CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	February 28, 2015
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 207925
Applicant	Vertex Pharmaceuticals
Date of Submission	September 17, 2014
PDUFA Goal Date	March 17, 2015/Priority Review
Proprietary Name / Established (USAN) names	Kalydeco/ivacaftor
Dosage forms / Strength	Oral granules 50 mg for patients 2-5 years < 14 kg 75 mg for patients 2-5 years ≥ 14 kg
Proposed Indication(s)	Extension of the ivacaftor indication for the treatment of cystic fibrosis in patients 2 to 5 years of age for whom ivacaftor is currently approved.
Recommended:	Approval

1. Introduction

Ivacaftor (trade name Kalydeco) is a potentiator of the cystic fibrosis transmembrane conductance regulator (CFTR) protein currently approved at a dose of 150 mg taken orally twice daily, for the treatment of cystic fibrosis (CF) in patients age 6 years and older with one of the following mutations in the *CFTR* gene: *G551D, G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P, G1349D, or R117H*. The Applicant (Vertex Pharmaceuticals) has now submitted this 505(b)(1) NDA to support the extension of the ivacaftor indication to children 2 to 5 years of age by providing for a new dosage form (ivacaftor granules) and by submitting a pharmacokinetic (PK) and safety study used to determine the appropriate ivacaftor weight-based dose for CF patients 2 to 5 years of age as well as to assess the safety of ivacaftor in the 2 to 5 year old CF patient population. As efficacy is being extrapolated from that demonstrated in clinical studies in CF patients 6 years of age and older to the younger 2 to 5 year of age CF patient population, this review will focus primarily on the clinical pharmacology and safety findings from Study 108 and on the safety profile of ivacaftor demonstrated in the placebo-controlled clinical trials used to support the initial approval of ivacaftor for the *G551D* mutation CF population and the lack of any new safety concerns identified in subsequent smaller clinical studies.

2. Background

Cystic fibrosis is an autosomal recessive, progressive, and life-shortening genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan drug population. Lack of a properly functioning CFTR chloride channel is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the presence of thick respiratory secretions which are difficult to mobilize, leading to recurrent/chronic pneumonia and lung damage. There is no cure for CF and, except for the subpopulations of CF patients for which ivacaftor is approved, therapies used by patients with CF are limited to those used to treat symptoms and complications of the disease and include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements.

Ivacaftor has been developed as a CFTR “potentiator” which increases the activity of the CFTR protein which is already present at the cell surface membrane. The CFTR protein is an epithelial chloride ion channel, encoded by the *CFTR* gene, which aids in the regulation of salt and water absorption and secretion throughout the body. Because ivacaftor increases the activity of the CFTR chloride channel, it is felt to be a possible therapy for mutations in the *CFTR* in which the CFTR protein is transported to the cell surface but lacks normal activity. Kalydeco was approved on January 31, 2012, for a subpopulation of CF patients ages 6 years and older who have a *G551D* mutation in the *CFTR* gene. The indication was extended to CF patients with a *G178R, G551S, S549N, S549R, G1244E, S1251N, S1255P, or G1349D* mutation in the *CFTR* gene on February 21, 2014, and to those with a *R117H* mutation in the *CFTR* gene on December 30, 2014.

Relevant to this NDA, in a communication dated March 1, 2012, the Division stated that:

- Efficacy in the 2 to 5 year old population can be extrapolated from the older population

- To support safety in the proposed population, the Division encouraged Vertex to enroll at least 30 patients with at least 10 who were 2-3 years in age
- The Division also encouraged Vertex to study CF patients other than those with the *G551D* mutation in the *CFTR* gene.

3. Chemistry, Manufacture, and Controls

This NDA provides for a new dosage form, ivacaftor granules, appropriate for use in young children ages 2-5 years of age.

Regarding the drug substance, (b) (4) ivacaftor drug substance is (b) (4) already marketed ivacaftor 150 mg tablet. For the drug product, each granule is approximately (b) (4) has a target weight of 6.87 mg of which (b) (4) is the drug substance, ivacaftor. The excipients include compendial grade colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, lactose monohydrate, magnesium stearate, mannitol, sucralose, and sodium lauryl sulfate. All are present in the marketed ivacaftor 150 mg tablets except for mannitol and sucralose (b) (4)

Two dosage strengths of the drug product are proposed to be marketed, i.e., 50 mg and 75 mg per packet with each packet equivalent to one dose. Both strengths are filled with the same granules but with different fill weight. The drug product packet itself will be a printed, foil laminate packet (b) (4). The drug will be supplied as 56 packets in a carton.

Stability data support a 24 month shelf life. For more detailed information please refer to the primary chemistry review by Dr. Edwin Jao.

4. Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data were required or submitted with this sNDA.

5. Clinical Pharmacology/Biopharmaceutics

Vertex conducted a clinical pharmacology program to support extrapolation of efficacy of ivacaftor, based on comparable ivacaftor exposure, from CF patients 6 years of age and above to patients with CF 2 to 5 years of age. This was appropriate since the pathophysiology of CF remains the same regardless of age such that CF patients 2 to 5 years of age who possess one of the mutations in the *CFTR* gene for which ivacaftor is indicated would be expected to obtain benefit.

The key components of the clinical pharmacology program were 2 studies:

- Study 015, a randomized, open-label, 4-sequence, 4-period, crossover study in healthy male subjects designed to investigate (1) the relative bioavailability of the approved 150 mg of ivacaftor dosed as the granule formulation versus the 150 mg commercial tablet formulation in the fed state, (2) the effect of food (high-fat meal) on the bioavailability of ivacaftor dosed as the 150 mg granule formulation, and (3) the dose

proportionality of the ivacaftor granule formulation between doses of 50 mg and 150 mg in the fed state.

- Study 108, a 2-part, open-label, single-arm PK and safety study of ivacaftor in CF patients 2 to 5 years of age at doses of 50 mg twice daily for subjects <14 kg and 75 mg twice for subjects ≥14 kg. Population PK modeling was applied in order to evaluate the sparse PK data obtained.

The results of the 2 studies demonstrated that:

- In Study 015, a 150 mg dose of ivacaftor granules had a similar bioavailability as the 150 mg tablet when given with fat-containing food in adult subjects. The effect of food on ivacaftor absorption was similar for ivacaftor granules and the 150 mg tablet formulation.
- Population PK analyses of data collected in Study 108 predicted similar drug exposure levels in adults and children 2 to 5 years of age with the proposed dosing regimen. Of note is that for CF patients 6 to 11 years of age, the ivacaftor exposure (AUCss) was 87% higher than the mean AUC in adult patients administered 150 mg ivacaftor tablets twice daily (Table 1).This is not surprising given that ivacaftor exposure for doses 50 mg to 150 mg is dose proportional and the smaller body size (volume of distribution) of the 6 to 11 year olds compared to adults.

Table 1. Predicted steady-state ivacaftor exposure for pediatric and adult CF patients

	Adult (≥18 yr)	**Pediatric (2 to <6 yrs, <14kg)**	**Pediatric (2 to <6 yrs, ≥14kg)**	**Pediatric (6 to <12 yrs)**	**Pediatric (12 to <18 yrs)**
Dose (mg, BID)	150	50	75	150	150
AUCss (ng/mL*h) mean (±SD)	10700 (4100)	10500 (4260)	11300 (3820)	20000 (8330)	9240 (3420)

Source: Dr. Jianmeng Chen's clinical pharmacology review

In summary, the data and population PK analyses support the proposed ivacaftor doses of 50 mg and 75 mg twice daily for CF patients 2 to 5 years of age who weigh < 14 kg and ≥ 14 kg, respectively. For additional information see the clinical pharmacology and pharmacometrics reviews by Drs. Jianmeng Chen and Dinko Rekic, respectively.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical- Efficacy

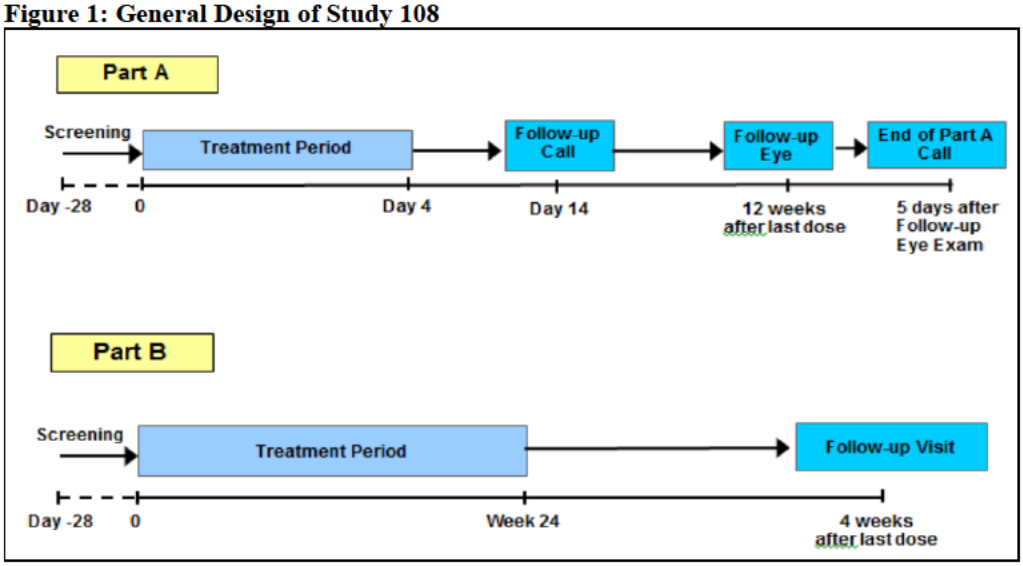
Overview of the Clinical Program

Vertex Pharmaceuticals submitted the results from a PK and safety study (Study 108) to support the extrapolation of efficacy and safety of ivacaftor granules for the treatment of CF patients 2 to 5 years of age at a dose of 50 mg twice daily for patients weighing < 14 kg and 75 mg twice daily for patients weighing > 14 kg for whom ivacaftor (Kalydeco) is approved.

Design and Conduct of Study 108

Study 108 was an open-label PK and safety study in CF patients 2 to 5 years in age. This study was conducted in two parts (A and B). Part A included a 4-day treatment period where the pharmacokinetics of ivacaftor granules was assessed and dosing determined for Part B based on matching the PK of ivacaftor observed in the adult CF patient population. Part B included an open-label 24-week treatment period where safety, pharmacodynamics (sweat chloride) and efficacy data were collected (Figure 1).

Figure 1: General Design of Study 108



CF patients enrolled were 2 to 5 years of age who weighed at least 8 kg and had a known "gating" mutation in the *CFTR* gene. Patients with evidence of colonization with *Burkholderia cenocepacia, Burkholderia dolosa*, or *Mycobacterium abcessus*, those with abnormal liver function defined as 3 or more liver function tests (ALT, AST, AP, GGT, total bilirubin) ≥3 times the upper limit of normal, and those with a lens opacity or cataract identified at the screening ophthalmologic examination, or an inability to undergo an adequate slit lamp examination were excluded. Medications known to be CYP3A inhibitors or inducers and grapefruit/grapefruit juice were not allowed for at least 14 days before day 1 of Part A or B and throughout the treatment period.

For Part A, following a 28-day screening period CF patients 2 to 5 years of age received either 50 mg (<14 kg) or 75 mg (≥14 kg) of ivacaftor granules every 12 hours for four days during which time PK samples were collected before the morning doses on day 1 and before the morning dose and at 2, 3, 6, 8, and 24-60 hours after the morning dose on day 4. Patients received an ophthalmologic exam prior the first dose and 12-weeks after the last dose. Patients enrolled in Part A were also allowed to participate in Part B.

For Part B, after a 28-day screening period CF patients 2 to 5 years of age received ivacaftor twice daily for a 24-week period. The dose, confirmed from Part A, was 50 mg twice daily for patients weighing < 14 kg and 75 mg twice daily for patients weighing ≥ 14 kg. Study visits occurred at day 1 and weeks 2, 4, 8, 12, 16, 20, 24, and 24+1 day. For patients who had not participated in Part A, an ophthalmologic exam was performed prior to the initial dose and at

weeks 12 and 24. Following the treatment period all patients were allowed to continue in an open-label extension study (Study 109).

The primary objectives of the study were to assess the PK and safety of ivacaftor in CF patients 2 to 5 years of age. Safety was determined by adverse events (AE), clinical labs, ECGs, vital signs, ophthalmologic assessments, and physical exams.

Secondary endpoints included PK estimation of ivacaftor metabolites M1 and M6 and change from baseline in sweat chloride, weight, stature, and BMI through 24-weeks of treatment. There were many tertiary assessments including z-scores for weight, stature, and BMI, respiratory cultures, spirometry, and pulmonary exacerbations.

Efficacy Determination

The determination of efficacy for extension of the ivacaftor indication down to CF patients 2 to 5 years of age who have a mutation in the CFTR gene for which ivacaftor is approved is based on extrapolation of efficacy demonstrated in randomized, placebo-controlled clinical studies conducted in CF patients 6 years of age and older. The following section, which is focused on the 24 week Part B of Study 108 describes the patient population and briefly mentions supportive pharmacodynamic data (change in sweat chloride) as well as selected efficacy parameters assessed in this small uncontrolled study.

Disposition:

Thirty- four patients participated in Study 108, Part B. One patient did not complete the 24-week treatment period due to an adverse event; a 2 year old male who developed an increase in a liver transaminase (ALT) > 8 times the upper limit of normal (ULN). This event is discussed in the Safety section (Section 8) below.

Demographics:

The demographics of the overall patient population were notable for a study population that was Caucasian. Thirty two CF patients had a *G551D* mutation in the *CFTR* gene while 2 were noted to have a *S549N* gene in the *CFTR*. The mean age was 3.2 years; there were 20 patients ages 2 to 3 years and 14 patients ages 4 to 5 years. Baseline per cent predicted FEV1 was reported as 87 to 92% but would typically be somewhat unreliable in patients this young. That being said, CF patients ages 2 to 5 years of age would generally have relatively normal spirometry/lung function as seems to be the case. Sweat chloride values approximated 100 mmol/L, consistent with that observed historically for patients with CF who have a *G551D* or similar gating mutation in the *CFTR* gene. Mean BMI was 16.0 kg/m^2.

Pharmacodynamic and Supplemental Efficacy Results:

Pharmacodynamic assessment: sweat chloride

In the open-label Study 108 Part B, CF patients ages 2 to 5 years of age with a *G551D* or *S549N* mutation in the *CFTR*, who were administered either 50 mg or 75 mg of ivacaftor demonstrated a mean absolute change from baseline in sweat chloride of -45 mmol/L (95% CI -53, -38) through Week 24. This reduction is very consistent with that demonstrated in older CF patients and adults with the same types of mutations in the *CFTR* (- 48 mmol/L for adults

with a *G551D* mutation) and supports a similar biologic activity for ivacaftor in the 2 to 5 year old patient population as for adults.

Other relevant efficacy assessments

A formal statistical evaluation of efficacy in this open-label, uncontrolled study was not conducted. Efficacy endpoints were analyzed as continuous variables using descriptive summary statistics and presented by visit and treatment. That being said, some of the efficacy variables assessed such as weight gain, stature, and pulmonary function are of interest. With regard to absolute change from baseline in weight, at week 24, both ivacaftor dose groups demonstrated absolute increases in weight compared to their respective baselines, 1.0 kg for the 50 mg ivacaftor treatment group and 1.5 kg for the 75 mg group. Absolute increases in stature/height were also observed; 2.5cm for the 50 mg and 3.5 cm for the 75 mg ivacaftor treatment groups, respectively. However, as mentioned in primary clinical and statistical reviews by Robert Lim MD and David Petullo MS, respectively, whether or not increases in weight or stature were related to ivacaftor treatment is uncertain, as there was no placebo control group and the studied age 2 to 5 year old group was actively growing. Based on CDC growth charts for healthy children, the average weight gain during a 6-month period for children between the age of 2 to 6 years is approximately 1 kg and for stature approximately 3 to 4 cm . As such, the observed absolute increases in weight and stature may reflect normal development, rather than a treatment effect. With regard to BMI, the mean change from baseline was 0.33kg/m^2 and 0.31kg/m^2 for the 50mg and 75mg ivacaftor treatment groups, respectively.

Twenty of the 34 CF patients in Part B had results of spirometry reported, 3 received the 50 mg ivacaftor dose and 17 received the 75 mg dose. At week 24, the change from baseline in per cent predicted FEV1 was -12.5% and 4.3% for patients in the ivacaftor 50 mg and 75 mg groups, respectively. Because of the small number of patients studied and inherent variability of the pulmonary function (FEV1) data, a determination of efficacy based on it cannot be made. Other efficacy and pharmacodynamic assessments such as exacerbations, unplanned antibiotic therapy, hospitalizations, microbiology cultures, fecal elastase, and immunoreactive trypsinogen were also collected however, due to the lack of a control group , infrequent number of events, or lack of known correlation to clinical benefit, the data are insufficient to determine a real benefit attributable to ivacaftor.

Efficacy Summary

Efficacy for the 2 to 5 year old patient subpopulation is extrapolated from efficacy data obtained from older children and adults based on the same pathophysiology of the disease, cystic fibrosis, and selection of an appropriate dose from modeling of pharmacokinetic data. The large decrease from baseline in sweat chloride of (-45 mmol/L) observed in the 2 to 5 year old CF patient population, consistent with that demonstrated in older CF patients and adults with the same types of mutations in the *CFTR* (- 48 mmol/L) supports a similar biologic activity for ivacaftor in the 2 to 5 year old patient population as for adults.

8. Safety

Database

The overall safety assessment for ivacaftor is derived primarily from data previously submitted and reviewed when it was approved in January 2012, for treatment of CF patients with a G551D mutation in the CFTR gene. Supportive safety information include additional safety data derived from small clinical studies in CF patients with "gating" mutations other than G551D, patients with a R117H in the CFTR gene and open-label extension studies. For this submission the principle safety issues were whether younger CF patients 2 to 5 years of age displayed a liver toxicity profile different than older CF patients and whether any eye findings, i.e., cataracts or lens opacities were detected.

With regard to Study 108, there were no deaths reported and there were relatively few (6) SAEs. SAEs included CF exacerbation, device-related sepsis, increased transaminases, positive pseudomonas culture, vomiting, and convulsion (one each).

One patient permanently discontinued treatment due to an adverse event; a 2 year old male who developed an increase in ALT > 8 times the ULN. Notably, the child had an ALT that was > 3 times the ULN at baseline. A liver biopsy was performed 3-weeks which showed non-specific findings. Approximately 2 months after discontinuation the patient's ALT had decreased to 58 U/L.

Eleven patients temporarily interrupted study drug treatment due to adverse events; 3 for LFT elevations, 2 for vomiting, and 1 for croup, device-related sepsis, gastroenteritis, retching, rash, and increased cough.

Common adverse events for both the 50 and 75 mg ivacaftor treatment groups were consistent with those commonly observed in the CF population and in young children such as increased cough, nasal congestion, rhinorrhea, upper respiratory tract infection, vomiting, pyrexia, and CF exacerbation.

Ivacaftor Program Specific Safety Issues

Increased liver transaminases/liver-related AEs

Increases in AST and ALT and liver-related AEs have been observed in both patients receiving ivacaftor and placebo in the ivacaftor clinical program making it difficult to discern whether any liver toxicities are due to ivacaftor or to CF-related liver disease which can be present in up to about a third of CF patients. Nevertheless, increased transaminases are included in the Warnings and Precautions section of the Kalydeco label. For Study 108, liver-related AEs and elevated transaminases laboratory tests were events of interest. Regarding adverse events, a total of 5 adverse events (one SAE and 4 non-serious AEs) were noted to be related to increased transaminases or hepatic enzymes. Of note, during prescribed monitoring of transaminases over the course of Study 108, 6 patients of 34 (18%) had maximum on-treatment LFTs of >2x ULN. Of these patients 5 had values which were >8x ULN. It is also worth noting that all these patients had a baseline LFTs >2x ULN. No patients with baseline LFTs ≤2x ULN had maximum LFT elevations of greater than 2x ULN suggesting that those with already elevated transaminases or pre-existing liver disease may be more susceptible to ivacaftor associated transaminase elevations or liver injury. However, the lack of a placebo arm in Study 108 makes it difficult to ascribe the events as definitely related to ivacaftor.

Cataracts/lens opacities

Ophthalmological exams were conducted at baseline, during, and after the 24-week treatment period to assess for the development of cataracts or lens opacities that were identified as ivacaftor-related toxicities a juvenile animal (rat) nonclinical study. For the 34 patients enrolled in Study 108 Part B, no cataracts or lens opacities were identified.

Safety Update

As described at 21 CFR 314.50(d)(5)(vi)(b), the Applicant was required to submit a safety update during the review period of the NDA. The update was submitted on February 27, 2015 and covered the period July 16, 2014 through January 17, 2015. The update consisted of reports of deaths, serious adverse events, discontinuations due to adverse events, and liver and eye adverse events for CF patients who had enrolled in Study 108 who had rolled over into the open-label extension period designated as Study 109. There were no deaths or permanent discontinuation from ivacaftor due to an adverse event. There were 11 SAEs reported, 5 of which were CF exacerbations. Other SAEs that occurred in single patients included increased transaminases, LFTs abnormal, enterovirus infection, subcapsular cataract, pyrexia, and anoxic seizure. With regard to the SAEs designated as increased transaminases/LFTs, one patient was a 4 years old male who received 75 mg ivacaftor twice daily who completed Study 108 without significant elevations in LFTs who on week 44 of dosing was noted to have LFT elevations of > 8 x ULN. Drug dosing was discontinued and work-up of the patient revealed an Ebstein Barr Virus infection. Ivacaftor was reinitiated after LFTs decreased and have remained low. The other patient was also a 4 years old male who had completed the 24-week dosing period for Study 108 without liver problems. At week 40, increased LFTs > 8 x ULN were noted. The patient was also noted to have a viral gastroenteritis at the time. Ivacaftor was continued and the LFTs returned to baseline while on active drug.

The cataract report was noted in a 6 year old who completed Study 108 without signs of cataracts or lens opacities. On eye exam at week 32, a subcapsular cataract was noted in the left eye without significant impact on vision. Ivacaftor was continued and upon repeat exam at week 48, the cataract could not be identified. Exams were conducted by ophthalmologists using the LOCS III scoring system. At this time, it is likely that the cataract visualized at week 32 was an error.

Safety Summary

Overall, the safety data for Study 108 and the extension (Study 109) do not reveal any new safety concerns. The safety risks of ivacaftor continue to appear relatively small and are balanced by the efficacy demonstrated. Although the exposure to ivacaftor in Studies 108/109 was relatively short, the data do not raise additional concerns for increased liver transaminases or other liver injury in patients receiving ivacaftor beyond what has been observed in older CF patients. The one cataract identified in a 5 year old after 32 weeks of ivacaftor was likely an error as it was not identified 16 weeks later at week 48 despite continuing on ivacaftor.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was not convened or required for this submission.

10. Pediatrics

The safety and efficacy of Kalydeco in patients with CF 6 to 17 years who have a *G551D, S1251N, G178R, S549N, G1244E, S549R, G551S, S1255P, G1349D, or R117H* mutation in the *CFTR* has been demonstrated. This NDA provides data to support the extrapolation of efficacy and determination of reasonable safety to extend the ivacaftor indication to pediatric patients with CF 2 to 5 years of age for whom ivacaftor is already approved.

11. Other Relevant Regulatory Issues

- Financial Disclosure: No investigators involved in the trial used to support this sNDA (Study 108) had interests that required financial disclosure.

- DSI audits information: No DSI audits were conducted at clinical study sites for this small clinical trial. Previous inspections of study sites participating in the ivacaftor development program and of the Vertex facility revealed no irregularities.

12. Labeling

The Applicant submitted a label for the approved product Kalydeco that was amended to contain safety, pharmacokinetic, and limited efficacy data from the open-label PK and safety study submitted to support the granule dosage form and extension of the ivacaftor indication to pediatric patients with cystic fibrosis 2 to 5 years of age. The label was reviewed by the appropriate disciplines within the Division as well as OSE, OPDP, and DRISK who recommended various changes to correct formatting errors and to better describe the drug product and indicated population to healthcare providers. Labeling discussions have revolved around how to best report the pharmacokinetic data used to extrapolate efficacy and the appropriateness of inclusion of the equivocal clinical efficacy information in the label. The final labeling language between Vertex and the Division remains under discussion. The carton and container labeling have been reviewed by the CMC team and agreed upon.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of ivacaftor for the treatment of CF in patients 2 to 5 years of age at a dose of 50 mg in patients < 14 kg and 75 mg for patients ≥ 14 kg taken twice daily with fat-containing food in patients with one of the following mutations in the CFTR gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H.* The safety profile of ivacaftor in CF patients 2 to 5 years of age appears similar to that observed for older pediatric patients and adults. As efficacy for the 2 to 5 year old patient subpopulation is extrapolated from efficacy data obtained from older children and adults, when additional data are submitted to support approval of ivacaftor for other CFTR mutation subpopulations, the indication can also be extrapolated to 2 to 5 year old CF patients.

- Risk Benefit Assessment

The potential benefits of ivacaftor in CF patients 2 to 5 years of age outweigh the potential risk. The safety profile of ivacaftor over 24 weeks treatment in observed in the limited number of CF patients 2 to 5 years of age studied is similar to that observed for older pediatric patients and adults. Adverse effects on the liver and eyes are already included in the Warnings and Precautions sections of the label and will be monitored in the post-market setting. Efficacy for the 2 to 5 year old patient subpopulation is extrapolated from efficacy data obtained from older children and adults based on the same pathophysiology of the disease, cystic fibrosis, and selection of an appropriate dose from modeling of pharmacokinetic data.

1. Recommendation for Post-marketing Risk Management Activities

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

2. Recommendation for other Post-marketing Study Commitments

No post-marketing commitment or required studies are recommended.

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/

ANTHONY G DURMOWICZ
02/28/2015