DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 203188/S-001

SUPPLEMENT APPROVAL

Vertex Pharmaceuticals, Inc.
130 Waverly Street
Cambridge, MA 02139-4242

Attention: Jennifer Dittman, MS
Manager, Regulatory Affairs

Dear Ms. Dittman:

Please refer to your Supplemental New Drug Application (sNDA) dated August 6, 2012, received August 6, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Kalydeco (ivacaftor) 150 mg tablets.

We acknowledge receipt of your amendment dated August 13, 2012.

We also refer to our letter dated July 13, 2012, notifying you, under Section 505(o)(4) of the FDCA, of new safety information that we believe should be included in the labeling for Kalydeco (ivacaftor). This information pertains to the risk of cataracts.

This supplemental new drug application provides for revisions to the labeling for Kalydeco (ivacaftor) 150 mg tablets. The agreed upon changes to the language included in our July 13, 2012, letter are as follows (additions are noted by underline and deletions are noted by ~~strikethrough~~). The final labeling includes minor modification to the Animal Toxicology and/or Pharmacology Section as well as a sentence that the finding [of cataracts] has not <u>been observed in older animals.</u> The final labeling also includes modifications to clarify the following sections: Adverse Reactions – Clinical Trials Experience (6.1), Clinical Pharmacology – Mechanism of Action (12.1), and Clinical Pharmacology – Pharmacokinetics (12.3).

6.1 Clinical Trials Experience
Overall, the most common adverse reactions in 221~~353~~ patients with CF <u>who had either a *G551D* mutation or were homozygous for the *F508del* mutation in the CFTR and treated with KALYDECO</u> were headache (17%), upper respiratory tract infection (16%), nasal congestion (16%), nausea (10%), rash (10%), rhinitis (6%), dizziness (5%), arthralgia (5%), and bacteria in sputum (5%).

12.1 Mechanism of Action
In vitro, ivacaftor increased CFTR-mediated transepithelial current (IT) in rodent cells expressing G551D-CFTR protein following addition of a cyclic adenosine monophosphate

(cAMP) agonist with an EC50 of 100 ± 47 nM; however, ivacaftor did not increase IT in the absence of cAMP agonist. Ivacaftor also increased IT in human bronchial epithelial cells expressing G551D-CFTR protein following addition of a cAMP agonist by 10-fold with an EC50 of 236 ±200 nM. Ivacaftor increased the open probability of G551D-CFTR protein in single channel patch clamp experiments using membrane patches from rodent cells expressing G551D-CFTR protein by ~~10~~6-fold versus untreated cells after addition of PKA and ATP.

12.3 Pharmacokinetics
Special Populations
Renal Impairment
KALYDECO has not been studied in patients with mild, moderate or severe renal impairment (creatinine clearance less than or equal to 30 mL/min) or in patients with end stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients because of ~~negligible~~minimal elimination of ivacaftor and its metabolites in urine (only 6.6% of total radioactivity was recovered in the urine in a human PK study); however, caution is recommended when administering KALYDECO to patients with severe renal impairment or end stage renal disease.

13.2 Animal Toxicology and/or Pharmacology
Cataracts were seen in juvenile rats dosed with ivacaftor (b) (4) from postnatal day 7-35 at dose levels of 10 mg/kg/day and higher (approximately 0.12 times the MRHD based on summed AUCs of (b) (4) ivacaftor and its metabolites). This finding has not been observed in older animals.

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, text for patient package insert), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/opacom/morechoices/fdaforms/cder.html; instructions are provided on page 2 of the form. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Wayne Amchin, Senior Regulatory Health Project Manager for Safety, at (301) 796-0421.

Sincerely,

{See appended electronic signature page}

Sally M. Seymour, M.D.
Deputy Director for Safety
Division of Pulmonary, Allergy, and Rheumatology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Content of Labeling

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

/s/

SALLY M SEYMOUR
08/28/2012