Brand Name: Kalydeco

Generic: ivacaftor

Manufacturer[1]: Vertex Pharmaceuticals Incorporated

Drug Class[2,3]: Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) Potentiator

Uses:

Labeled Uses[1,2,3,4,5]: Treatment of cystic fibrosis in patients age 2 years and older who have one mutation in the CFTR gene that is responsive to ivacaftor
Unlabeled Uses[4]: No results available

Mechanism of Action[1,2,4,]: Ivacaftor is a potentiator of the CFTR protein, which is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor facilitates increased chloride transport by potentiating the channel open probability (or gating) of CFTR protein located at the cell surface.

Pharmacokinetics[1,2,3,4,5]:

Absorption:

T_{max}	**4 hours**
V_d	**353L**
$t_{1/2}$	**12 hours**
Clearance	**17.3 L/hr**
Protein binding	**99%**
Bioavailability	**87.8%**

Metabolism: In vitro and clinical studies indicate that ivacaftor is primarily metabolized by CYP3A. M1 and M6 are the two major metabolites of ivacaftor in humans. M1 has approximately one-sixth the potency of ivacaftor and is considered pharmacologically active. M6 is not considered pharmacologically active.

Elimination: Following oral administration, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. The major metabolites M1 and M6

accounted for approximately 65% of the total dose eliminated with 22% as M1 and 43% as M6. There was negligible urinary excretion of ivacaftor as unchanged parent drug.

Efficacy:

Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365(18):1663-72.

Study Design: Phase 3, randomized, double-blind, placebo-controlled international study

Description of Study: *Methods:* 161 subjects with cystic fibrosis and at least one G551D-CFTR mutation underwent randomization and received ivacaftor (83 subjects) or placebo (78) at a dose of 150 mg every 12 hours for 48 weeks. The primary efficacy endpoint was the absolute change from baseline through week 24 in the percent of predicted FEV1. Safety was evaluated by the adverse-event profile. *Results:* The change from baseline through week 24 in the percent of predicted FEV1 was greater by 10.6 percentage points in the ivacaftor group than in the placebo group ($P<0.001$). Subjects receiving ivacaftor were 55% less likely to have a pulmonary exacerbation than were patients receiving placebo, through week 48 ($P<0.001$). Additionally, through week 48, subjects in the ivacaftor group scored 8.6 points higher than did subjects in the placebo group on the respiratory-symptoms domain of the Cystic Fibrosis Questionnaire–revised instrument ($P<0.001$). By 48 weeks, patients treated with ivacaftor had gained, on average, 2.7 kg more weight than had patients receiving placebo ($P<0.001$). The incidence of adverse events was similar with ivacaftor and placebo, with a lower proportion of serious adverse events (such as pulmonary exacerbation, hemoptysis, and hypoglycemia) with ivacaftor than with placebo (24% vs. 42%).

Limitations: This study was sponsored by Vertex Pharmaceuticals, the manufacturer of ivacaftor. Also, nine employees of the company (not authors), helped with medical-writing, editorial, coordination support, preparing the study document, providing advice on the study design and data interpretation, performing the patient-safety analysis, providing clinical-operations support, and performing pharmacokinetic analysis. Also, the mean age was 25.5 years old. This makes the results difficult to extrapolate to younger and older patients.

Conclusion: Ivacaftor was associated with improvements in lung function at 2 weeks that were sustained through 48 weeks. Substantial improvements were also observed in the risk of pulmonary exacerbations, patient-reported respiratory symptoms, weight, and concentration of sweat chloride. More studies need to be conducted on the specificities of

the pre study medications patients were using. The combined therapies may or may not have an effect on FEV1.

Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor treatment: randomized trial in subjects with cystic fibrosis who have an R117H-CFTR mutation. Lancet Respir Med. 2015;3(7):524-33.

Study Design: Multicenter, phase 3, randomized, double-blind, placebo-controlled parallel-group study

Description of Study: *Methods:* 69 subjects with cystic fibrosis were randomized and received either placebo or ivacaftor 150 mg every 12 hours for 24 weeks. The primary outcome measure was the absolute change from baseline in ppFEV1 through week 24. Secondary outcome measures included the change from baseline through week 24 in BMI, the respiratory domain of the CF questionnaire-revised (CFQ-R), and sweat chloride. Safety was assessed by the adverse events, clinical laboratory values for serum chemistry, hematology, and coagulation, ECGs, and vitals signs. *Outcome Results:* After 24 weeks, treatment difference in mean absolute change in ppFEV1 between ivacaftor (n=34) and placebo (n=35) was 2.1 percentage points (p=0.20). Ivacaftor treatment resulted in significant treatment differences in sweat chloride (−24.0 mmol/L; $p<0.001$) and CFQ-R respiratory domain (8.4; p=0.009). In prespecified subgroup analyses, ppFEV1 significantly improved with ivacaftor in subjects aged ≥18 years (treatment difference vs placebo: 5.0 percentage points; p=0.01), but not in subjects aged 6 to 11 years (−6.3 percentage points; p=0.03). No new safety concerns were identified.

Limitations: This study was funded by Vertex Pharmaceuticals, the manufacturer of ivacaftor. Two authors are employees of Vertex Pharmaceuticals and may own stock or options in that company. Another limitation was that a majority of subjects were from North America and were ≥ 18 years of age. This limits the generalizability of the results to only this population. More studies need to be done on patients outside North America and have more patients who are <18 years old in order to increase the external validity. Sample size in general was adequate and fulfilled the pre-determined value.

Conclusion: This study did not meet the primary outcomes, but it did show statistical significance in the secondary outcomes. However, it does suggest that ivacaftor may be clinically significant in improving lung function in adult patients with *R117H-CFTR* and may benefit patients with cystic fibrosis.

Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest. 2012;142(3):718-24.

Study Design: Multicenter, two-part, phase 2, randomized (4:1), double-blind, placebo-controlled study

Description of Study: *Methods:* 140 subjects were randomized in a 4:1 ratio to receive 150 mg ivacaftor po or placebo administered every 12 h for 16 weeks. The primary end point of safety was evaluated by assessment of adverse events, clinical laboratory values, ECGs, vital signs, and physical examinations. The primary efficacy endpoint was the absolute change in FEV1 % predicted from baseline through week 16. Secondary efficacy endpoints were change from baseline through week 16 in sweat chloride concentration, change in weight, and patient-reported health using the disease-specific Cystic Fibrosis Questionnaire-Revised. *Outcome Results*: The overall adverse event frequency was similar in the ivacaftor (87.5%) and placebo (89.3%) groups through 16 weeks. The difference in the change of FEV1 % predicted from baseline through week 16 (primary end point) between the ivacaftor and placebo groups was 1.7% ($p = 0.15$). Sweat chloride, a biomarker of CFTR activity, showed a small reduction in the ivacaftor versus placebo groups of -2.9 mmol/L ($p=0.04$) from baseline through week 16.

Limitations: One limitation was the randomized 4:1 ratio where there was four times asmuch ivacaftor patients than there were placebo patients. Proper randomization would be a 1:1 ratio. Also, there were no p-values for the adverse events. Thus, we would not know if the adverse events of ivacaftor were statistically significant or not in comparison to placebo. Vertex Pharmaceuticals Incorporated also provided the financial support and study medication for the conduct of the study. Another limitation was that the mean age of subjects were around 25 years of age. This limits the generalizability of the results to only this population.

Conclusion: The results show that there is not a statistical significance for the difference in the change of FEV1% predicted from baseline through week 16 between ivacaftor and placebo. Sweat c hloride showed a statistically significant but small reduction in the ivacaftor versus placebo group from baseline through week 16. The results do expand the safety information for ivacaftor and support its continued evaluation. Lack of a clinical effect suggests that a CFTR potentiator alone is not an effective therapeutic approach for patients who have cystic fibrosis and are homozygous for F508del-CFTR mutation.

Contraindications[1,2,3,4,5]:

There are no contraindications listed in the manufacturer's labeling.

Precautions[1,2,3,4,5]:

Cataracts: Noncongenital lens opacities and cataracts have been reported in pediatric patients treated with ivacaftor; other risk factors were present in some cases (eg, corticosteroid use, exposure to radiation), but a possible risk related to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients.

CNS effects: May cause dizziness, which may impair physical or mental abilities; patients must be cautioned about performing tasks that require mental alertness (eg, operating machinery or driving).

Hepatic effects: May increase hepatic transaminases. Monitor liver function; increased monitoring may be necessary in patients with a history of elevated hepatic transaminases. Temporarily discontinue treatment if ALT or AST >5 times ULN. Following resolution of transaminase elevations, consider the benefits and risks of resuming therapy.

Hepatic impairment: Use with caution; dosage adjustment recommended in patients with moderate to severe (Child-Pugh class B or C) impairment.

Renal impairment: Use with caution in patients with severe renal impairment (CrCl ≤30 mL/minute) or ESRD.

Drug-drug interactions: Potentially significant interactions may exist, requiring dose or frequency adjustment, additional monitoring, and/or selection of alternative therapy. Consult drug interactions database for more detailed information.

Adverse Effects:

Occurring in >10% of patients

Central nervous system:

Headache (24%)

Dermatologic:

Skin rash (13%)

Gastrointestinal:

Abdominal pain (16%)

Diarrhea (13%)

Nausea (12%)

Respiratory:

Oropharyngeal pain (22%)

Upper respiratory tract infection (22%)

Nasal congestion (20%)
Nasopharyngitis (15%)

Occurring in >1% to <10% of patients

Central nervous system:

Dizziness (9%)

Dermatologic:

Acne vulgaris (4-7%)

Endocrine and metabolic:

Increased serum glucose (4-7%)
Hypoglycemia

Hepatic:

Increased liver enzymes (4-7%)
Increased serum ALT (4-7%)

Neuromuscular and skeletal:

Arthralgia (4-7%)
Musculoskeletal chest pain (4-7%)
Myalgia (4-7%)

Ophthalmic:

Cataract (children ≤ 12)

Respiratory:

Change in bronchial secretion (4-7%)
Pharyngeal erythema (4-7%)
Pleuritic chest pain (4-7%)
Rhinitis (4-7%)
Sinus congestion (4-7%)
Sinus headache (4-7%)
Wheezing (4-7%)

Miscellaneous:

Bacteria in sputum (4-7%)

Drug Interactions[1,2,3,4,5]:

CYP3A4 Inducers:

May decrease the serum concentration of ivacaftor (CYP3A4 substrates). This includes: bosentan, flibanserin, St. John's Wort, and vincristine.

CYP3A4 Inhibitors:

May increase the serum concentration of ivacaftor. This includes: brentuximab vedotin, colchicine, conivaptan, dasatinib, idealislib, mifepristone, pimozide, ranolazine, and silodosin.

P-glycoprotein Substrates:

P-glycoprotein inhibitors may increase the serum concentration of p-glycoprotein substrates. P-glycoprotein inhibitors may also enhance the distribution of p-glycoprotein substrates to specific cells/tissues/organs where p-glycoprotein is present in large amounts (e.g., brain, T-lymphocytes, testes, etc.). P-gp substrates includes: afatinib, aripiprazole, dabigatran, doxorubicin, edoxaban, rifaximin, topetecan, and venetoclax.

Dosing/Administration[1,2,3,4,5]:

Children >6 years, Adolescents, and Adult Dosing:

150 mg every 12 hours (oral tablet)

Pediatrics (2 to <6 years of age)

<14 kg: 50 mg packet every 12 hours (oral granules)

≥14 kg: 75 mg packet every 12 hours (oral granules

Elderly

Dose selection should be cautious. Start at the low end of the dosing range.

Renal impairment

CrCl >30 mL/minute: No dosage adjustment necessary (has not been studied).

CrCl ≤30 mL/minute: There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.

End-stage renal disease (ESRD): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied); use with caution.

Hepatic impairment

Mild impairment (Child-Pugh class A): No dosage adjustment necessary.

Moderate impairment (Child-Pugh class B):

Children 2 to <6 years:

<14 kg: 50 mg granule packet once daily

≥14 kg: 75 mg granule packet once daily

Children ≥6 years, Adolescents, and Adults: 150 mg once daily

Severe impairment (Child-Pugh class C): Has not been studied; use with caution

Children 2 to <6 years:

<14 kg: 50 mg granule packet once daily or less frequently

≥14 kg: 75 mg granule packet once daily or less frequently

Children ≥6 years, Adolescents, and Adults: 150 mg once daily or less frequently.

Use in special circumstances:

Adjustment for Toxicity:

ALT or AST >5 times ULN: Hold ivacaftor; may resume if elevated transaminases resolved and after assessing benefits vs risks of continued treatment.

Pregnancy Considerations:

Information related to ivacaftor use in pregnancy is limited

Lactation Considerations:

It is not known if ivacaftor is excreted in breast milk. According to the manufacturer, the decision to continue or discontinue breastfeeding during therapy should take into account the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.

Conclusion:

Ivacaftor can improve lung function in adult patients. However, two findings show that the outcomes were not statistically significant. Due to these limited studies, more studies need to be conducted on combination therapy of ivacaftor and another therapeutic agent for patients who have cystic fibrosis. Ivacaftor has numerous drug interactions and must be used with caution. Studies determining ivacaftor's place in therapy for cystic fibrosis needs to be completed. The most common side effects >20% are headache, oropharyngeal pain, and upper respiratory tract infection. Ivacaftor should only be given to patients with specific cystic fibrosis mutations that have been studied. Additionally, the average wholesale package price (56 tablets in a pack) is $28,675.36 and the average wholesale unit price for the 150 mg PO tablet is $512.06. Due to the high price of ivacaftor, this drug may not be the most cost effective.

Recommended References:

1. Kalydeco [package insert]. Boston, MA: Vertex Pharmaceuticals Inc.: 2017.
2. Ivacaftor. Clinical Pharmacology [Internet Database]. Elsevier Inc., 2017. Available at: http://www.clinicalpharmacology.com Accessed: May 24, 2017.
3. Ivacaftor. Lexi-Drugs [database online]. Lexi-Comp, Inc; May 23, 2017.
4. Ivacaftor. In: DRUGDEX® System [Internet Database]. Greenwood Village, Colo: Thomson Micromedex. Updated periodically. Accessed: May 24, 2017.
5. Ivacaftor. Oral. Facts & Comparisons 4.0 Online [Internet Database]. Wolters Kluwer. Available at: http://online.factsandcomparisons.com. Accessed: May 24, 2017..
6. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365(18):1663-72.
7. Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor treatment: randomized trial in subjects with cystic fibrosis who have an R117H-CFTR mutation. Lancet Respir Med. 2015;3(7):524-33.
8. Flume PA, Liou TG, Borowitz DS, et al. Ivacaftor in subjects with cystic fibrosis who are homozygous for the F508del-CFTR mutation. Chest. 2012;142(3):718-24.

Prepared by: Michelle Amena, WVU 2018 Doctor of Pharmacy Candidate