. The volume of air drawn through the delivery system should be 4 L.

[1] Based on the labeled number of actuations, the terms, B lifestage, M lifestage, and E lifestage represent the first actuation(s), the actuation(s) corresponding to 50 percent of the labeled number of actuations, and the actuation(s) corresponding to the labeled number of actuations, respectively.

[2] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM319977.pdf

Additional comments:
Drug deposition on individual sites, including the mouthpiece adapter, the induction port, the pre-separator, and each stage of the cascade impactor (CI) and the filter, is requested. Mass balance accountability should be reported based on the sum of all deposition sites. For electronic submission of the individual CI data for the T and R products, please provide a table using the format in the appendix, and send them as part of the abbreviated new drug application (ANDA) submission for BE evaluation.

Equivalence based on: PBE analysis of impactor-sized mass (ISM).[3] The CI profiles representing drug deposition on the individual stages of the CI along with the mass median aerodynamic diameter (MMAD), geometric standard deviation (GSD) and fine particle mass (FPM) should be submitted as supportive evidence for equivalent APSD.

Pharmacokinetic (PK) BE Study

The following PK BE study is recommended to be conducted for all strengths of the T and R products.

3. Type of Study: Fasting
   Design: Single-dose, two-way crossover
   Dose: Minimum number of inhalations that is sufficient to characterize a PK profile by using a sensitive analytical method.
   Subjects: Normal healthy males and non-pregnant females, general population.
   Additional comments: Subjects should adhere to labeling as follows: "Rinse your mouth with water after breathing in the medicine. Spit the water out. Do not swallow."

   Analyte(s) to measure (in appropriate biological fluid): Fluticasone propionate and salmeterol in plasma

   Equivalence based on: AUC and C_{max} for fluticasone propionate and salmeterol. The 90% confidence intervals (CIs) for the geometric mean T/R ratios of AUC and C_{max} should fall within the limits of 80.00–125.00%.

Clinical Endpoint Study

The following BE study with a clinical endpoint is recommended to be conducted for the lowest strength of the T and R products.

4. Type of Study: Clinical endpoint study

[3] ISM is defined as a sum of the drug mass on all stages of the CI plus the terminal filter, but excluding the top CI stage because of its lack of a specified upper cutoff size limit.

Design: A randomized, multiple-dose, placebo-controlled, parallel group design consisting of a 2 week run-in period followed by a 4-week treatment period of the placebo, T or R product
Strength: 100/50 (fluticasone propionate 100 mcg and salmeterol 50 mcg powder for inhalation)
Dose: 100/50, twice daily
Subjects: Males and non-pregnant females with asthma
Additional comments:

- Inclusion criteria should, at minimum, include:
    a. Male or female subjects (≥ 12 years of age) of non-child bearing potential or of child bearing potential committing to consistent and correct use of an acceptable method of birth control.
    a. Diagnosed with asthma as defined by the National Asthma Education and Prevention Program (NAEPP)[4] at least 12 weeks prior to screening.
    b. Pre-bronchodilator FEV_1 of ≥40% and ≤85% of the predicted value during the screening visit and on the first day of treatment.
    c. Currently non-smoking; had not used tobacco products (i.e., cigarettes, cigars, pipe tobacco) within the past year, and had ≤ 10 pack-years of historical use.
    d. ≥15% reversibility of FEV_1 within 30 minutes following 360 mcg of albuterol inhalation (pMDI).
    e. Able to discontinue their asthma medications (inhaled corticosteroids and long-acting β agonists) during the run-in period and for remainder of the study.
    f. Able to replace current short-acting β agonists (SABAs) with salbutamol/albuterol inhaler for use as needed for the duration of the study (subjects should be able to withhold all inhaled SABAs for at least 6 hours prior to lung function assessments on study visits).
    g. Able to continue the following medications without a significant adjustment of dosage, formulation, dosing interval for the duration of the study, and judged able by the investigator to withhold them for the specified minimum time intervals prior to each clinic visit:
        - short-acting forms of theophylline 12 hours
        - twice-a-day controlled-release forms of theophylline 24 hours
        - once-a-day controlled-release forms of theophylline 36 hours
    h. Able to discontinue the following medications for the specified minimum time intervals prior to the run-in period and for the remainder of the study, if the study is conducted in the US:
        - oral corticosteroids 1 month
        - parenteral corticosteroids 1 month
        - oral short-acting β-agonists 12 hours
    i. Willingness to give their (and in the case of a minor their parent/guardian was able to give) written informed consent to participate in the study.

[4] Guidelines for the Diagnosis and Management of Asthma: Expert Panel Report 3. National Asthma Education and Prevention Program; National Institute of Health; National Heart, Lung, and Blood Institute. 2007, Publication No. 07-4051.

- Exclusion criteria should, at minimum, include:
    a. Life-threatening asthma, defined as a history of asthma episode(s) requiring intubation, and/or associated with hypercapnoea; respiratory arrest or hypoxic seizures, asthma related syncopal episode(s), or hospitalizations within the past year or during the run-in period.
    b. Evidence or history of clinically significant disease or abnormality including congestive heart failure, uncontrolled hypertension, uncontrolled coronary artery disease, myocardial infarction, or cardiac dysrhythmia. In addition, historical or current evidence of significant hematologic, hepatic neurologic, psychiatric, renal, or other diseases that in the opinion of the investigator, would put the patient at risk through study participation, or would affect the study analyses if the disease exacerbated during the study.
    c. Hypersensitivity to any sympathomimetic drug (e.g., salmeterol or albuterol) or any inhaled, intranasal, or systemic corticosteroid therapy.
    d. Medication(s) with the potential to affect the course of asthma or to interact with sympathomimetic amines, e.g.:
        - β-blockers
        - oral decongestants
        - benzodiazepines
        - digitalis
        - phenothiazines
        - polycyclic antidepressants
        - Monoamine oxidase inhibitors
    e. Viral or bacterial, upper or lower respiratory tract infection or sinus or middle ear infection within 4 weeks prior to the screening visit or during the run-in period.
    f. Factors (e.g., infirmity, disability or geographic location) that the investigator felt would likely limit the patient's compliance with the study protocol or scheduled clinic visits.
- The study is recommended to begin with a placebo run-in period (at least 2 weeks in duration) to wash out any pre-study corticosteroids/ long acting bronchodilators and to establish FEV_1 baseline values.
- The study protocol should provide a definition of compliant subjects (e.g., used at least 75% and no more than 125% of study drug doses) and specify how compliance will be verified (e.g., by the use of subject diaries).
- To ensure adequate study sensitivity, the T and R products should both be statistically superior to placebo ($p<0.05$) with regard to the BE study primary endpoints.
- It is the sponsor’s responsibility to enroll a sufficient number of subjects for the study to demonstrate BE of the T to the R product.
- The start and stop date of concomitant medication use during the study should be provided in the data set in addition to the reason for the medication use. The sponsor should clearly explain whether the medication was used prior to baseline visit, during the study, or both.

- All adverse events (AEs) should be reported, whether or not they are considered to be related to the treatment. The report of AEs should include date of onset, description of the AE, severity, relation to study medication, action taken, outcome and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the T and R products.

BE study endpoints: (i) Area under the serial FEV_1-time curve calculated from time zero to 12 hours ($AUC_{0\text{-}12h}$) on the first day of the treatment, and (ii) FEV_1 measured in the morning prior to the dosing of inhaled medications on the last day of a 4-week treatment.

The above two primary endpoints should be baseline adjusted (change from baseline). A FEV_1 baseline is defined as the average of pre-dose FEV_1 values of at least two time points measured in the morning of the first day of a 4 week treatment period. Sampling is recommended to correspond to the same time of day as used on the last day of a 4-week treatment.

On the first day of the treatment, FEV_1 should be determined at 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 12 hour post-dose.

Equivalence based on: T/R ratio for the primary endpoints. The 90% CIs for the T/R ratios for the primary endpoints should fall within the limits of 80.00-125.00%.

Additional information

Formulation

The T product is recommended to be qualitatively (Q_1)[5] and quantitatively (Q_2)[6] the same as the R product.

If a sponsor uses a Q_2-different formulation for its T product, the sponsor should explain the reason(s) for not using a T formulation that is Q_2 the same as the R formulation. In addition, the sponsor should provide pharmaceutical development data, involving in vitro testing of multiple drug-to-excipient ratios that encompass combinations below and above the ratios used in the T and R products.

Device

A sponsor is encouraged to submit a working model and engineering drawings of the product to the Office of Generic Drugs (OGD) prior to the abbreviated new drug application (ANDA) submission, in order to ensure eligibility of the T device under a 505(j) pathway.

[5] Q_1 (qualitative sameness) means that the test product uses the same inactive ingredient(s) as the reference product.
[6] Q_2 (quantitative sameness) means that concentrations of the inactive ingredient(s) used in the test product are within ±5% of those used in the reference product.

The T product should have the following characteristics:

- Passive (breath-actuated) device
- Pre-metered multi-dose format
- 60 doses
- External operating procedures consisting of (1) Open, (2) Click, (3) Inhale, and (4) Close
- Similar size and shape to the R product
- Comparable device resistance to the R product
- Dose counter

In addition, the robustness of the T product should be demonstrated.

APPENDIX

Variable Name	Variable Type	Content	Notes
Product Name	Character	TEST or REF	Identifier for product
LOT Number	Alphanumeric/Numeric	Alphanumeric/Numeric	Identifier for product lot
UNIT Number	Numeric	Numeric values	Identifier for unit must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
Stage 1	Numeric	Numeric Values	S1
Stage 2	Numeric	Numeric Values	S2
Stage 3	Numeric	Numeric Values	S3
Stage 4	Numeric	Numeric Values	S4
Stage 5	Numeric	Numeric Values	S5
Stage 6	Numeric	Numeric Values	S6
Stage 7	Numeric	Numeric Values	S7
Stage 8 or Filter	Numeric	Numeric Values	S8
ISM	Numeric	Numeric Values	ISM
MMAD	Numeric	Numeric Values	MMAD
GSD	Numeric	Numeric Values	GSD
FPM	Numeric	Numeric Values	FRM

Example

PRODUCT	LOT	Unit	S1	S2	S3	S4	S5	S6	S7	S8 or Filter	ISM	MMAD	GSD	FPM
TEST	1234	1												
		2												
		3												
		4												
		5												
		6												
		7												
		8												
		9												
		10												