DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 208798 and 208799

WRITTEN REQUEST

Teva Pharmaceutical Industries Ltd.
c/o Teva Branded Pharmaceutical Products R&D Inc.
41 Moores Road
Frazer, PA 19355

Attention: Michael J. McGraw, PharmD, MS
Senior Director, Global Regulatory Affairs

Dear Dr. McGraw:

Reference is made to your July 27, 2017 Proposed Pediatric Study Request for fluticasone propionate and fluticasone propionate/salmeterol.

BACKGROUND:

This study will investigate the potential use of fluticasone propionate multi-dose dry powder inhaler and fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler in the treatment of asthma in children 4 to 11 years.

Asthma is a chronic inflammatory disorder of the airways and a leading chronic disease in children with an estimated prevalence of asthma in children 0-17 years of age of 9.6 %.[1] Approved medications used to treat asthma include single-ingredient inhaled corticosteroids (ICS), fixed-dose ICS and long-acting beta2-agonists (LABAs) combination products, single- ingredient LABAs + single-ingredient ICS, leukotriene antagonists, anticholinergics, methylxanthines, and anti-IgE, and anti-IL-5 antibodies.

Single-ingredient fluticasone propionate is approved as an ICS, single-ingredient salmeterol xinafoate is approved as a LABA, and the fixed dose combination of fluticasone propionate and salmeterol xinafoate approved as an ICS/LABA, in a dry-powder formulation and as a HFA-pressurized metered-dose inhaler (pMDI) for the treatment of asthma in children ≥ 4 years of age. Fluticasone propionate multi-dose dry powder inhaler and fluticasone propionate/salmeterol xinafoate multi-dose dry powder inhaler are approved at lower doses for both the ICS and the LABA compared to the previously marketed products.

[1] Akinbami LJ, Moorman JE, Liu X. Asthma prevalence, health care use, and mortality; United States, 2005-2009. National health statistics reports; no 32. Hyattsville, MD: National Center for Health Statistics. 2011.

The study outlined in this Written Request is designed to evaluate the efficacy and safety of fluticasone propionate multi-dose dry powder inhaler and fluticasone propionate/salmeterol multi-dose dry powder inhaler in 4-11 year olds. Studies in patients <4 years of age, including neonates, are considered unnecessary due to the nature of the drug-device delivery. The multi-dose dry powder inhaler is an active device that requires users to be able to understand and follow instructions that may not be developmentally appropriate for children < 4 years of age. Other dry powder inhalers for asthma are not approved for < 4 years of age for the same reasons. Moreover, *in vitro* testing wiith a spacer showed that spacers are not to be used with this multi-dose dry powder inhaler.

To obtain needed pediatric information on fluticasone propionate and fluticasonepropionate/ salmeterol, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- ***Nonclincial study(ies)****:*

Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- ***Clinical Studies:***

A randomized, placebo-controlled, double-blind, parallel-group, 12-week study of two doses (25 and 55 mcg twice daily) fluticasone propionate multi-dose dry powder inhaler compared with one dose of fluticasone propionate/salmeterol (55/12.5 mcg twice daily) to determine the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol multi-dose dry powder inhaler in pediatric patients ages 4 to 11 years with persistent asthma.

- ***Objective of the study:***

To demonstrate the efficacy and safety of fluticasone propionate and fluticasone propionate/salmeterol in a multi-dose dry powder inhaler in children 4 to 11 years with persistent asthma.

- ***Patients to be Studied:***

  - *Age group in which study(ies) will be performed*: Children aged 4 to 11 years.

  - *Number of patients to be studied:*

    The study will include a sufficient number of enrolled patients to produce a sample size adequately powered for detecting a treatment difference between the high dose (55 mcg) fluticasone propionate over placebo in change from baseline in percent predicted trough morning FEV1 at Week 12 and the superiority of fluticasone propionate/salmeterol (55/12.5 mcg) over fluticasone propionate (55 mcg) in change from baseline in 1-hour postdose percent predicted morning FEV1 at Week 12 based on

estimates of the effect size of the primary efficacy endpoint. Patients should remain on their assigned, blinded treatment arms for the 12-week duration of the study.

Approximately 20% or more of randomized patients should be children under the age of 8 years and approximately evenly distributed between the ages of 4 and 8.

Representation of Ethnic and Racial Minorities: The study must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- ***Study endpoints:***

  The primary efficacy endpoint must include the change from baseline in weekly average of the percent predicted trough morning FEV1 at Week 12 for fluticasone propionate multi-dose dry powder inhaler compared to placebo and the change from baseline in 1-hour post-dose percent predicted morning FEV1 at Week 12 for fluticasone propionate/salmeterol compared to fluticasone propionate at Week 12.

  Other efficacy variables must include spirometry, asthma symptom scores, asthma control, use of reliever medication, and the number of withdrawals for asthma exacerbation.

  Safety variables must include adverse events, discontinuations due to adverse events, serious adverse events, vital signs (blood pressure and pulse), and physical examinations including oropharyngeal examinations.

- ***Known Drug Safety concerns and monitoring:***

  Safety concerns with inhaled corticosteroids include local effects such as oropharyngeal fungal infections (i.e., Candida albicans), growth suppression, increased intraocular pressure, glaucoma, cataracts, decreased bone mineral density, immunosuppression, and hypothalamic-pituitary-adrenal (HPA) axis suppression. Monitoring for safety concerns must be performed in the clinical trials.

  Safety concerns with LABAs include asthma-related death, increased hospitalizations metabolic effects including hypokalemia and hyperglycemia, signs and symptoms of adrenergic stimulation, and effects on coexisting conditions such as cardiovascular or central nervous system disorders. Monitoring for safety concerns must be performed in the clinical trials.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- ***Drug information:***

  - *dosage form:* Multi-dose dry powder inhaler
  - *route of administration:* oral inhalation
  - *regimen:* one inhalation twice daily

  Use an age-appropriate formulation in the study described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice,

  the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for preparing an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using such a formulation, the following information must be provided for inclusion in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents; detailed step-by-step preparation instructions; packaging and storage requirements; and formulation stability information.

  Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- ***Statistical information, including power of study(ies) and statistical assessments:***

The primary analysis of efficacy should be based on an analysis set that includes all randomized patients who took at least 1 dose of study medication. For the change from baseline in percent predicted trough morning FEV1 at Week 12, a sample size of 127 patients per treatment group will have 85% power to detect a 5% difference, assuming that the common standard deviation is 13.25%, at

a 0.05 significance level for the 2-sided test of fluticasone propionate 55 mcg twice daily versus placebo. For the change from baseline in 1-hour postdose percent predicted morning FEV1 at Week 12, a sample size of 127 patients per group wil have 97% power to detect a 4.5% difference, assuming that the common standard deviation is 9.3%, at a 0.05 significance level for the 2-sided test of fluticasone propionate/salmeterol (55/12.5 mcg) versus fluticasone propionate (55 mcg).

Assuming a dropout rate of 15%, 150 patients per treatment group will be randomized.

Clinically meaningful estimands must be defined and justified for comparison between FP monotherapy and placebo and for comparison between FS combination therapy and FP monotherapy. Your analyses must include an exploration of the treatment policy estimand when clinically relevant that is described in ICH E9 (R1) (https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm582738.pdf) where patients are analyzed as randomized at the primary endpoint without regard to treatment adherence. The analyses must include a tipping point analysis which explores the sensitivity of your assumptions in the treatment policy analysis for the patients who do not continue to provide outcome data after treatment discontinuation.

Labeling that may result from the study(ies): You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that fluticasone propionate and fluticasone propionate/salmeterol

- is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

  Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before December 31, 2019. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, CDER, FDA, Document Control Room, Metro Park North VII, 7620 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or
4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, call Laura Musse, Regulatory Health Project Manager, at (240) 402-3720.

Sincerely,

{See appended electronic signature page}

Badrul A. Chowdhury, M.D., Ph.D.
Director
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BADRUL A CHOWDHURY
11/17/2017