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APPLICATION NUMBER:

203188Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: January 27, 2012

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Director, Division of Pulmonary, Allergy, and Rheumatology,
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 203188

Applicant Name: Vertex Pharmaceuticals

Date of Submission: October 18, 2011

PDUFA Goal Date: April 18, 2012

Proprietary Name: Kalydeco

Established Name: Ivacaftor

Dosage form: Tablets for oral ingestion

Strength: 150 mg

Proposed Indications: Cystic Fibrosis

Action: Approval

1. Introduction

Vertex submitted this 505(b)(1) new drug application for use of Kalydeco (ivacaftor) Tablets 150 mg for the treatment of cystic fibrosis in patients 6 years of age and older who have a G551D mutation in the cystic fibrosis transmembrane regulator (CFTR) gene. The proposed dose is 150 mg tablet taken orally every 12 hours with fat-containing foods. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal 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 properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 1800 mutations in the CFTR gene, which, when present in both CFTR alleles, results in the clinical constellation that is CF. There is no cure for CF, treatment is limited to alleviation of symptoms and treatment of complications. Current therapies used by patients with CF include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements.

Ivacaftor is a new molecular entity, which is classified as a cystic fibrosis transmembrane conductance regulator potentiator. 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. Ivacaftor has been developed to treat a specific mutation in the CFTR, called the G551D mutation, where the mutated CFTR protein reaches the cell surface, but does not activate normally resulting in a low probability of being open. On approval, ivacaftor will be the first drug that acts to treat the underlying defect in the CFTR ion channel, which is the cause of CF, albeit in the small subpopulation of patients with CF with at least one copy of the G551D mutation in the gene.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Kalydeco tablets, contains 150 mg ivacaftor and standard compendial excipients. The drug product will be packaged as a 56-count carton (containing 4 individual blister cards of 14 tablets per card) and bottles containing 60 tablets. The drug substance manufactured as the (b) (4) (b) (4)

All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 30 months is proposed and supported by submitted data.

The manufacturing process for ivacaftor employed Quality-by-Design (QBD) elements meant to ensure that production of a consistent drug product was built into the manufacturing process. One of the significant issues in the QBD framework was the fact that (b) (4) therefore (b) (4)

Because of the critical nature of this procedure, the CMC and Biopharmaceutics teams have recommended tighter dissolution specifications that were proposed and accepted by Vertex Pharmaceuticals.

4. Nonclinical Pharmacology and Toxicology

Vertex Pharmaceuticals conducted a complete and adequate toxicology program that included general toxicology studies in rodent and non-rodent species, reproductive and embryofetal development studies, and carcinogenicity studies. The liver was identified as a target organ of toxicity in 3 month studies with relatively high doses in rats and mice; however, no liver toxicity was observed in chronic studies with rats and dogs or lifetime studies with rats and mice. Liver toxicity appeared to be monitorable. The gastrointestinal tract and heart were identified as target organs in the chronic toxicity study with dogs although these findings were considered monitorable in a clinical setting. Drug exposure in nonclinical test species and humans was composed of exposure to the parent drug, ivacaftor, and its metabolites, M1 and M6. In humans, plasma levels of M1

and M6 were significantly greater than the parent drug, ivacaftor; however, exposures to parent drug were significantly higher than M1 and M6 in toxicity studies with the mouse, rat, and dog. M1 and M6 were regarded as disproportionate metabolites in humans. The proposed human dose has adequate safety margins for the animal toxicity findings. Rats provided a sufficient safety margin for M1, the predominant form in humans. Coverage for the M6 metabolite was approximately 50% of human exposure in rats, although this was considered to be sufficient as the structures of ivacaftor and M6 are relatively similar and only differ by the presence of a carboxylic acid group in M6. The reproductive and embryofetal development studies showed decreased fertility in rats at doses that were overtly toxic. The drug was not teratogenic with no effects on peri- and post-natal development in rats. The submitted data support pregnancy category B classification for ivacaftor. The carcinogenicity study showed no increased incidence of tumors in 2-year mouse and rat studies.

5. Clinical Pharmacology and Biopharmaceutics

Vertex Pharmaceuticals submitted a complete and adequate clinical pharmacology program for ivacaftor. Exposure to ivacaftor increases approximately 2- to 4-fold when given with food containing fat. Therefore, it is recommended that ivacaftor to be taken with fat-containing food. Ivacaftor is extensively metabolized primarily by CYP3A enzymes. M1 and M6 are two major metabolites, which are partially active. Following oral administration, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. Since ivacaftor is mainly metabolized by CYP3A, exposure of ivacaftor is expected to increase when administered with inhibitors of CYP3A, and decrease when administered with inducers of CYP3A. Ivacaftor has been demonstrated to be a P-gp inhibitor in vitro. Vertex Pharmaceuticals will conduct a post-marketing required study to generate data for inclusion in the label on the potential for in vivo drug-drug interaction of ivacaftor with sensitive P-gp substrates.

A thorough QT study was conducted for ivacaftor and reviewed by the QT study interdisciplinary review team. No significant QTc prolongation effect of ivacaftor at the doses tested was detected.

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant COPD clinical studies with ivacaftor tablets

ID Year*	Study type	Study duration	Patient Age, yr	Treatment groups#	N (ITT)	Primary efficacy variables	Countries
101 2008	Dose ranging, Proof of activity	4 week	G551D ≥ 18	Part 1: Iva 25, 75, 150 mg BID Placebo Part 2: Iva 150, 250 mg BID Placebo	20 19	Predose FEV1 Sweat chloride Nasal potential	North America, Germany
102 2011	Efficacy Safety	48 week	G551D ≥ 12	Iva 150 mg BID Placebo	83 78	Predose FEV1	North America, Europe, Australia
103B 2011	Efficacy Safety	48 week	G551D 6-11	Iva 150 mg BID Placebo	26 26	Predose FEV1	North America, Europe, Australia
104A 2011	Efficacy Safety	16 week	F508/ F508 ≥ 12	Iva 150 mg BID Placebo	112 28	Predose FEV1	North America (US)
105	Safety	Up to 96 week	G551D ≥ 6	Iva 150 mg BID	~144		North America, Europe, Australia
*Year study subject enrollment ended; In Product Label Study 102 is identified as Trial 1. Study 103B is identified as Trial 2, and Study 104A is identified as Trial 3. # Iva = Ivacaftor Tablets							

b. Design and conduct of studies

Study 101 was randomized, double blind, placebo-controlled in design, conducted in patients with CF with at least one copy of the G551D mutation in the CFTR gene. The study was conducted in two parts. Part 1 was of placebo-controlled, crossover design and consisted of a 14-day treatment period followed by a 7-28 day washout period before crossing over. Part 2, conducted in a separate set of patients, was of parallel-group design and consisted of 28 days of treatment. The major clinical and pharmacodynamic endpoints relevant for dose selection included FEV1, nasal potential difference (NPD), and sweat chloride.

Studies 102 and 103B were randomized, double blind, parallel group in design, conducted in patients with CF with at least one copy of the G551D mutation in the CFTR gene. The studies were similar in design with different age of patients. The studies had a 14-day run-in period, followed by double blind treatment period for an initial 24 weeks for efficacy assessment and a subsequent 24 weeks for assessment of durability of response. The primary efficacy endpoint in both studies was improvement in lung function as determined by the mean absolute change from baseline in percent-predicted predose FEV1 through 24 weeks of treatment. Secondary efficacy endpoints included change in sweat chloride, change in CFQ-R (CF questionnaire – revised, respiratory domain), time to pulmonary exacerbation, change in weight gain. Safety assessment included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECG. The majority of patients completing these studies enrolled in the open-label safety study 105 (Table 1).

Study 104A was similar in design to studies 102 and 103B with the notable difference that the study was conducted in patients with CF with CF homozygous for the F508del mutation in the CFTR gene, and the duration of the study was for 16 weeks.

c. Efficacy findings and conclusions

The clinical program support efficacy of ivacaftor for the treatment of CF in patients 6 years and older who have a G551D mutation. The efficacy results were robust.

Dose selection and dosing regimen for ivacaftor was based on results of study 101 along with PK/PD data and modeling and simulation. Results of study 101 showed that doses of 75 mg and 150 mcg every 12 hours clearly separated from the 25 mg dose for FEV₁, sweat chloride, and nasal potential difference. The 250 mg dose did not provide additional benefit over the 150 mg dose. The 150 mg dose was appropriately chosen for further studies based on slight nominal difference between 75 mg and 150 mg dose and lack of additional safety concern.

Change from baseline in percent predicted predose FEV₁ at 24 Weeks showed significant improvement in both studies (Figure 1). The treatment difference between ivacaftor and placebo for the mean absolute change in percent predicted FEV₁ from baseline through Week 24 was 10.6 % ($p < 0.0001$) in Study 102 and 12.5% ($p < 0.0001$) in study 103B. Because the overall dropout rate at Week 24 was low (6% in each study), missing data is not expected to be an issue for this application. In fact, when different analytical methods and imputation strategies were applied, the results were consistent and highly significant. Major secondary endpoints also showed significant improvement as shown in Table 2. Furthermore, analyses of subpopulations showed improvement regardless of age, disease severity as measured by lung function, gender, and geographic region. Study 104 (F508del mutation in the CFTR gene) did not show significant improvements in efficacy measures (data not shown in this review), demonstrating that improvement with ivacaftor was specific to patients with CF with at least one copy of the G551D mutation in the CFTR gene.

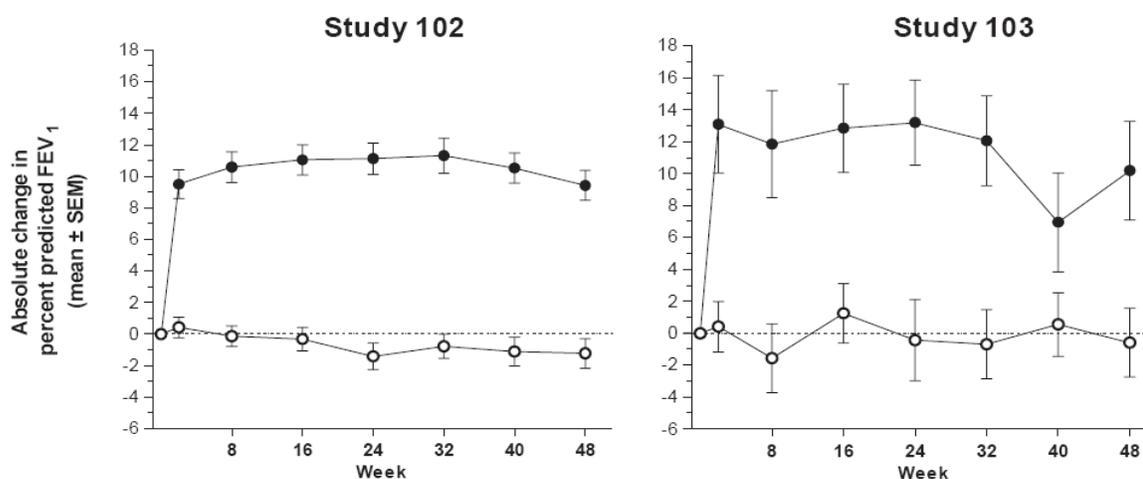
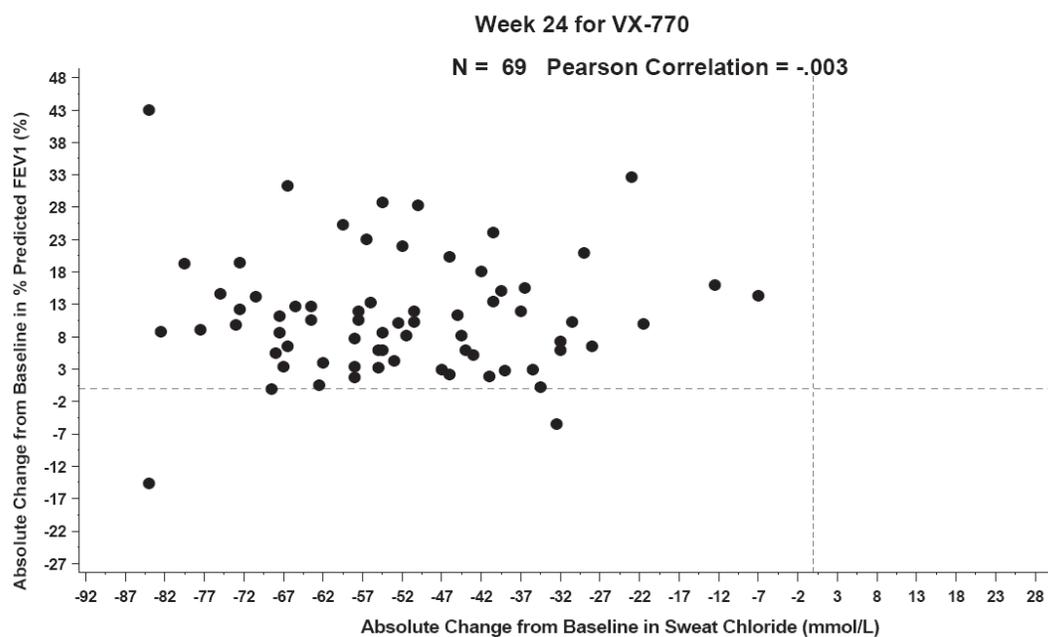


Figure 1, Mean absolute change from baseline in percent predicted predose FEV₁

Table 2. Effect of ivacaftor on other efficacy endpoints

	Study 102		Study 103	
	Treatment Difference (95% CI)	P-value	Treatment Difference (95% CI)	P-value
Mean absolute change from baseline in CFQ-R				
Through week 24	8.1 (4.7, 11.4)	<0.0001	6.1 (-1.4, 13.5)	0.1092
Through week 48	8.6 (5.3, 11.9)	<0.0001	5.1 (-1.6, 11.8)	0.1354
Time to first pulmonary exacerbation (hazard ratio)				
Through week 24	0.40 (0.2, 0.7)	0.0016	NA	NA
Through week 48	0.46 (0.3, 0.7)	0.0012	NA	NA
Mean absolute change from baseline in weight				
Through week 24	2.8 (1.8, 3.7)	<0.0001	1.9 (0.9, 2.9)	0.0004
Through week 48	2.7 (1.3, 4.1)	0.0001	2.8 (1.3, 4.2)	0.0002

**Figure 2. Scatter plot of absolute change from baseline in percent predicted FEV1 and absolute change from baseline in sweat chloride for study 102.**

Sweat chloride elevation (generally >60 mmol/L) along with clinical constellation of symptoms is used to diagnose CF. In the ivacaftor clinical studies, sweat chloride was

used as a PD endpoint to support efficacy. In CF patients with the G551D mutation in the CFTR gene, ivacaftor lead to statistically significant reduction in sweat chloride concentration compared to placebo. The mean change in sweat chloride concentration was - 48.7 mmol/L in the ivacaftor group compared to -0.6 mmol/L in the placebo group from baseline through week 48. However, reduction in sweat chloride did not correlate with improvement in pulmonary function. Results of study 102 are shown in Figure 2. Results of study 103B also did not show any correlation (results not shown in this review). The reason for lack of this correlation is not clear. It does not seem to be explained by patient compliance or plasma concentration of ivacaftor. Change of sweat chloride, while of interest, does not seem to be predictive of clinical outcome.

8. Safety

a. Safety database

The safety assessment of ivacaftor for CF patients is based on studies shown in Table 1. The safety database is reasonable considering that CF is an orphan disease and the subpopulation of patients with G551D mutation is a small fraction of the CF patients.

b. Safety findings and conclusion

The safety data do not raise safety concerns in the CF patients that would preclude approval or place any major limitation on the use of ivacaftor.

There were no deaths in the ivacaftor clinical studies during the controlled treatment period. The more commonly observed SAE was exacerbation of CF lung disease, which is expected for this patient population. The frequency of CF lung disease was 27% in placebo treated patients and 10% in ivacaftor treated patients. SAEs that occurred more frequently in ivacaftor treated patients compared to placebo treated patients were abdominal pain, increased liver enzymes, and hypoglycemia. On review of adverse events, laboratory measures, and ECGs, the safety finding of note with ivacaftor was elevation is ALT and AST. There was a small imbalance in transaminase elevations reported as adverse events that favored the placebo group with 15 patients (14%) compared to 20 patients (18%) in the ivacaftor group. Interpretation of adverse events resulting from liver-related laboratory findings is complicated by the underlying relatively high rates of laboratory abnormalities in the CF patients.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

An advisory committee was not convened for this application. After initial review of the data the Agency decided that the efficacy and safety were sufficiently robust that holding up approval to discuss at an advisory committee meeting was not necessary.

10. Pediatric

CF is an orphan disease and not subject to PREA. Based on the knowledge that CF is a genetic disease, which can manifest at birth, Vertex plans to conduct clinical studies in patients below 6 years of age.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited two sites recommended by the clinical review team. These two sites enrolled slightly larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. One investigator had significant equity interest in Vertex. This investigator enrolled (b) (6) patients in study 102 out of the total enrollment of 161. The multi-center nature of the study, along with robust efficacy, makes it unlikely that one center with a possible interest could have influenced or biased the results of the study.

c. Other

There are no outstanding issues with consults received from the Office of Prescription Drug Promotion (OPDP, formerly DDMAC), DMEPA, or from other groups in CDER. The CDRH was consulted to help address the adequacy of available tests for identification of specific CF gene mutation identification. CDRH noted that there are several FDA-cleared diagnostic test available that can detect G551D mutation. Furthermore, identification of specific CFTR genotype in patients with CF is now almost a standard of care of CF patients.

12. Labeling

a. Proprietary Name

The proposed proprietary name Kalydeco was reviewed by DMEPA and found to be acceptable. The name was also found to be acceptable to OPDP from a promotional perspective.

b. Physician Labeling

Vertex submitted a label in the Physician's Labeling Rule format that contained information generally supported by the submitted data. The label was reviewed by various disciplines of this Division, the Office of Medical Policy Programs (OMPP), the Office of Surveillance and Epidemiology (OSE)/DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The senior Pharmacology and Toxicology staff designated ivacaftor as a cystic fibrosis transmembrane conductance

regulator (CFTR) potentiator, which constitutes a new established pharmacological class. The Division and Vertex have agreed on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division, ONDQA, OPMP, and DMEPA, and were found to be acceptable.

d. Patient Labeling and Medication Guide

There is a Patient Counseling Information (Instruction for Use and Patient Package Insert) that has been reviewed by the Division, OMPP, and other groups within the Center and found to be acceptable. There will no Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Vertex has submitted adequate data to support approval of ivacaftor at a dose of 150 mcg tablet taken orally every 12 hours with fat-containing food for the treatment of CF in patients age 6 years and older who have a G551D mutation in the CFTR gene. The recommended regulatory action for this application is approval.

b. Risk Benefit Assessment

The overall risk-benefit assessment of ivacaftor for the treatment of CF patients age 6 years of age and older who have a G551D mutation in the CFTR gene supports its approval. In terms of safety, the concerns are relatively small, especially given the severity of the disease. There is a finding of possible increased liver transaminases in patients receiving ivacaftor, and it will be recommended that transaminases be monitored in patients prescribed ivacaftor. In terms of efficacy, the potential benefits of ivacaftor in CF patients with a copy of the G551D mutation in the CFTR gene are substantial and outweigh the identified safety concerns. In the clinical studies submitted, efficacy of ivacaftor in the indicated population was robust with demonstration of clinically meaningful benefit in several aspects of CF, such as lung function as demonstrated by increase in pre-dose FEV1 and fewer pulmonary exacerbations, and gastrointestinal function as demonstrated by substantial weight gain. Ivacaftor will be the first treatment for patients with CF that actually addresses the defective ion channel that is the cause of CF.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

There will be a PMR study as described in section 5 above.

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