Therapeutic Class Overview
Cystic Fibrosis Transmembrane Conductance Regulator Potentiator

Therapeutic Class

- **Overview/Summary:** Cystic fibrosis is an autosomal recessive disease caused by mutations in the gene on chromosome seven that encodes the cystic fibrosis transmembrane conductance regulator (CFTR).[1] Normally, the CFTR protein functions as a chloride channel which regulates the activity of other cell-surface chloride and sodium channels. Currently, there are more than 1,300 known possible mutations of the CFTR gene, which are divided into five classes. Class I mutations are characterized by defective protein production, resulting in the complete absence of the CFTR protein, while class II mutations involve defective protein processing. Class III and IV mutations are characterized by diminished channel activity and defective conduction, respectively. Lastly, Class V mutations result in reduced amounts of functional CFTR protein.[2] Mutations in the CFTR gene result in deranged transport of ions which include chloride, sodium and bicarbonate; this may lead to viscous secretions in the respiratory, gastrointestinal and reproductive tract, as well as increased salt content in sweat gland secretions.[1]

  In the United States, cystic fibrosis occurs most commonly in Caucasians, with a prevalence of one in approximately 3,000 people. Typical respiratory manifestations of cystic fibrosis include a persistent and productive cough, hyperinflation of the lung fields on chest radiograph, pulmonary function tests consistent with obstructive airway disease, as well as colonization of the airway with pathogenic bacteria early in life. In terms of the gastrointestinal manifestations, patients experience progressive pancreatic disease in the form of pancreatic insufficiency, pancreatitis and cystic fibrosis -related diabetes. Furthermore, malnutrition due to pancreatic insufficiency may cause rectal prolapse and musculoskeletal disorders. Patients with cystic fibrosis are also at an increased risk of liver disease, infertility, venous thrombosis and nephrolithiasis.[1]

  Kalydeco® (ivacaftor) is a CFTR potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least two years of age who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R. If the patient's genotype is unknown, a FDA-cleared cystic fibrosis mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the F508*del* mutation in the CFTR gene. As a potentiator of the CFTR protein, ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.[3] According to the consensus guidelines from the Cystic Fibrosis Foundation, in patients six years of age and older with at least one G551D CFTR mutation, treatment with ivacaftor is strongly recommended to improve lung function and quality of life, as well as to reduce exacerbations.[4] Guidelines do not currently address the use of ivacaftor in children two to six years of age.[4] Ivacaftor tablets are FDA-approved for pediatric patients and adults aged six and older while the oral granules are approved for patients two to less than six years of age. Additionally, ivacaftor oral granules are dosed by weight. Both formulations are given twice daily and with fat-containing foods.[3] There are no generic formulations currently available.

Table 1. Current Medications Available in the Therapeutic Class[3]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Ivacaftor (Kalydeco®)	Treatment of cystic fibrosis in patients two years of age and older who have one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R	Tablet: 150 mg Oral Granule: 50 mg/pack 75 mg/pack	-

Evidence-based Medicine

- The safety and efficacy of ivacaftor for up to 48 weeks in patients with cystic fibrosis for its Food and Drug Administration-approved indications are supported by randomized and controlled clinical trials.[3,5-7]
- In two placebo-controlled trials (N=213), treatment with ivacaftor in patients with cystic fibrosis and at least one G551D-cystic fibrosis transmembrane conductance regulator (CFTR) mutation significantly increased forced expiratory volume in one second (FEV_1) after 24 weeks, and the significant treatment effect was maintained throughout a total of 48 weeks. In addition, treatment with ivacaftor was associated with significant improvements in respiratory symptoms and significant decreases in sweat chloride concentrations and pulmonary exacerbations in one trial. In both trials patients receiving ivacaftor gained significantly more weight compared to placebo.[6,7]
- According to the labeling information for ivacaftor, the efficacy and safety of ivacaftor in patients with cystic fibrosis with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene were evaluated in a currently unpublished two-part, randomized, double-blind, placebo-controlled, crossover clinical trial (N=39). For the overall population of the nine mutations studied, treatment with ivacaftor compared to placebo resulted in significant improvement in percent predicted FEV_1, body mass index, and cystic fibrosis respiratory symptom score.[3]
- There is currently a lack of long term data with ivacaftor, and its benefits on mortality are unclear at this time.
- The efficacy of ivacaftor in children two to less than six years of age was extrapolated from efficacy in patients six years of age and older with support from population pharmacokinetic analyses.[3]
    - The safety of ivacaftor in children two to less than six years of age (mean age three years) is derived from a 24-week, open-label, clinical trial in 34 patients. The type and frequency of adverse reactions in this trial were similar to those in patients six years and older.[3]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
    - According to the consensus guidelines from the Cystic Fibrosis Foundation, in patients six years of age and older with at least one G551D cystic fibrosis transmembrane conductance regulator (CFTR) mutation, treatment with ivacaftor is strongly recommended to improve lung function and quality of life, as well as to reduce exacerbations. The clinical guideline does not address the use of ivacaftor in patients with a non-G551D CFTR mutation.[4]
    - Guidelines do not currently address the use of ivacaftor in children two to six years of age.[4]
- Other Key Facts:
    - Ivacaftor is the first and only CFTR potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least two years of age who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, or S549R.[3]
    - Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene.[3]
    - Currently, ivacaftor is only available as a branded agent.

References

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Therapeutic Class Review
Cystic Fibrosis Transmembrane Conductance Regulator Potentiator

Overview/Summary

Cystic fibrosis is an autosomal recessive disease caused by mutations in the gene on chromosome seven that encodes the cystic fibrosis transmembrane conductance regulator (CFTR).[1] Normally, the CFTR protein functions as a chloride channel which regulates the activity of other cell-surface chloride and sodium channels. Currently, there are more than 1,300 known possible mutations of the CFTR gene, which are divided into five classes. Class I mutations are characterized by defective protein production, resulting in the complete absence of the CFTR protein, while class II mutations involve defective protein processing. Class III and IV mutations are characterized by diminished channel activity and defective conduction, respectively. Lastly, Class V mutations result in reduced amounts of functional CFTR protein.[2] Mutations in the CFTR gene result in deranged transport of ions which include chloride, sodium and bicarbonate; this may lead to viscous secretions in the respiratory, gastrointestinal and reproductive tract, as well as increased salt content in sweat gland secretions.[1]

In the United States, cystic fibrosis occurs most commonly in Caucasians, with a prevalence of one in approximately 3,000 people. Typical respiratory manifestations of cystic fibrosis include a persistent and productive cough, hyperinflation of the lung fields on chest radiograph, pulmonary function tests consistent with obstructive airway disease, as well as colonization of the airway with pathogenic bacteria early in life. In terms of the gastrointestinal manifestations, patients experience progressive pancreatic disease in the form of pancreatic insufficiency, pancreatitis and cystic fibrosis -related diabetes. Furthermore, malnutrition due to pancreatic insufficiency may cause rectal prolapse and musculoskeletal disorders. Patients with cystic fibrosis are also at an increased risk of liver disease, infertility, venous thrombosis and nephrolithiasis.[1]

Kalydeco® (ivacaftor) is a CFTR potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least two years of age who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R. If the patient's genotype is unknown, a FDA-cleared cystic fibrosis mutation test should be used to detect the presence of a CFTR mutation followed by verification with bi-directional sequencing when recommended by the mutation test instructions for use. Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the F508*del* mutation in the CFTR gene. As a potentiator of the CFTR protein, ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein.[3] According to the consensus guidelines from the Cystic Fibrosis Foundation, in patients six years of age and older with at least one G551D CFTR mutation, treatment with ivacaftor is strongly recommended to improve lung function and quality of life, as well as to reduce exacerbations. Guidelines do not currently address the use of ivacaftor in children two to six years of age.[4] Ivacaftor tablets are FDA-approved for pediatric patients and adults aged six and older while the oral granules are approved for patients two to less than six years of age. Additionally, ivacaftor oral granules are dosed by weight. Both formulations are given twice daily and with fat-containing foods.[3] There are no generic formulations currently available.

Medications

Table 1. Medications Included Within Class Review[3,5]

Generic Name (Trade name)	Medication Class	Generic Availability
Ivacaftor (Kalydeco®)	Cystic fibrosis transmembrane conductance regulator potentiator	-

Indications

Table 2. Food and Drug Administration-Approved Indications[3]

Generic Name	Treatment of Cystic Fibrosis in Patients Two Years of Age and Older who have One of the Following Mutations in the Cystic Fibrosis Transmembrane Conductance Regulator Gene: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R
Ivacaftor	✔

Pharmacokinetics

Table 3. Pharmacokinetics[3,6]

Generic Name	Bioavailability (%)	Renal Excretion (%)	Metabolism	Active Metabolites	Serum Half-Life (hours)
Ivacaftor	Not reported	Negligible (% not reported)	CYP3A	M1	12

Clinical Trials

A dose ranging trial in 39 adults with cystic fibrosis and at least one G551D-cystic fibrosis transmembrane conductance regulator (CFTR) allele evaluated twice daily dosing of ivacaftor (VX-770) 25, 75, 150 mg, or placebo for 14 days (part 1 of the study) or VX-770 150 or 250 mg or placebo for 28 days (part 2 of the study). Eligibility included patients who were 18 years or older with cystic fibrosis, G551D mutation on at least one CFTR allele, and forced expiratory volume in one second (FEV_1) of 40% or more of the predicted value for age, sex, and height. In part 1 of the study, patients were randomly assigned to receive VX-770 every 12 hours at doses of 25, 75, 150 mg or placebo. The medication was administered during two 14-day periods separated by a washout period. In part 2 of the study, new patients were randomly assigned to receive VX-770 every 12 hours at a dose of 150 or 250 mg or placebo for 28 consecutive days. Primary endpoints included the safety and adverse events profile of VX-770. Secondary endpoints were evidence of improved CFTR-mediated ion transport, evaluated by the nasal potential difference; pulmonary status, evaluated on the basis of change in the FEV_1 from baseline; and improvement in health related quality of life, based on the Cystic Fibrosis Questionnaire-Revised (only in part 2 of the study).[7]

At day 28, in the group of patients who received 150 mg of VX-770, the median change in the nasal potential difference from baseline was -3.5 mV (range, -8.3 to 0.5; P=0.02 for the within-patient comparison; P=0.13 vs placebo), and the median change in the level of sweat chloride was -59.5 mmol/L (range, -66.0 to -19.0; P=0.008 within-patient; P=0.02 vs placebo). The median change from baseline in the percent of predicted FEV_1 was 8.7% (range, 2.3 to 31.3; P=0.008 for the within-patient comparison, P=0.56 vs placebo). None of the patients withdrew from the study. Six severe adverse events occurred in two patients (diffuse macular rash in one subject and five incidents of elevated blood and urine glucose levels in one subject with a history of type 1 diabetes). All severe adverse events resolved without the discontinuation of VX-770. Results of the dose ranging study revealed the safety profile of ivacaftor as well as the drug's effect on CFTR channel activity using biomarkers of CFTR function and on clinical endpoints (FEV_1) was associated with within-patient improvements.[7]

The efficacy of ivacaftor was established in two, phase 3 clinical trials.[3] Trial 1 (STRIVE) is a randomized, double-blind, placebo-controlled trial (N=161) to evaluate ivacaftor in patients 12 years of age or older with cystic fibrosis and at least one G551D-CFTR mutation. Patients were randomly assigned to receive 150 mg of ivacaftor every 12 hours or placebo for 48 weeks. The primary endpoint was the estimated mean change from baseline through week 24 in the percent of predicted FEV_1. The change from baseline through week 24 in the percent of predicted FEV_1 was greater by 10.6% points, favoring ivacaftor over

placebo group (P<0.001). Effects on pulmonary function were evident by two weeks, and a significant treatment effect was maintained through week 48. Patients receiving ivacaftor were 55% less likely to have a pulmonary exacerbation compared to placebo through week 48 (P<0.001). In addition, through week 48, patients in the ivacaftor group scored 8.6 points higher vs the placebo group on the respiratory symptoms domain of the Cystic Fibrosis Questionnaire-Revised (P<0.001). By week 48, patients treated with ivacaftor had gained, on average 2.7 kg more weight vs placebo (P<0.001). The change from baseline through week 48 in the concentration of sweat chloride, with ivacaftor compared to placebo was -48.1 mmol/L (P<0.001). The incidence of adverse events was similar amongst the groups; however, there was a lower proportion of serious adverse events with ivacaftor than placebo (24 vs 42%).[8]

The second phase 3 trial (ENVISION) was a randomized, double-blind, placebo-controlled study (N=52). Patients were randomized to receive either ivacaftor 150 mg every 12 hours or matching placebo for 48 weeks. All enrolled patients could continue their prescribed chronic cystic fibrosis medication with the exception of hypertonic saline. Results showed a statistically significant improvement in FEV_1, CFTR activity (measured by sweat chloride), and measures of nutritional status (body mass index and weight) (P<0.001 for all endpoints). Improvements were noticed within two weeks and sustained through 48 weeks of treatment. There were no new clinically important safety concerns identified. The most commonly reported adverse events were respiratory in nature and are comparable to placebo.[9]

A retrospective study that evaluated 21 patients with cystic fibrosis and severe lung disease (best FEV1 less than 40% or on the lung transplant list) for 12 months before and 90 to 270 days after starting ivacaftor. The study found that patients receiving ivacaftor had a greater increase in FEV_1 % predicted compared with control patients with a median, within-subject, absolute change of 3.8 (0.2 to 7.7) % predicted in the ivacaftor-treated group compared with 0.6 (-2.1 to 2.8) in control subjects (P=0.009). Median change in intravenous (IV) antibiotic requirements were significantly greater in cases than control subjects for both in-hospital days per year (-14 as compared to 1, P=0.0006), and total IV antibiotic days per year (-36 as compared to 10, P=0.0003). There was no significant difference in weight, change in body mass index (BMI) between the case or control subjects (P=0.25 and P=0.234, respectively).[10]

According to the labeling information for ivacaftor, the efficacy and safety of ivacaftor in patients with cystic fibrosis with G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N, or S549R mutation in the CFTR gene were evaluated in a currently unpublished two-part, randomized, double-blind, placebo-controlled, crossover clinical trial (N=39). Patients who completed part 1 of this trial continued into the 16-week, open-label, part 2 of the study. Patients were six years of age and older with FEV_1 ≥40% at screening and were randomized to receive either 150 mg of ivacaftor or placebo every 12 hours in addition to their prescribed cystic fibrosis therapies during the first treatment period and crossed over to the other treatment for the second eight weeks. The two eight-week treatment periods were separated by a four- to eight-week washout period. For the overall population of the nine mutations studied, treatment with ivacaftor compared to placebo resulted in significant improvement in percent predicted FEV_1 [10.7 through week eight (P<0.0001)], body mass index [0.66 kg/m^2 at week eight (P<0.0001)], and cystic fibrosis respiratory symptom score [9.6 through week eight (P=0.0004)]. There was a high degree of variability of efficacy responses among the nine mutations. Efficacy of ivacaftor in patients with the G970R mutation could not be established and therefore, ivacaftor is not Food and Drug Administration-approved for use in patients with cystic fibrosis with G970R mutation in the CFTR gene.[3]

The safety and efficacy of ivacaftor in cystic fibrosis patients at least six years of age with the R117H mutation was established in an unpublished randomized, double-blind, placebo-controlled, parallel-group clinical trial. Sixty-nine patients were enrolled in the study and randomized 1:1 to receive 150 mg of ivacaftor or placebo every 12 hours with fat-containing food in addition to their normally prescribed cystic fibrosis therapies. Although the FDA has approved its use in patients with the R117H mutation, the primary outcome, mean absolute change from baseline in percent predicted FEV_1 through 24 weeks of treatment was 2.1% and not significantly different than placebo (P-value not reported). In addition, change from baseline BMI and time to first pulmonary exacerbation were both not statistically significant (no P-value reported).[3]

The efficacy of ivacaftor in children two to less than six years of age was extrapolated from efficacy in patients six years of age and older with support from population pharmacokinetic analyses showing similar drug exposure levels in adults. The safety of ivacaftor in children two to less than six years of age (mean age three years) is derived from a 24-week, open-label, clinical trial in 34 patients. Either 50 mg or 75 mg of ivacaftor granules was given twice daily. Eligible patients were those with the G551D, G1244E, G1349D, G178R, G551S, G970R, S1251N, S1255P, S549N or the S549R mutation in the CFTRgene. Of 34 patients enrolled, 32 had the G551D mutation and two had the S549N mutation. The type and frequency of adverse reactions in this trial were similar to those in patients six years and older.[3]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Accurso et al.[7] (2010) Part 1: VX-770* 25 mg every 12 hours vs VX-770* 75 mg every 12 hours vs VX-770* 150 mg every 12 hours vs placebo Part 2: VX-770* 150 mg every 12 hours vs VX-770* 250 mg every 12 hours vs placebo	Part 1: DB, MC, PC, XO Part 2: DB, MC, PC, PG Patients 18 years of age and older with cystic fibrosis, G551D mutation on at least one CFTR allele, and FEV_1 of 40% or more of the predicted value for age, sex, and height Part 1: Patients randomly assigned to receive VX-770 every 12 hours at doses of 25, 75, or 150 mg, or placebo; drug was administered during two 14-day periods separated by a washout period Part 2: Involved new patients who were randomly assigned to receive	N=39 Part 1: N=20 Part 2: N=19 28 days	Primary: Safety and adverse events associated with VX-770 Secondary: Evidence of improvement in CFTR-mediated ion transport and pulmonary status and health-related quality of life	Primary: The frequency of adverse events was similar between the groups and between the parts of the study. The most frequently reported adverse events included fever (four patients in the group of patients who received 75 mg of VX-770), cough (in three patients in the placebo group in part 1 of the study and in three patients who received 250 mg of VX-770 in part 2 of the study); and nausea, pain, and rhinorrhea (in three patients each in the group of patients who received 75 mg of VX-770). Six adverse events occurring in two patients were considered severe; all occurring in part 1 of the study. These events included diffuse macular rash in one patient (receiving 150 mg VX-770) which required hospitalization (only case considered to be serious), another patient who had elevated blood glucose on three occasions, and had urine that was positive for glucose on two occasions. The patient with glucose problems had a history of insulin-dependent diabetes. Secondary: Improvement in CFTR ion transport-potentiation difference The improvement in CFTR-mediated ion transport was measured by potential difference across the nasal mucosa (in response to administration of a chloride-free isoproterenol solution) and on the chloride concentration of sweat. In part 1 of the study, significant within- patients changes from baseline to day 14 were observed in the VX-770 75 mg group (mean, -4.7 mV; 95% CI, -7.5 to -1.9; P<0.003) and in the 150 mg group (mean, -5.4 mV; 95% CI, -9.3 to -1.6; P<0.01). There was no significant change from baseline in the placebo group (-1.7 mV; 95% CI, -6.1 to 2.6; P=0.41) or in the VX-770 25 mg group (-1.6 mV; 95% CI, -5.6 to 2.5; P=0.43). None of the changes from baseline were significant as compared to the placebo group (P=0.95, P=0.24, and P=0.21 for the VX-770 25, 75, and 150 mg groups, respectively). In part 2 of the study, the median within-patient change from baseline to day

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	VX-770 every 12 hours at a dose of 150 or 250 mg or placebo for 28 consecutive days			28 was significant in the VX-770 150 mg group (-3.5 mV; range, -8.3 to 0.5; P=0.02), and in the 250 mg group (-5.5 mV; range, -28.5 to 2.0; P=0.05), but not in the placebo group (-0.4 mV; range, -2.3 to 4.0; P=0.88). In the VX-770 treatment groups, the changes from baseline were not significantly different from placebo (P=0.13 and P=0.16 in the VX-770 150 and 250 mg groups, respectively). Responses to the treatment groups were similar to baseline values after the washout period in part 1 of the study. After 14 days of treatment with VX-770, some patients in which data were available in parts 1 and 2 of the study were considered to have had a response according to the predefined response criterion of a decrease from baseline of 5 mV or more in the nasal potential difference. These patients were the following: One of seven patients in the 25 mg group (14%), five of 15 patients in the 75 mg group (33%), 10 of 16 in the 150 mg group (62%) and three of seven in the 250 mg group (43%). <u>Improvement in CFTR ion transport-sweat chloride test</u> In part 1 of the study, the mean change in the sweat chloride concentration from baseline to day 14 was -32.9 mmol/L (95% CI, -42.4 to -23.3) in the group that received 25 mg of VX-770, -40.4 mmol/L (95% CI, -48.7 to -32.2) in the 75 mg group, and -42.3 mmol/L (95% CI, -52.8 to -31.8) in the group that received 150 mg of VX-770. The changes were significant (P<0.001) in both within-patient comparisons and vs placebo in all VX-770 groups. In part 2, the median change from baseline to day 28 was -59.5 mmol/L (range,-66.0 to -19.0) in theVX-770 150 mg group and -38.0 mmol/L (range, -47.0 to -10.5) in the 250 mg group. Results in both groups were significant for within-patient comparisons (P=0.008 for 150 mg and P=0.02 for 250 mg) and vs placebo (P=0.02 for the 150 mg group and P=0.03 for the 250 mg group). Considering parts 1 and 2 of the study, after 14 days, the number of patients with available data who achieved the prespecified response criterion of a decrease from baseline of 20 mmol/L or more was six of eight patients in the 25 mg group (75%), 11 of the 13 patients in the 75 mg group (85%), 13 of the 14 patients in the 150 mg group (93%) and four of the seven patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				250 mg group (57%). No patients had a response in the placebo group. Pulmonary status: FEV_1 testing In part 1 of the study, at day 14, the mean within-patient change in FEV_1 from baseline was 0.09 L (95% CI, -0.06 to 0.24) in the 25 mg group, 0.19 L (95% CI, 0.08 to 0.29) in the 75 mg group, and 0.22 L (95% CI, 0.08 to 0.36) in the 150 mg group. In the placebo group, the mean change was -0.03 L (95%CI, -0.20 to 0.15). Improvements in the 75 mg and 150 mg groups were significant within-patient change (P=0.003 and P=0.006, respectively) as compared to placebo (P=0.05 and P=0.04, respectively); changes were not significant in the 25 mg or placebo group. Among the patients who received VX-770, the mean relative change from baseline in the percentage of predicted FEV_1 was 4.9% (95% CI, -2.6 to 12.5) in the 25 mg group, 10.0% (95% CI, 4.5 to 15.6) in the 75 mg group, and 10.5% (95% CI, 3.3 to 17.7) in the 150 mg group. The mean change in the placebo group was 0.7% (95% CI, -8.8 to 10.2). Within-patient improvements in the percentage of predicted FEV_1 were significant in the 75 and 150 mg groups (P=0.002 and P=0.008, respectively), but not in the 25 mg or placebo groups. Differences in comparisons with the placebo group did not reach significance. In part 2 of the study, at day 28, the median within-patient change from baseline in FEV_1 was 0.25 L (range, 0.05 to 0.75) in the 150 mg group, 0.17 L (range, 0 to 0.37) in the 250 mg group. Within-patient change was significant in both treatment groups (P=0.008 and P=0.03 for the 150 mg and 250 mg, respectively), but not in the placebo group (P=0.38). The median relative change from baseline in the percentage of predicted FEV_1 was 8.7% (range, 2.3 to 31.3; within-patient comparison, P=0.008) in the 150 mg group and 4.4% (range, 0 to 18.3; within-patient comparison, P=0.03) in the 250 mg group. There was no statistical significance in the placebo group. Health-Related Quality of Life-Cystic Fibrosis Questionnaire-Revised The Cystic Fibrosis Questionnaire-Revised was administered in part 2 of the study only. No change in baseline in any Cystic Fibrosis Questionnaire-Revised domain was significant. After 14 days of treatment, patients reported median improvements from baseline in the respiratory domain of 5.6 points

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				(range, 0 to 16.7; P=0.06 within-patient) in the 150 mg group, 5.6 points (range, -11.1 to 11.1; P=0.16) in the 250 mg group, and 2.8 points (range, -5.6 to 11.1; P=0.75) in the placebo group. Comparisons between the treatment and placebo groups were not significant. At day 28, the median improvements from baseline were 8.3 points (range, 0 to 16.7; P=0.06 within-patient) for the 150 mg group and 11.1 points (range, -5.6 to 33.3; P=0.08) in the 250 mg group, whereas the placebo group were identical to those at day 14.
Ramsey et al.[8] STRIVE (2011) Ivacaftor 150 mg every 12 hours vs placebo	DB, PC, RCT Patients 12 years of age or older, had received a diagnosis of cystic fibrosis, had the G551D mutation on at least one CFTR allele, and had an FEV_1 of 40 to 90% of the predicted value for persons of their age, sex and height; patients were allowed to take their pre-study medications (except hypertonic saline) throughout the 48 weeks	N=161 N=83, ivacaftor N=78, placebo 48 weeks	Primary: Absolute change from baseline through week 24 in the percent of predicted FEV_1 Secondary: Change from baseline through week 24 and 48 in the percent of predicted FEV_1; the time to the first pulmonary exacerbation through week 24 and week 48; subject-reported respiratory symptoms through week 24 and 48 as assessed with the use of Cystic Fibrosis Questionnaire-Revised; the	Primary: Through week 24, there was an increase from baseline of 10.4% points in the percent of predicted FEV_1 in the ivacaftor group as compared to a decrease of 0.2% points in the placebo group (treatment effect, 10.6% points; P<0.001). The improvement in the ivacaftor group reflects a mean increase in FEV_1 of 0.367 L, as compared to an increase of 0.006 L in the placebo group (treatment effect, 0.361 L; P<0.001) through week 24, which corresponded to a relative change from baseline of 17.2% in the ivacaftor as compared to 0.1% in the placebo group. An effect of ivacaftor was noted by day 15 of treatment (P<0.001). The distribution of individual changes from baseline through week 24 showed that nearly 75% of the patients who were treated with ivacaftor had a mean improvement of 5% points more. The change in the percent of predicted FEV_1 was also analyzed within predefined subgroups, including subgroups defined according to baseline FEV_1, age and sex. The effect of ivacaftor compared to placebo was significant in each group analyzed. Secondary: <u>Change from baseline through week 24 and 48 in the percent of predicted FEV_1</u> A significant treatment effect was maintained throughout the study, with a change in the percent of predicted FEV_1 from baseline through week 48 that was 10.5 percentage points greater with ivacaftor than with placebo (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			change in weight from baseline to week 24 and week 48; and the change from baseline in the concentration of sweat chloride; the number and duration of pulmonary exacerbations, the total number of days of hospitalization for pulmonary exacerbations, and the need for antibiotic therapy for sinopulmonary signs or symptoms; safety	Time to the first pulmonary exacerbation through week 24 and week 48 At week 48, a total of 67% of patients in the ivacaftor group, as compared to 41% in the placebo group, were free from pulmonary exacerbations, corresponding to a hazard ratio with ivacaftor of 0.455 (P=0.001), or a 55% reduction in the risk of pulmonary exacerbation. Subject-reported respiratory symptoms through week 24 and 48 as assessed with the use of Cystic Fibrosis Questionnaire-Revised Patients compared to those receiving placebo, had an improvement in scores on the Cystic Fibrosis Questionnaire-Revised respiratory domain. From baseline to week 48, the scores increased by 5.9 points in the ivacaftor group, as compared to a decrease of 2.7 points in the placebo group (P<0.001). Change in weight from baseline to week 24 and week 48 By week 48, patients in the ivacaftor group had gained 3.1 kg, as compared to a gain of 0.4 kg in the placebo group (P<0.001). Change from baseline in the concentration of sweat chloride Through week 24, the change from baseline in sweat chloride was -48.7 mmol/L in the ivacaftor group and -0.8 mmol/L in the placebo group (treatment effect, -47.9 mmol/L, P<0.001). The man values for sweat chloride were 47.8 and 100.0 mmol/L in the ivacaftor and placebo groups, respectively, at week 24. A treatment effect was initially seen at day 15 and was maintained through week 48 (treatment effect, -48.1; P<0.001). Number and duration of pulmonary exacerbations There were 99 exacerbations (in 44 patients) in the placebo group, as compared to 47 exacerbations (in 28 patients) in the ivacaftor group. Total number of days of hospitalization for pulmonary exacerbations A total of 31 events (in 23 patients) in the placebo group, as compared to 21 events (in 11 patients) in the ivacaftor group, led to hospitalization. The mean (±SD) total number of days of hospitalization for pulmonary exacerbations per patient (normalized to a 48 weeks period) was 3.9±13.6 in the ivacaftor

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				group, as compared to 4.2±8.7 in the placebo group (P=0.03). Need for antibiotic therapy for sinopulmonary signs or symptoms The number of pulmonary exacerbations requiring intravenous antibiotics was reduced in the ivacaftor group compared to placebo (6.68 vs 11.03 days respectively; P=0.0183). In the year before the study and during the course of the study, patients received dornase alpha (69%), oral azithromycin (63%), and inhaled tobramycin (39%). When added to these therapies, ivacaftor as compared to placebo, was associated with a relative improvement of 17.2% in FEV_1 over baseline values at 24 weeks, and sustained to 48 weeks. Safety Compared to placebo, the ivacaftor group had a higher incidence of adverse events leading to discontinuation of the study drug (13 vs 6%). All of the patients who interrupted treatment were able to resume taking the study drug and to complete the trial, with the exception of one patient in the placebo group who withdrew from the study due to severe respiratory distress. Patients in the ivacaftor group had a lower incidence of adverse events leading to discontinuation of the study drug (1 vs 5%). Overall five adverse events led to discontinuation: four in the placebo group (increased hepatic enzyme levels, atrioventricular block, panic attack, and respiratory failure) and one in the ivacaftor group (increased hepatic enzyme levels). Pulmonary exacerbation, cough, hemoptysis, and decreased pulmonary function occurred less frequently in the ivacaftor than in the placebo group (>5% point difference between the groups in incidence; minimum 10% incidence in either group). Adverse events that occurred more frequently in the ivacaftor group were headache, upper respiratory infection, nasal congestion, rash, and dizziness; none of these were considered serious or led to therapy discontinuation. There were a total of 53 serious adverse events that were reported. There was a lower rate of serious adverse events in the ivacaftor group than in the placebo group (24 vs 42%). Pulmonary exacerbations and hemoptysis

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				occurred more frequently in the placebo group than in the ivacaftor group.
Davies et al.[9] ENVISION (2013) Ivacaftor 150 mg every 12 hours vs placebo	DB, PC, RCT Patients between the ages of six and 11 years old with cystic fibrosis and the G551D-CFTR mutation on at least one allele, with FEV_1 of 40% to 105% of the predicted normal value for age, gender, and height and body weight greater than or equal to 15 kg; all patients continued with their prescribed chronic cystic fibrosis treatment regimen, with the exception of inhaled hypertonic saline	N=52 48 weeks	Primary: Absolute change in the percent of predicted FEV_1 from baseline through week 24 Secondary: Absolute changes from baseline in 1) the percent of predicted FEV_1 through week 48, 2) body weight at weeks 24 and 48, 3) concentration of sweat chloride from baseline through weeks 24 and 48, 4) patient-reported respiratory symptoms through weeks 24 and 48 assessed using the child version of the respiratory domain of the Cystic Fibrosis Questionnaire-Revised; safety	Primary: Statistically significant improvements were seen through 24 weeks in the percentage of predicted FEV_1 for the ivacaftor group compared to placebo group (treatment effect, 12.5 percentage points; P<0.001). The change in absolute percent predicted FEV_1 at week 24 corresponded to a relative improvement from baseline percent predicted FEV_1 values of 15.8%. Secondary: Change in the percent of predicted FEV_1 from baseline were observed by the first on treatment time point and maintained throughout the 48 weeks (treatment effect at week 48, 10.0%; P<0.001). <u>Change in body weight</u> Increases from baseline in body weight were observed in both study groups. Patients receiving ivacaftor had significantly larger weight gain compared to patients receiving placebo. The treatment difference was 1.9 kg from baseline to week 24 (P<0.001) and 2.8 kg from baseline to week 48 (P<0.001). <u>Change in sweat chloride concentrations</u> Statistically significant reductions from baseline were observed in sweat chloride levels. The mean change from baseline in sweat chloride was -55.5 mmol/L in the ivacaftor group and -1.2 mmol/L in the placebo group. This effect was initially observed at day 15 and was maintained through week 48 (treatment effect, -54.3 mmol/L; P<0.001). <u>Patient reported respiratory symptoms</u> The patients receiving ivacaftor scored 6.1 points higher than patients receiving placebo on the respiratory-symptoms domain of the Cystic Fibrosis Questionnaire-Revised instrument through week 24; however, the treatment differences were not statistically significant (week 24, P=0.109). <u>Adverse events</u> The most frequent adverse events that occurred more often in patients receiving ivacaftor than in patients receiving placebo by at least 5% were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				oropharyngeal pain, headache, nasopharyngitis, upper respiratory tract infection, otitis media, diarrhea, and increased eosinophil count. Serious adverse events occurred in 19% of patients in the ivacaftor group and in 23% of patients in the placebo group.
Barry et al (2014)[10] Ivacaftor 150 mg every 12 hours vs standard of care	RETRO Patients with a diagnosis of cystic fibrosis with the presence of at least one G551D allele, highest FEV_1 less than 40% predicted in the preceding six months and/or lung transplant listing and treatment with ivacaftor for at least three months	N=21 1 year before and 90 to 270 after starting ivacaftor	Primary: Change in FEV_1% predicted, weight, hospital days, IV antibiotic days and transplant free survival Secondary: Not reported	Primary: Following ivacaftor administration there was a significant improvement in best FEV_1 from a mean (SD) of 0.91 (0.30) L to 1.062 (0.42) L (P=0.0095). This represents a 16.7% relative increase. FEV_1 % predicted increased from a mean of 26.5 (7.2) % predicted to 30.7 (9.9) % predicted (P=0.0068). There was also an increase in FVC from 2.03 (0.87) L to 2.28 (1.02) L (mean increase of 13.6%, P=0.0091). Median time to best spirometry was 100 days (56 to 160). Median weight improved from 49.8 kg (44.4 to 60.7)to 51.6 kg (48.6 to 66.8)(P=0.0058). Median change in weight was an increase of 4.5% (-1.0 to 9.5) over baseline, or 2.3 kg (-0.4 to 4.2). The BMI changed from 19.1 to 20.2 kg/m^2 (P=0.010). In the 12 months preceding ivacaftor commencement, cases received a median of 23 (14 to 83) days/year of inpatient IV antibiotics and 20 (0 to 61) days/year of home IV antibiotics. Following administration of ivacaftor, median time receiving antibiotics fell to 0 (0 to 48) days/year (P=0.0014). Patients receiving ivacaftor had a greater increase in FEV_1 % predicted compared with control subjects with a median, within-subject, absolute change of 3.8 (0.2 to 7.7) % predicted in the ivacaftor-treated group compared with 0.6 (-2.1 to 2.8) in control subjects (P=0.009).There was no significant difference in weight, change in BMI between the case or control subjects (P=0.25 and P=0.234, respectively).Median change in IV antibiotic requirements were significantly greater in cases than control subjects for both in-hospital days per year (-14 as compared to 1, P=0.0006), and total IV antibiotic days per year (-36 as compared to 10, P=0.0003). Secondary: Not reported

*VX-770=ivacaftor.
Study abbreviations: CI=confidence interval, DB=double-blind, MC=multicenter, PC=placebo-controlled, PG=parallel group, RCT=randomized controlled trial, SD=standard deviation, XO=crossover
Miscellaneous abbreviations: CFTR=cystic fibrosis transmembrane conductance regulator, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, IV=intravenous

Special Populations

Table 5. Special Populations[3]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ivacaftor	Clinical trials did not include sufficient numbers of patients ≥65 years of age to determine whether they respond differently from younger patients. Safety and efficacy in children less than two years of age have not been established.	Safety and efficacy in patients with renal dysfunction have not been established. However, caution is recommended in patients with severe renal impairment (creatinine clearance ≤30 mL/minute) or end stage renal disease.	No dosage adjustment is required with mild hepatic impairment. Hepatic dosage adjustment is required with moderate impairment (Child-Pugh Class B; a dose of 150 mg (age ≥ 6 years), 75 mg (age two to less than six years and body weight ≥ 14 kg) or 50 mg (age two to less than six years and body weight < 14 kg) once-daily is recommended. Not studied with severe hepatic impairment (Child-Pugh Class C). However, the dose of ivacaftor should generally not exceed 150 mg daily in patients with severe hepatic impairment.	B	Unknown; use with caution.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[3]

Adverse Event	Ivacaftor
Abdominal pain	16
Acne	4 to 7
Arthralgia	4 to 7
Aspartate aminotransferase increased	4 to 7
Bacteria in sputum	4 to 7
Blood glucose increased	4 to 7
Diarrhea	13
Dizziness	9

Adverse Event	Ivacaftor
Headache	24
Hepatic enzyme increased	4 to 7
Musculoskeletal chest pain	4 to 7
Myalgia	4 to 7
Nasal congestion	20
Nasopharyngitis	15
Nausea	12
Oropharyngeal pain	22
Pharyngeal erythema	4 to 7
Pleuritic pain	4 to 7
Rash	13
Rhinitis	4 to 7
Sinus congestion	4 to 7
Sinus headache	4 to 7
Upper respiratory tract infection	22
Wheezing	4 to 7

Contraindications/Precautions

There are no documented contraindications with ivacaftor.[3]

Alanine and aspartate transaminases should be assessed prior to initiating ivacaftor, every three months during the first year of treatment, and annually thereafter. If elevated levels are observed, the patient should be closely monitored until the abnormalities resolve. Dosing should be interrupted in patients with alanine or aspartate transaminase levels greater than five times the upper limit of normal. Following resolution of transaminase elevations, the benefits and risks of resuming treatment should be considered.[3]

Drug Interactions

The use of ivacaftor with strong cytochrome P450 3A4 inducers is not recommended. The dose of ivacaftor should be reduced to 150 mg twice a week with concomitant administration of strong CYP3A inhibitors (e.g. ketoconazole).The dose of ivacaftor should be reduced to 150 mg once daily with concomitant administration of moderate CYP3A inhibitors (e.g. fluconazole). Use of ivacaftor with food containing grapefruit or Seville oranges should be avoided. Cases of non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor; baseline and follow-up ophthalmological examinations are recommended in pediatric patients.[3]

Dosage and Administration

Table 7. Dosing and Administration[3]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ivacaftor	Treatment of cystic fibrosis* (age six years and older): Tablet: 150 mg orally every 12 hours with fat-containing food Treatment of cystic fibrosis* (age two to less than six years): Oral granule: body weight < 14 kg, one 50 mg packet every 12 hours with fat-containing food; body weight ≥ 14 kg, one 75 mg packet every 12 hours with fat-containing food	Cystic fibrosis* (age two to less than six years): Oral granule: 50 mg (weight <14 kg) or 75 mg (weight ≥14 kg) every 12 hours with fat-containing food	Oral Granule: 50 mg/pack 75 mg/pack Tablet: 150 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
		Safety and efficacy in children less than two years of age have not been established	

*In patients two years of age and older who have one of the following mutations in the cystic fibrosis transmembrane conductance regulator gene: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R

Clinical Guidelines

Table 8. Clinical Guidelines

Clinical Guideline	Recommendations
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[4]	Aerosolized antibiotics • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. Anti-inflammatory agents • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended.

Clinical Guideline	Recommendations
	• For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. Antipseudomonal antibiotics • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. Antistaphylococcal antibiotics • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. Bronchodilators • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. Hypertonic saline • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. Ivacaftor • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. Macrolide antibiotics • For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways,

Clinical Guideline	Recommendations
	chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. Recombinant human DNase • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.

Conclusions

Cystic fibrosis, caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, usually presents in a typical patient with multisystem disease involving several organs such as lungs, pancreas, liver, intestine, and reproductive tract. Defective CFTR protein in patients with cystic fibrosis leads to the production of abnormally viscid mucus which impacts the airways through obstruction and alters the normal mechanisms of mucociliary clearance.[1] Kalydeco® (ivacaftor) is the first and only CFTR potentiator Food and Drug Administration (FDA)-approved for the treatment of cystic fibrosis in patients at least two years of age who have one of the following mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, R117H, S1251N, S1255P, S549N, or S549R. Ivacaftor facilitates increased chloride transport via potentiation of the channel-open probability (or gating) of the CFTR protein. If the patient's genotype is unknown, a FDA-cleared cystic fibrosis mutation test should be used to detect the presence of a CFTR mutation. Ivacaftor is not effective in patients with cystic fibrosis who are homozygous for the F508*del* mutation in the CFTR gene.[3]

The safety and efficacy of ivacaftor for up to 48 weeks in patients aged six years and older with cystic fibrosis are supported by randomized and controlled clinical trials. Efficacy in children two to six years of age was extrapolated from adult data and support from population pharmacokinetic analyses showing similar drug exposure levels in adults patients. A separate 24-week trial assessed the safety in children two to six years of age. The type and frequency of adverse reactions in this trial were similar to those in patients six years and older.[3,7-9] There is currently a lack of long term data with ivacaftor, and its benefits on mortality, are unclear at this time. The consensus guidelines published by the Cystic Fibrosis Foundation recommends treatment with ivacaftor in patients six years of age and older with at least one G551D CFTR mutation to improve lung function and quality of life, as well as to reduce exacerbations. The clinical guideline does not address the use of ivacaftor in patients with a non-G551D CFTR mutation or patients less than six years of age.[4] Currently, ivacaftor is only available as a branded agent.

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