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Ivacaftor: a guide to its use in cystic fibrosis

Katherine A. Lyseng-Williamson · Lily P. H. Yang · Emma D. Deeks

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Abstract Ivacaftor (Kalydeco®) is the first drug approved for the treatment of cystic fibrosis that treats the underlying cause of the disease. It potentiates the open probability (i.e. gating) of cystic fibrosis transmembrane conductance regulator (CFTR) channels with a *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N* or *S549R* gating mutation, thus enhancing their transport of chloride. When combined with standard care, ivacaftor significantly improved outcomes related to lung function, body mass index, pulmonary exacerbations and patient-reported respiratory symptoms relative to placebo in phase 3 trials in patients aged ≥6 years carrying a *G551D* or a specific non-*G55ID* mutation in the *CFTR* gene. The drug was generally well tolerated for up to 144 weeks.

Adis evaluation oral ivacaftor in patients with cystic fibrosis carrying specific *CFTR* gene mutations
What are its key clinical benefits?
The first licensed agent to target the underlying cause of disease, rather than providing symptomatic treatment
Improves lung function and body mass index parameters in patients aged ≥ 6 years carrying a *G551D* or specific non-*G551D (i.e. G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N* or *S549) CFTR* mutations
Generally well tolerated
What are its key clinical limitations?
Associated with high drug acquisition costs

K. A. Lyseng-Williamson (✉) · L. P. H. Yang · E. D. Deeks
Springer, Private Bag 65901, Mairangi Bay, North Shore 0754, Auckland, New Zealand
e-mail: dtp@adis.com

What is the rationale for developing the drug?

Cystic fibrosis is an incurable genetic disorder that affects multiple organ systems, with most patients developing fatal pulmonary insufficiency during early adulthood [1, 2]. Although aggressive use of treatments (such as antibacterials, anti-inflammatory agents, bronchodilators and pancreatic enzymes) may improve life expectancy, these treatments target disease symptoms rather than the underlying cause [1, 2].

Cystic fibrosis results from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an epithelial membrane glycoprotein that predominantly functions as a chloride channel [1, 7]. It is largely accepted that defective ion transport caused by CFTR dysfunction leads to depletion of airway surface liquid in the lungs, which impairs ciliary function, resulting in mucus obstruction of the airways and, consequently, infection and inflammation [8].

Advances in the understanding of the molecular biology of CFTR have identified mutations in the *CFTR* gene as targets for drug development [7]. Ivacaftor (Kalydeco®) [2] is a potentiator of CFTR-mediated chloride transport, and is the first drug approved to treat the underlying cause of cystic fibrosis.

How does the drug work?

Ivacaftor potentiates the open probability (i.e. gating) of the CFTR channel, thus enhancing its transport of chloride [3–5]. In various in vitro studies, ivacaftor increased the CFTR transepithelial current (a measure of chloride secretion) by increasing the channel open probability [9]. The drug's effect on CFTR may rescue the function of airway epithelial cells [9].

Treatment with ivacaftor reduced sweat chloride concentration (a measure of improved CFTR function) in patients with cystic fibrosis with a specific *CFTR* mutation for which is use is approved [10–14]. In clinical trials in paediatric and/or adult patients aged ≥6 years with a *G551D* mutation [10–13], ivacaftor 150 mg every 12 h significantly reduced sweat chloride concentration relative to placebo after up to 28 days ($p \leq 0.02$) [12, 13] or 48 weeks ($p < 0.0001$) [10, 11]. Ivacaftor 150 mg every 12 h also reduced sweat chloride concentration relative to placebo in patients aged ≥6 years with selected non-*G55ID* mutations of the *CFTR* gene [14]; mean changes from baseline at 8 weeks were −52.5 to −80.3 mmol/L in patients with a *G1244E*, *G1349D*, *G178R*, *G551S*, *S125N*, *S1255P*, *S549N* or *S549R* mutation, and −6.3 mmol/L in patients with a *G970R* mutation. Where reported [10, 12], reductions in sweat chloride did not correlate directly with improvements in lung function, as measured by forced expiratory volume in 1 s (FEV_1).

Treatment with the same dosage of ivacaftor for 28 days also generally reduced total ventilation defects [15] and ventilation inhomogeneity [12] by a significantly ($p < 0.01$) greater extent than with placebo, with improvements in percent predicted FEV_1. A 1-year ex vivo study showed that treatment with ivacaftor (dosage not specified) significantly ($p < 0.05$) corrected the level of degranulation of secondary and tertiary neutrophil granules in patients with cystic fibrosis and a *G551D* mutation to levels seen in healthy controls [16].

Interestingly, data from bacterial assays suggest that ivacaftor may have an antibacterial effect against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*, and that it exhibits positive interactions with antibacterials against strains of *S. aureus* and *S. pneumoniae* [17].

For whom is the drug indicated?

In the EU [3] and USA [4], ivacaftor is indicated for the treatment of patients with cystic fibrosis aged ≥6 years who have one of the following mutations in the *CFTR* gene: *G970R*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*. Ivacaftor is also approved for the treatment of patients with cystic fibrosis aged ≥6 years with these mutations in Canada, where it is additionally approved to treat those with a *G970R CFTR* mutation, Table 1 presents a summary of the prescribing information for ivacaftor in the EU [3], USA [4] and Canada [5].

What is its efficacy in patients with a *G551D* mutation?

Two randomized, double-blind, placebo-controlled, phase 3 trials evaluated the clinical efficacy of ivacaftor 150 mg every 12 h in treating cystic fibrosis when used in addition to existing therapy (excepting inhaled hypertonic saline) in patients with a *G551D* mutation of the *CFTR* gene [10, 11]. In the STRIVE trial, 161 adults and adolescents aged ≥12 years (78 % were aged ≥18 years) were randomized and received one or more doses of ivacaftor or placebo [10]. In the ENVISION trial, 52 children aged 6–11 years were randomized and received one or more doses of ivacaftor or placebo [11]. Patients were required to have an FEV_1 40–90 % of predicted in STRIVE and 40–105 % of predicted in ENVISION. Among the exclusion criteria of both studies were pulmonary exacerbation, acute respiratory infection, *Mycobacterium abscessus*, *Burkholderia cenocepacia* or *B. dolosa* in sputum and changes in pulmonary disease therapy in the last 4 weeks [10, 11].

Patients who completed the 48-week STRIVE or ENVISION trials were eligible to receive a further 96 weeks of ivacaftor 150 mg every 12 h in addition to their existing therapy (inhaled hypertonic saline permitted) in the open-label, phase 3 PERSIST extension study (144 adults/adolescents from STRIVE and 48 children from ENVISION were enrolled) [18].

What is its efficacy in adults and adolescents?

Oral ivacaftor 150 mg every 12 h improved lung function when used in combination with standard care in adults and adolescents with cystic fibrosis and a *G551D CFTR* mutation in STRIVE [10]. Relative to placebo, ivacaftor significantly increased the percent predicted FEV_1 from baseline through to week 24 of treatment (primary endpoint), and sustained this benefit through to week 48 (Table 2). A significant ($p \leq 0.008$) benefit relative to placebo was shown regardless of age (<18 or ≥18 years), sex, percent predicted FEV_1 at baseline (<70 or ≥70 %) or geographic region [10].

Ivacaftor therapy also significantly improved other endpoints relative to placebo, such as mean absolute change in FEV_1 (Table 2), risk of pulmonary exacerbation ($p < 0.001$), days spent hospitalized for pulmonary exacerbation ($p = 0.0275$), gain in body weight ($p < 0.0001$) and patient-reported respiratory symptoms as measured by the respiratory domain of the Cystic Fibrosis Questionnaire-Revised (CFQ-R) [Table 2] [10].

The beneficial effects of ivacaftor on lung function, respiratory symptoms and bodyweight in adults and adolescents were sustained during longer-term ivacaftor treatment (up to 144 weeks) in PERSIST [18]. Patients who received placebo in STRIVE responded to active treatment when they were switched to ivacaftor therapy in PERSIST.

Table 1 Prescribing summary of oral ivacaftor (Kalydeco®) in cystic fibrosis in the EU [3], USA [4] and Canada [5]. Consult local prescribing information for further details

What are its approved indications?	
Treatment of patients with cystic fibrosis aged ≥6 years who have one of the following mutations in the *CFTR* gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R* (EU, USA and Canada) or *G970R* (Canada only)	
Patients with an unknown *CFTR* genotype should be tested by an approved method; Clinical Pharmacogenetics Implementation Consortium guidelines [6] are available to aid interpretation of *CFTR* genotypes	
What is its administration regimen and availability?	
Recommended daily dosage	150 mg every 12 h with fat-containing food
Availability	150 mg film-coated tablets
How should it be used in special populations?	
Patients with renal impairment	Mild to moderate impairment: dosage adjustment is not required
	Severe impairment or end-stage renal disease: use with caution
Patients with hepatic impairment	Mild impairment: dosage adjustment is not required
	Moderate impairment: reduce dosage to 150 mg once daily
	Severe impairment: use is not recommended unless the benefits outweigh the risks (data are lacking); suggested starting dosage is 150 mg once daily or less frequently (USA) or once every two days (EU and Canada), then adjusted as necessary
What is its pharmacokinetic profile?	
Time to steady state	3–5 days
Effect of coadministration with fat-containing food	Increases drug exposure by ≈2- to 4-fold
Plasma protein binding	≈99 %, mostly to albumin and α_1-acid glycoprotein
Metabolism	Extensive; predominantly by CYP3A4
	One major metabolite is pharmacologically active (less potent than parent drug)
Plasma half-life	≈12 h
Elimination	Mostly (87.8 %) in the faeces as metabolites
What are the special warnings and precautions concerning its use?	
Regularly monitor liver function (ALT, AST) prior to and during ivacaftor use; patients with unexplained test result abnormalities should be closely monitored, with discontinuation considered if abnormalities do not resolve	
What are its potential interactions with other drugs and food?	
CYP3A inhibitors (may increase exposure to ivacaftor)	Strong inhibitors (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, clarithromycin): reduce ivacaftor dosage to 150 mg twice a week
	Moderate inhibitors (e.g., fluconazole, erythromycin): reduce ivacaftor dosage to 150 mg once daily
	Grapefruit or Seville oranges: avoid during ivacaftor therapy
CYP3A inducers (may reduce the efficacy of ivacaftor)	Strong inducers [e.g. rifampicin (rifampin), rifabutin, phenobarbital, carbamazepine, phenytoin, St John's Wort (hypericum)]: concomitant use is not recommended
CYP3A or P-glycoprotein substrates (may increase exposure to substrate)	Drugs with narrow therapeutic indices (digoxin, ciclosporin, tacrolimus) and benzodiazepines (midazolam, alprazolam, diazepam, triazolam): use with caution and monitor for adverse effects
Warfarin (may increase exposure to this CYP2C9 substrate)	Monitor international normalized ratio

CFTR cystic fibrosis transmembrane conductance regulator, *CYP* cytochrome P450

What is its efficacy in children aged ≥6 years?

Ivacaftor 150 mg every 12 h, in combination with standard care, was effective in improving lung function in children aged 6–11 years with cystic fibrosis and a *G551D CFTR* mutation in the ENVISION trial [11]. Percent predicted FEV_1 increased from baseline to a significantly greater extent with ivacaftor than with placebo through to week 24 of treatment (primary endpoint; Table 2). The between-group difference favoured ivacaftor from day 15 of therapy and remained significant through to week 48 (Table 2). Predefined subgroup analyses suggested this measure was significantly improved with ivacaftor relative to placebo among patients who had an FEV_1 ≤90 % of predicted at baseline, were female, or participated at a European study centre [11].

Table 2 Effect of oral ivacaftor 150 mg every 12 h on lung function and respiratory symptoms in patients with cystic fibrosis and a *G551D* mutation in the *CFTR* gene in two 48-week, phase 3 trials

Endpoint	Time (weeks)	STRIVE (pts aged ≥12 years) [10]			ENVISION (pts aged 6–11 years) [11]		
		Ivacaftor ($n = 83$)	Placebo ($n = 78$)	BGD (95 % CI)	Ivacaftor ($n = 26$)	Placebo ($n = 26$)	BGD (95 % CI)
% predicted FEV_1 [percentage points] (mean absolute change from baseline)[a,b]	24	10.4	−0.2	10.6 (8.6–12.6)**	12.6	0.1	12.5 (6.6–18.3)**
	48	10.1	−0.4	10.5 (8.5–12.5)**	10.7	0.7	10.0 (4.5–15.5)*
FEV_1 [L] (mean absolute change from baseline)[a]	24	0.4	0.0	0.4 (0.3–0.4)**	0.30	0.07	0.24 (0.12–0.35)**
	48	0.4	0.0	0.4 (0.3–0.4)**	0.33	0.13	0.20 (0.09–0.31)*
CFQ-R respiratory domain score (mean absolute change from baseline)[a,c]	24	NR	NR	8.1 (4.7–11.4)**[d]	6.3	0.3	6.1 (−1.4 to 13.5)
	48	5.9	−2.7	8.6 (5.3–11.9)**[d]	6.1	1.0	5.1 (−1.6 to 11.8)

BGD between-group difference, *CFQ-R* Cystic Fibrosis Questionnaire-Revised, *CFTR* cystic fibrosis transmembrane conductance regulator, *FEV_1* forced expiratory volume in 1 s, *NR* not reported, *pts* patients

* $p < 0.001$, ** $p \leq 0.0001$ vs. placebo

[a] Data were adjusted for baseline parameters, such as age (in STRIVE), % predicted FEV_1 and/or CFQ-R domain score

[b] Primary endpoint. Baseline FEV_1 in ivacaftor and placebo groups was 63.5 and 63.7 % of predicted in STRIVE and 84.7 and 83.7 % of predicted in ENVISION

[c] Where reported, baseline scores were 78 and 80 in the ivacaftor and placebo groups [11]; 4 points is considered the minimal clinically important difference in pts with stable disease, with higher scores indicating better health-related quality of life. Data from STRIVE are pooled from child and adolescent/adult versions of the CFQ-R. Data presented for ENVISION are from the child version of the CFQ-R

[d] As reported in the EU summary of product characteristics

Ivacaftor also provided a benefit over placebo in terms of other endpoints, such as: the mean absolute change in FEV_1 (Table 2); gain in body weight ($p \leq 0.0004$) and improvement in body mass index (BMI)-for-age *z*-scores ($p < 0.001$); clinically relevant (but not statistically significant) improvements in respiratory symptoms, as measured by the child version of the CFQ-R respiratory domain (Table 2); and scores for respiratory symptoms on the parent/caregiver CFQ-R ($p = 0.033$ where reported) [11].

Ivacaftor for up to 144 weeks of treatment continued to provide beneficial effects on parameters such as lung function and bodyweight in children enrolled in the PERSIST extension trial [18]. Placebo recipients in ENVISION responded to ivacaftor when they were switched to active treatment in PERSIST.

What is its efficacy in patients with other specific mutations?

The clinical efficacy of ivacaftor 150 mg every 12 h in treating cystic fibrosis patients aged ≥6 years with a non-*G551D* gating mutation (i.e. *G1244E*, *G1349D*, *G178R*, *G551S*, *G970R*, *S1251N*, *S1255P*, *S549N* or *S549R*) of the *CFTR* gene and an FEV_1 ≥40 % of predicted at screening was evaluated in a double-blind phase 3 trial ($n = 39$, with 2–8 patients in each mutation group) [14]. Patients were randomized to receive either ivacaftor 150 mg every 12 h or placebo for 8 weeks; following a washout period of 4–8 weeks, patients crossed over to the other treatment for 8 weeks. Patients continued to use their existing cystic fibrosis therapy, with the exception of inhaled hypertonic saline.

In the overall population of patients of this trial, treatment with ivacaftor was associated with statistically significant improvements versus placebo in the following outcomes [14]:

- *Lung function*: Through week 8, the mean absolute change from baseline in percent predicted FEV_1 (primary endpoint) was +7.5 and −3.2 percentage points during ivacaftor and placebo treatment, respectively (observed treatment difference 10.7 percentage points; 95 % CI 7.3–14.1).
- *BMI*: At week 8, the observed treatment difference in the mean absolute improvement from baseline was 0.7 kg/m^2 (95 % CI 0.34–0.99).
- *Respiratory symptoms*: Through week 8, the observed treatment difference in mean improvement from baseline in the CFQ-R respiratory domain score was 9.6 (95 % CI 4.5–14.7).

Efficacy responses varied greatly between patients with the nine specific mutations; conclusions about the relative efficacy of ivacaftor in various genotypes should not be drawn at this stage, as the number of patients in each mutation group was extremely small [14].

Of note, ivacaftor is not indicated for patients who are homozygous for the class II *F508del* mutation in the *CFTR*

gene (the most common *CFTR* mutation in those with cystic fibrosis) [3, 4]. In a randomized, double-blind, phase 2 trial in this patient population, which was powered to assess safety rather than efficacy, treatment with ivacaftor 150 mg every 12 h ($n = 112$) did not significantly improve lung function relative to placebo ($n = 28$), as measured by the change from baseline in percent predicted FEV_1 through week 16 (primary efficacy endpoint) [19].

What is its tolerability profile?

Treatment with ivacaftor was generally well tolerated in patients with cystic fibrosis [3–5]. According to a pooled analysis of three phase 3 trials (the 48-week STRIVE and ENVISION trials in patients with a *G551D CFTR* mutation, and the 8-week crossover study in patients with a non-*G551D CFTR* mutation) reported in the EU summary of prescribing characteristics [3], the adverse events that were reported most frequently with ivacaftor were upper respiratory tract (URT) reactions (including URT infection, nasal congestion, pharyngeal erythema, oropharyngeal pain, rhinitis, sinus congestion and nasopharyngitis), headache, abdominal pain, diarrhoea, rash, dizziness and bacteria in sputum (Fig. 1). These events were not considered serious (with the exception of one case of abdominal pain in a patient receiving ivacaftor) [3], and did not require treatment discontinuation [3, 4].

The incidence of adverse events considered to be serious was numerically lower with ivacaftor than with placebo in STRIVE (24 vs. 42 %) [10] and ENVISION (19 vs. 23 %) [11]. Serious adverse events reported in ivacaftor recipients in these trials included pulmonary exacerbation, productive

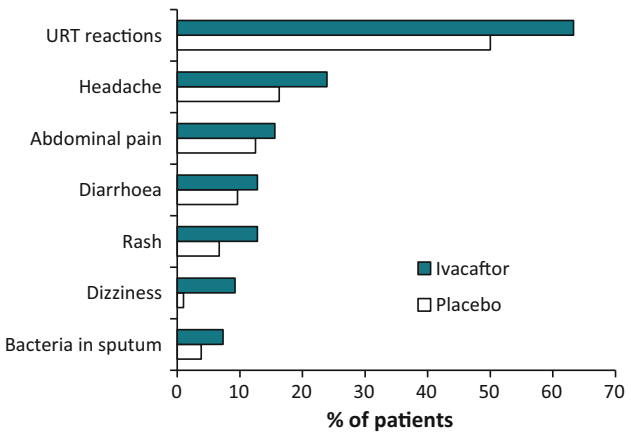

Fig. 1 Most common adverse events in patients with cystic fibrosis receiving ivacaftor 150 mg every 12 h in placebo-controlled phase 3 trials [pooled analysis of the 48-week STRIVE and ENVISION trials in patients with a *G551D CFTR* mutation ($n = 109$ ivacaftor and 104 placebo recipients), and the 8-week crossover study in patients with a non-*G551D CFTR* mutation ($n = 39$)] [3]. *URT* upper respiratory tract

cough, haemoptysis and hypoglycaemia; no deaths were reported [10, 11]. In STRIVE [10], adverse events resulted in drug interruption in 13 % of ivacaftor recipients (vs. 6 % of placebo recipients), and discontinuation in 1 % (vs. 5 %). In ENVISION [11], adverse events resulted in drug interruption in 3.8 % of ivacaftor recipients (vs. 11.5 % of placebo recipients), and discontinuation in 0 % (vs. 3.8 %).

Some differences in the adverse event profile of ivacaftor were observed among children (aged 6–11 years; $n = 23$) and adolescents (aged 12–17 years; $n = 22$) in the phase 3 trials [3]. For example, dizziness was very common (incidence ≥10 %) among adolescents but was not seen in children, whereas diarrhoea, pharyngeal erythema and tympanic membrane hyperaemia were common (incidence ≥1 to <10 %) or very common (incidence ≥10 %) among children but were not observed in adolescents.

Ivacaftor did not appear to have any clinically important effect on vital signs, ECGs, physical examination measurements or clinical laboratory tests in patients in STRIVE [10] or ENVISION [11]. However, other clinical studies have reported more frequent transaminase elevations with ivacaftor than placebo in patients with a history of such elevations [3]; regular monitoring is recommended (Table 1).

The tolerability profile of long-term (up to a total of 144 weeks) ivacaftor treatment [18] was generally consistent with that seen during the 48-week phase 3 trials [10, 11], with no new safety signals of any clinical importance being identified in the PERSIST extension trial [18]. Over the 96-week extension period, serious adverse events were reported in 20 % of ivacaftor recipients during the first 48 weeks of treatment and 23 % during the subsequent 48 weeks. Two adults/adolescents and one child discontinued the treatment because of an adverse event. The most common adverse events were respiratory in nature [18].

What is its current positioning?

Ivacaftor is the first agent that targets the underlying cause of cystic fibrosis, rather than providing treatment for the symptoms of the disease. Recent Pulmonary Clinical Practice Guidelines Committee guidelines strongly recommend the use of ivacaftor in patients aged ≥6 years who have a *G551D CFTR* mutation [20]. In this patient population, ivacaftor has been shown to significantly improve lung function and other parameters, with the drug being generally well tolerated for up to 144 weeks of therapy. A *G551D* mutation is present in ≈3 % of patients with cystic fibrosis, making it one of the most common mutations in the *CFTR* gene [7]. The efficacy demonstrated by ivacaftor in patients with this gating mutation has prompted investigation into the potential use of the drug in

patients with other rarer specific *CFTR* gating mutations. Based on the results of a placebo-controlled, 8-week crossover trial, ivacaftor was also approved for the treatment of patients with the following rarer specific *CFTR* mutations: *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R* (the EU, the USA and Canada) or *G970R* (Canada only).

Despite its efficacy, the uptake of the use of ivacaftor may be limited by its high acquisition cost. According to a UK pharmacoeconomic model [21], the use of ivacaftor to treat cystic fibrosis in patients aged ≥6 years with a *G551D* mutation was associated with an incremental cost of £335,000–1,274,000 per quality-adjusted life-year gained relative to standard care. Moreover, the total additional lifetime cost to treat all eligible patients with cystic fibrosis in England with ivacaftor was £438M–479M compared with a lifetime cost for standard care of £72M [21]. Further data on the long-term efficacy and cost effectiveness of ivacaftor are awaited with interest.

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References

1. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373(9678):1891–904.
2. Deeks ED. Ivacaftor: a review of its use in patients with cystic fibrosis. Drugs. 2013;73(14):1595–604.
3. Kalydeco 150 mg film-coated tablets: summary of product characteristics. London: European Medicines Agency; 2014.
4. Kalydeco (ivacaftor) tablets: US prescribing information. Boston: Vertex Pharmaceuticals Incorporated; 2014.
5. Kalydeco (ivacaftor tablets 150 mg): Canadian prescribing information. Laval: Vertex Pharmaceuticals (Canada) Incorporated; 2014.
6. Clancy JP, Johnson SG, Yee SW, et al. Clinical Pharmacogentics Implementation Consortium (CPIC) guidelines for ivacaftor therapy in the context of CFTR genotype. Clin Pharmacol Ther. 2014;95(6):592–7.
7. Rogan MP, Stoltz DA, Hornick DB. Cystic fibrosis transmembrane conductance regulator intracellular processing, trafficking, and opportunities for mutation-specific treatment. Chest. 2011;139(6):1480–90.
8. Ratjen FA. Cystic fibrosis: pathogenesis and future treatment strategies. Respir Care. 2009;54(5):595–605.
9. Van Goor F, Hadida S, Grootenhuis PDJ, et al. Rescue of CF airway epithelial cell function in vitro by a CFTR potentiator, VX-770. Proc Natl Acad Sci. 2009;106(44):18825–30.
10. 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.
11. Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6–11 years with cystic fibrosis with a *G551D* mutation. Am J Respir Crit Care Med. 2013;187(11): 1219–25.
12. Davies J, Sheridan H, Bell N, et al. Assessment of clinical response to ivacaftor with lung clearance index in cystic fibrosis patients with a G551D-*CFTR* mutation and preserved spirometry: a randomised controlled trial. Lancet Respir Med. 2013;1(8): 630–8.
13. Accurso FJ, Rowe SM, Clancy JP, et al. Effect of VX-770 in persons with cystic fibrosis and the G551D-*CFTR* mutation. N Engl J Med. 2010;363(21):1991–2003.
14. De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-*G551D* gating mutation. J Cyst Fibros. 2014;13(6):674–80.
15. Altes T, Johnson MA, Miller GW, et al. Hyperpolarized gas MRI of ivacaftor therapy in persons with cystic fibrosis and the *G551D-CFTR* mutation [abstract no. 196]. Pediatr Pulmonol. 2012;47:291.
16. Pohl K, Reeves EP, McElvaney NG. The CFTR potentiator ivacaftor corrects defective degranulation of secondary and tertiary granules by cystic fibrosis neutrophils [abstract no. WS9.9]. J Cyst Fibros. 2012;11(Suppl. 1):S21.
17. Reznikov LR, Abou Alaiwa MH, Dohrn CL, et al. Antibacterial properties of the CFTR potentiator ivacaftor. J Cyst Fibros. 2014;13(5):515–9.
18. McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-*CFTR* mutation: a phase 3, open-label extension study (PERSIST). Lancet Respir Med. 2014;2(11):902–10.
19. 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.
20. Mogayzel PJ Jr, Naureckas ET, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. Am J Respir Crit Care Med. 2013;187(7):680–9.
21. Whiting P, Al M, Burgers L, et al. Ivacaftor for the treatment of patients with cystic fibrosis and the G551D mutation: a systematic review and cost-effectiveness analysis. Health Technol Assess. 2014;18(18):1–106.