NHS England

Evidence Review:

Ivacaftor for children aged 2-5 years with cystic fibrosis (named mutations)

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First published:	December 2015
Updated:	Not applicable
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Contents

1. Introduction

Cystic fibrosis is the most common, life-limiting, recessively inherited disease in the UK, affecting c. 10,500 people. The underlying problem is a mutation in a gene that encodes for a chloride channel called the cystic fibrosis transmembrane conductance regulator (CFTR). This is essential for the regulation of salt and water movements across cell membranes. Absent or reduced function of CFTR results in dehydration of secretions leading to problems with mucus clearance, resulting in damage to the lungs, gut and pancreas. Impaired functioning of this protein may be due to a number of mutations, the most common being the ΔF508 mutation, which occurs in around 88% of patients with cystic fibrosis in the UK, whereas the G551D mutation occurs in around 6%.

Current standard treatments for CF aim to treat the symptoms of cystic fibrosis but do not treat the underlying cause. Ivacaftor (Kalydeco, Vertex Pharmaceuticals) is the first in a new class of medicines (CFTR potentiators) that target CFTR and so treat the underlying cause of the disease.

Ivacaftor was designated as an orphan medicine in the EU in 2008. In July 2012, it received EU marketing authorisation for the “treatment of cystic fibrosis in patients aged six years and above who have the G551D mutation in their gene for the protein called cystic fibrosis transmembrane conductance regulator (CFTR)”. This approval was extended in 2014 to cover a further 8 mutations. On 18th November 2015, the the license was expanded again to include use of the granule formuation in children aged 2 years and older with the named mutations.

NHS England routinely commissions Ivacaftor for patients with a diagnosis of cystic fibrosis and at least one copy of one of the nine specified gene mutations (G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D) and who are aged 6 years or over (Clinical Commissioning Policy: Ivacaftor for cystic fibrosis (named mutations) A01/P/a, first published January 2013 and updated July 2015).

2. Summary of results

Is ivacaftor clinically effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?

There is relatively limited evidence that is specific to children in the age group 2-5 years who have Cystic Fibrosis with one of the specified gating mutations. To date there are no Randomised Controlled Trials (RCT) in this paediatric population. However, there is high grade evidence (level -1/1) supporting the use of ivacaftor 150mg twice a day in children who have Cystic Fibrosis and the nine named gating mutations who were aged greater than 6 years. In this older paediatric population, four RCTs have evaluated and measured the following outcomes:

- Changes in lung function
- Changes in nutritional status
- Changes in sweat chloride concentration.

The results of all four RCTs show a statistical significance; increase in FEV1 ($P<0.001$), decrease in sweat chloride concentration ($P< 0.0001$) and increase in weight ($P =0.0004$) in patients receiving treatment with ivacaftor 150mg twice a day at 48 weeks. A double blind study (Davies et al, 2013) in which the mean paediatric age was 8.9 years of age also benefited from treatment, as improvements in lung function 12% of predicted FEV1 compared with standard care at 24 weeks were measured. There was significant weight gain of 2.7kg at 48 weeks and a very marked decrease in sweat chloride concentration (treatment effect -54.3mmol/L) which was most dramatic on day 15. An additional RCT looked at ivacaftor 150mg in patients ≥6 years old with CF and non-G551D gating mutations (G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, or G1349D). This also confirmed positive impacts on main outcomes including FEV1 and sweat chloride, indicating benefit for both the main clinical and biochemical outcomes.

As ivacaftor has been licensed since 2012 for children aged 6 and over, new RCT evidence is not expected. However, there is some recent evidence (level 2-) indicating that the rate of decline of lung function was slowed by half over a 3 year period in the treatment group when matched with up to 5 homozygous F508del control patients, not eligible to receive Ivacaftor (Sawicki et al, 2015).

The formal evidence level to support the use of ivacaftor directly in children aged 2-5 years who have Cystic Fibrosis with a specified gating mutation is low (grade 3). This comes from a phase III open label study (Davies et al, 2015) undertaken to determine safety and confirm pharmacokinetics/pharmacodynamics in this age group. It confirmed that marked improvements in sweat chloride concentration (-46.9 ± 26.2 mmol/L, P<0.0001), weight (0.2 ± 0.3, P< 0.0001) and faecal elastase (99.8 ± 138.5ug/g) were seen at 24 weeks, consistent with positive outcomes seen in the above RCTs and indicating that extrapolation of the results from older children is biologically plausible. As the drug is now licensed for both US and European patients aged 2 and above, new RCTs are unlikely.

The evidence to date suggests most adverse events encountered by patients following treatment with ivacaftor were no more frequent than those in the placebo group. Most frequent mild adverse events noted were cough, headaches, dizziness and pulmonary exacerbations. Non-congenital lens opacities (cataracts), without impairment of vision, have been reported in children <12 years old treated with Ivacaftor. Causality is not proven but an association cannot be excluded.

Is ivacaftor cost effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?

There is sparse evidence on the cost effectiveness of ivacaftor. A systematic review (Whiting et al, 2014) showed the incremental cost effectiveness ratio (ICER) for ivacaftor varied between £335,000 and £1,274,000 per Quality Adjusted Life Year (QALY). The total additional lifetime cost for all eligible cystic fibrosis patients in England ranged from £438 million to £479 million for the lifetime cost and for standard care the lifetime cost was £72 million.

3. Research questions

Is ivacaftor clinically effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?

Is ivacaftor cost effective in children aged 2-5 years who have cystic fibrosis with the specified gating mutations?

4. Methodology

A review of published, peer reviewed literature has been undertaken based on the research questions set out in Section 3 and a search strategy agreed with the lead clinician and public health lead for this policy area. This has involved a PubMed search and search of the Cochrane database for systematic reviews, in addition to review of any existing NICE or SIGN guidance. The evidence review has been independently quality assured.

An audit trail has been maintained of papers excluded from the review on the basis of the inclusion and exclusion criteria agreed within the search strategy. The full list has been made available to the clinicians developing the policy where requested.

5. Results

A detailed breakdown of the evidence is included in the Appendix.

Appendix One

Grade	Study design and intervention			Patient characteristics		Outcomes					Reference	Other		
Grade of evidence	Study design	Study size	Intervention	Ages	Disease severity	Category	Primary Outcome	Primary Result	Secondary Outcome	Secondary Result	Reference	Complications noted	Benefits noted	Comments
3	Case series	2 part study Part A: 9 patients, Part B:34 patients	Administrating of 50mg, or 75mg Q12 of Ivacaftor for weight <14kg or ≥ 14kg respectively over 4 days and 24 weeks.	2 to 5 years of age. In Part B of the study mean age 3.2 years	CF with a gating mutation	Clinical effectiveness of the intervention	To measure the safety and Pharmacokinetics after administration of Ivacaftor over the given time period in Part A (4 days) & Part B (24 weeks) of the study.	At week 24 changes were seen in sweat chloride (-46.9± 26.2mmol/L, P <0.0001, weight and BMI z scores 0.2 ±0.3 and 0.4 ±0.4, respectively P<0.0001. Improvement in IRT (-20.70 ±24ng/mL and faecal elastase (99.8 ± 138.35ug/g).	-	-	J Davies et al.. An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2 to 5 years with cystic fibrosis and a CFTR gating mutation: The KIWI study. J. Cyst. Fibros. 2015;14 Suppl 1(0):S2.	9 patients enrolled in Part A of the study and 34 patients in Part B. In Part A the most common AE was pyrexia (44%) in Part B cough (56%). 5 patients (14.7%) experienced elevations in ALT or AST of 8> ULN (all had 2 >ULN at baseline and returned to normal after withdrawal.	Yes	In this small 2 part study the authors evaluate the clinical effectiveness of administrating Ivacaftor in CF patients with a gating mutation aged 2-5 years of age. The study demonstrates that administrating Ivacaftor at 50mg and 75mg at Q12 regimes are appropriate for children aged 2- 5 years of age. Improvements were seen in sweat chloride, nutrition status and pancreatic function at 24 weeks. Adverse events were mostly mild to moderate and elevations in ALT or AST were seen in some patients with abnormal baseline LFTs. This evidence has been downgraded in view of the sample size and no comparative group.
3	Case report	1 patient as case report	Administrating Ivacaftor 150mg twice a day for 6 weeks.	12 years of age.	CF with severe lung disease and gating mutation S549N	Clinical effectiveness of the intervention	To measure the clinical effectiveness of Ivacaftor i.e. I) Normalisation or reduction in sweat chloride concentration. II) Changes in nutritional status III) Changes in lung function.	Prior to treatment sweat chloride concentration level was 95mmol. After 2 & 4 week treatment was 19, and 20mmol respectively. Significant changes in lung function 39% increase in FVC and 87% in FEV1 best lung function seen in last 3 years. Weight gain which resulted in changing in a high calorie diet to normal diet.	-	-	McGarry, Meghan E.; Nielson, Dennis W.. Normalization of sweat chloride concentration and clinical improvement with ivacaftor in a patient with cystic fibrosis with mutation S549N. Chest 2013;144(4):1376-1378.	None declared	Yes	This case report is a low grade evidence in which the authors conclude the effective use of Ivacaftor in a single patient with a S549N gating mutation. The use of Ivacaftor is limited to 6 weeks with no evaluation of the complications.

3	Case series	Two double blind study. Total patients 213 Study 1 n= 161, Study 2 n= 52	Ivacaftor 150mg every 12 hours.	Study 1 patient ≥ 12 years and Study 2 patient 6-11 yrs. of age.	CF patients with G551D mutation	Clinical effectiveness of the intervention	Follow on study to determine whether a short term (15 day) change in sweat chloride concentration could be used to predict a long term (16 week) improvement in FEV1 or weight gain in CF patients with a gating mutation and treated with Ivacaftor.	Decrease in both mean sweat chloride and mean change from baseline was observed at day 15 in both age groups. significant increase in mean FEV1 (p=0.0006) and mean percent change from baseline (p<0.0001) in FEV1 were observed at week 16. No statistical correlation was found between FEV1 and sweat chloride measures which measures long term predication of an improvement in FEV1 ≥5% from baseline. No correlation was found for weight gain at week 16. Further investigated using an algorithm (calculated using binned intervals to determine sweat chloride concentration threshold as a predictor of PPV. for positive predictive values (PPV,s) for both improvements in FEV1 ≥5% and weight gain ≥ 10% at week 16. Sweat chloride threshold concentration was 80mmol/L and raw change in concentration was 20mmol/L. Combining both thresholds in the 6-11 year group (90.9 % (PPV), 90.5% sensitivity than the older age group. Placebo group was much lower. With weight gain sweat chloride threshold was 60mmol/l and raw change concentration of 40mmol/l. Patient who had a decrease of 40mmol and greater, median percent weight gain from baseline was 11.2% at week 16. Less than 40mmol/l weight gain of 6.0% from baseline.	-	-	Seliger, Verena I.; Rodman, David; Van Goor, Fredrick; Schmelz, Andreas; Mueller, Peter. The predictive potential of the sweat chloride test in cystic fibrosis patients with the G551D mutation. J. Cyst. Fibros. 2013;12(6):706-713.	None declared	Yes	In this case series the authors conclude that determining a sweat chloride concentration threshold in patients with a CF gating mutation at day 15, maybe sufficient in predicting the likelihood of weight gain and improvement in lung function after 16 weeks of treatment with Ivacaftor. High likelihood of bias in this study as some of the authors employed by manufacturer, and in view of the evidence type this has been downgraded.

1-	RCT	Konnection study 2 part double blind RCT. Part 1: group 1 (treatment, then placebo n =20), group 2 (placebo then treatment n=19), total n=39	Ivacaftor 150mg twice a day for 8 weeks	Patients ≥6yrs of age. Group 1 mean age 23.8 years, Group 2 mean age 21.7 yrs of age	CF patients with a non G551D gating mutation.	Clinical effectiveness of the intervention	To evaluate the safety and efficacy of Ivacaftor in patients aged ≥ 6yrs of age with a non G551D gating mutation. To measure the change from baseline in percent predicted FEV1 through to 8 weeks with treatment.	Patients that received Ivacaftor had a significant (P<0.0001) improvement in FEV1 predicted (7.5% through to 8 weeks in comparison to the placebo group.	To measure the absolute change from baseline in BMI and sweat chloride through to 8 weeks of treatment	Absolute mean change from baseline in BMI at week 8 was greater with treatment than placebo, (0.7kg/m2, 0.02kg/m2 respectively). Treatment effect of 0.7kg/m2 (95% Confidence Int 0.34, 0.99, P<0.0001). Change in sweat chloride from baseline after 8 weeks of treatment was -52.3mmol/l compared with -3.1mmol/l treatment effect -49.2mmol/L (95% CI -57.0, -41.4, P<0.0001)	De Boeck, Kris; Munck, Anne; Walker, Seth; Faro, Albert; Hiatt, Peter; Gilmartin, Geoffrey; Higgins, Mark. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. J. Cyst. Fibros. 2014;13(6):674-680.	Adverse events reported in Part 1 of the treatment group were (73.7%) compared to the placebo group (83.8%). Most common AE's in the treatment group were: Pulmonary Exacerbation (23.7%), cough (15.8%). 4 patients in the treatment group had serious AE's	Yes	In this small double blind crossover study the authors conclude that Ivacaftor is clinical effective in CF patients with a non G551D gating mutation. Significant improvements were seen in percent predicted FEV1, BMI and sweat chloride concentrations. Improvements with Ivacaftor were seen as early by week two of treatment and sustained through to 8 weeks and improvement in lung function improvement sustained through to 24 weeks. There is a degree of bias as the authors work for Vertex Pharmaceuticals.

1+	Systematic	Variable depending on study design.	none	children ≤ 6 years of age	CF patients all genotypes, disease progressions in the respiratory and digestive system of young children with CF.	-	Three main outcomes; I) At what age have CF related dysfunction and structural difference been demonstrated in children ≤ 6years of age. II) What age has disease progression reported in CF. III) At what age are there improved outcomes with early versus late treatment initiation in young children with CF?	I) Structural abnormalities and dysfunction in the digestive and respiratory system were observed prenatally, in infants and throughout childhood among children with CF. These include bowel, pancreatic, liver abnormalities, nutritional deficiencies and pulmonary exacerbations. 41 studies with CF and abnormalities observed. Morbidity was observed in 50% or more of the study sample for majority respiratory and digestive system outcome. II) Disease progression in respiratory and digestive system were demonstrated in infants as young as 6 months of age. with worsening of lung function observed in infants from 6 months to 1 year. 59% to 71% of infants with CF were pancreatic insufficient at birth an additional 16 to 20% were insufficient by 6 months. Increased risk of P aeruginosa infection up to 1 year of age. III) Children with access to earlier routine CF care secondary to earlier diagnosis had better outcomes. Benefits of earlier diagnosis and treatment included reduced airway inflation, improved growth, reduced hospitalisations and reduced colonization. Initiation of treatment and medical management within 2 months from birth was associated with improved outcomes in both respiratory and digestive systems in children ≤6yrs	-	-	VanDevanter, Donald R.; Kahle, Jennifer S.; O'Sullivan, Amy K.; Sikirica, Slaven; Hodgkins, Paul S.. Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment. J. Cyst. Fibros. 2015;0(0):0.	None declared	Yes	In this review the authors conclude CF associated growth impairment and respiratory system abnormalities are reported at birth. Disease progression is detected as early as 6 months of age impacting both digestive and respiratory system function decline throughout childhood. Early access to routine CF management results in better health outcomes. In view of potential bias as the study was supported by manufacturer, this evidence has been downgraded.
3	Case report	One patient 8 years old	Ivacaftor 150mg twice a day	8 year old	CF with S549R mutation	Clinical effectiveness of the intervention	Clinical effectiveness of Ivacaftor i.e.; I) Changes in lung function II) Changes in sweat chloride concentration. III) Changes in nutritional status.	After 6 weeks of treatment, clinical improvements in cough frequency, sputum production. Weight gain of 1.4kg. Sweat chloride concentration decreased from 115 mmol/ before treatment to 40mmol/l after 6 weeks and 52mmol/l after 41 weeks. FEV1 increased from 1.25 to 1.65 after 41 weeks. Decrease in lung function clearance from 14.5 to 8.3 after 6 weeks and 7.8 after 41 weeks.	-	-	Lenherr, Nina; Lurà, Marco; Trachsel, Daniel; Latzin, Philipp; Hammer, Juerg. Ivacaftor in a young boy with the rare gating mutation S549R - use of lung clearance index to track progress: a case report. BMC Pulm Med 2015;15(1):123.	none declared	Yes	Low grade evidence in which the authors conclude potential benefit of using Ivacaftor in a young patient with CF and S549R mutation. The report highlights the value of using lung function clearance index as an outcome measure especially where performance and interpretation of spirometry is challenging possible use in preschool children.

1-	Systematic	Total number of patients ,STRIVE n=167 and ENVISION n=52	Administration of oral Ivacaftor 150mg every 12 hours for 48 weeks. In patients with CF when used in addition to existing therapy (exception inhaled hypertonic saline)	aged ≥ 12 years of age (STRIVE) 78% of patients aged ≥18 years . ENVISION, age range 6-11 yrs., mean age 9 years)	CF and G551 mutation, most had the F508del mutation in second allele (80.8%). 15% had FEV1< 70% predicted.	-	Measure the clinical efficacy (lung function, nutritional status and sweat chloride concentration) and tolerability data relevant to the use of Ivacaftor in CF patients with a G551D mutation.	Focus here is on the ENVISION study only : Oral Ivacaftor was effective in improving lung function, reported a mean absolute change from baseline in FEV1 of 12.5% predicted (p<0.0001) through to 24 weeks and 10% (p=0.0006) at 48 weeks. With difference between the group favouring treatment from day 15 through to week 48. significant reduction in sweat chloride through to week 48 (treatment difference -53.5 mmol, p<0.0001). Decreased pulmonary exacerbations as defined by trial protocol were noted. In the treatment group 4 were noted and three in the placebo group. significant weight gain in the treatment group after 24 weeks of treatment. Treatment difference of 2.8kg, P=0.0002. Both BMI for age and weight for age z scores also significantly favoured in the treatment group (p<0.001) over the placebo group at 48 weeks. The Ivacaftor group also reported improvements from baseline in their respiratory symptoms as measured by the child version of the CFQ-R respiratory domain. Although no statistical significance between the two groups at 24 or 48 weeks. The extension study (PERSIST) showed Ivacaftor to benefit lung function and body weight for up to 72 weeks.	-	-	Deeks, Emma D.. Ivacaftor: a review of its use in patients with cystic fibrosis. Drugs 2013;73(14):1595-1604.	Serious adverse advents were lower in the Ivacaftor group than placebo, (19 vs 23% respectively). Serious events reported more than once included pulmonary exacerbation(two vs three patients), productive cough (one patient in each group). No patients died in either study.	Patients who completed STRIVE or ENVISION were eligible to receive further treatment with Ivacaftor in open label extension study, PERSIST	The author concludes the use of Ivacaftor in patients with Cystic Fibrosis aged ≥ 6 years of age who have the G551D CFTR mutation. In both of these studies STRIVE and ENVISION , administering 150mg of Ivacaftor twice a day demonstrated a significant improvement in lung function and bodyweight. Benefits were maintained for up to 96 weeks of therapy in the on going extension study. Although long term data would be required to fully evaluate given the treatment is required lifelong. In view of potential bias, as manufacturer was invited to comment on the review, the evidence has been downgraded.

1-	RCT	21 patients , group 1 (placebo then treatment, n=11) group 2 (treatment then placebo n =10)	150mg of Ivacaftor twice daily for 28 days.	Both groups ≥6 years, Group 1 mean age 19.8 yrs., SD 13.35, Group 2 mean age 13.4 yrs. SD (7.12)	CF with G551D mutation	Clinical effectiveness of the intervention	Clinical effectiveness of Ivacaftor in patients with CF a G551D-CTFR mutation with a FEV1 higher than 90% predicted using Lung clearance index (LCI) as outcome measure.	Improvement in baseline LCI was greater with treatment in both groups than placebo. Difference between groups, in the average of mean changes from baseline at days 15 and 29 was -2.16 (95% CI -2.88 to -1.44), p<0.0001	Changes from baseline in sweat chloride. Score on CFQ-R at day 15 and day 29. Change in predicted FEV1	Absolute mean change of percent predicted FEV1 from baseline was greater with Ivacaftor treatment than placebo. Difference in the average of mean changes at day 15 and day 29 was 8.67 percentage points p=0.0103. In the Ivacaftor treated group significant reduction in sweat chloride concentrations, average for day 15 and 29 was -47.5mmol/l (95% CI -54.57 to -40.44, p<0.0001). Treatment effect was not significant for CFQ-R score.	Davies, Jane; Sheridan, Helen; Bell, Nicholas; Cunningham, Steve; Davis, Stephanie D.; Elborn, J. Stuart; Milla, Carlos E.; Starner, Timothy D.; Weiner, Daniel J.; Lee, Po-Shun; Ratjen, Felix. 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):630-638.	79% patients reported at least one adverse event in the placebo group and 72% in the Ivacaftor group. Most frequent events cough (45%), headache (25%), vomiting (25%), pyrexia (20%) and nasal congestion (15%) 3 serious events in the Ivacaftor group (distal ileal obstruction syndrome, both pulmonary exacerbation and pseudomonas infection). No deaths occurred during the study.	Yes	In this relatively small double blind 2x2 crossover study the authors conclude Ivacaftor is clinically effective in CF patients with a G551D-CFTR mutation with a baseline FEV1 > 90% predicted. The authors have demonstrated that using LCI as an measure of efficacy is more sensitive than spirometry in CF patients with served lung function. There is a degree of bias as the study was funded by Vertex Pharmaceuticals in view of this the evidence has been downgraded.

1-	RCT	52 patients	Patients randomly assigned to receive a dose of Ivacaftor 150mg every 12 hours for 48 weeks.	6-11 years of age. Mean age 8.9 years	CF patients with a G551D-CFTR mutation	Clinical effectiveness of the intervention	To evaluate the efficacy and safety of Ivacaftor in a young (6-11 years of age) and more mildly affected group of patients with CF and at least one G551D-CFTR mutation.	Mean percent of predicted FEV1 values at baseline were 84.7 in the treatment group and 83.7 in the placebo group. Through week 24 the model adjusted mean in the treatment group was 12.6 % and 0.1% in the placebo group. A treatment effect of 12.5% , P<0.001. At week 24 patients in the Ivacaftor group had gained an average of 3.7Kg compared with 1.8Kg in the placebo group (treatment effect 1.9Kg ,P<0.001) at 48 weeks treatment effect 2.8kg, P<0.0001. Improvement in the respiratory domain of the CFQ-R scores seen in the treatment group. Mean baseline scores were 78 pts in the Ivacaftor group and 80 points in the placebo group. From baseline to week 24 model adjusted scores increased by 6.3 points in the Ivacaftor group and 0.3 points in the placebo group. (treatment effect 6.1, P=0.109). Pulmonary exacerbation rate was low and did not differ between the Ivacaftor (4 events) and placebo group (3 events). Sweat Chloride concentrations dropped rapidly effect observed first on treatment day 15 in the Ivacaftor group and stable through weeks 24 ad 48. The mean change from baseline in sweat chloride was -55.5mmol/L in the Ivacaftor group and -1.2mmol/L in the placebo group (treatment effect -54.3mmol/L, P<0.001) and was maintained through week 48.	-	-	Davies, Jane C.; Wainwright, Claire E.; Canny, Gerard J.; Chilvers, Mark A.; Howenstine, Michelle S.; Munck, Anne; Mainz, Jochen G.; Rodriguez, Sally; Li, Haihong; Yen, Karl; Ordoñez, Claudia L.; Ahrens, Richard; VX08-770-103 (ENVISION) Study Group. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a G551D mutation. Am. J. Respir. Crit. Care Med. 2013;187(11):1219-1225.	Incidence of adverse events through week 48 similar for both groups. One patient from the treatment group and 3 from the placebo group had an event which led to drug interruption. A total of 11 patients reported serious adverse events (5 patients in the Ivacaftor group and 6 in the placebo group).Pulmonary exacerbations (2 patients in treatment group and 3 in the placebo group) and productive cough (one patient in each group) were reported more than once. No deaths occurred during the study. No clinically important trends attributable to Ivacaftor were identified in results on clinical laboratory tests.	Yes	In this randomised double blind placebo controlled trial the authors conclude the potential benefit of Ivacaftor 150mg twice a day for 48 weeks in patients with CF aged 6-11 years with a G551D-CFTR mutation. The evidence suggests significant improvements in lung function (with an absolute improvement of 12.5 percentage pts of predicted FEV1 through 24 weeks. There were also significant weight gain after 48 weeks (2.7kg) in the treatment group with improved BMI z scores in the Ivacaftor group. Serious adverse events were not increased by Ivacaftor in comparison to the placebo group. However the study recognises to date this treatment has been administered to a small population and efficacy has been measured over a short time period given the expectation of this being a lifetime treatment. To better understand the long term safety of Ivacaftor a 5 year safety surveillance study is on going in the United States.

1+	RCT	213 patients in total	Ivacaftor 150mg, twice a day for 48 weeks in patients aged ≥ 6 years with CF and the G551D mutation.	Study 1 ≤ 20 years of age n=105 (52 treatment group), mean age 12. Study 2 > 20 years of age n=108 (57 patients in treatment group) mean age 30	CF and G551 mutation, 199 patients were pancreatic insufficient.	-	Improvements in weight and BMI after administering Ivacaftor 150mg, twice a day for 48 weeks in patients aged ≥ 6 years with CF and the G551D mutation.	In study 1 change from baseline to week 48 in body weight was 4.9Kg in the Ivacaftor group compared with 2.2kg in the placebo group, (treatment difference of 2.7kg , p=0.0008). Statistical significant difference between the two groups were observed within the first 2 weeks. At week 48 the Ivacaftor treatment group in study 1 had an increase in mean z score of 0.29 compared with -0.06 in the placebo group, (treatment effect 0.35, p<0.0001).No differences with regard to sex and absolute weight gain were noted however there was a greater increase in weight for age z score in females treatment effect 0.43, than in males treatment effect 0.24. Overall by week 48 in study 1 the treatment group had an increase in BMI for age z score of 0.26 compared with the placebo group of -0.13, treatment effect 0.39, p<0.0001. In study 2 mean change from baseline to week 48 in body weight was 2.7kg in the Ivacaftor group and -0.2kg in the placebo group. Treatment difference of 2.9kg , p=0.0003. There was no evidence of a linear correlation between changes in body weight and improvements in lung function or sweat chloride in both age groups.	-	-	Borowitz, Drucy; Lubarsky, Barry; Wilschanski, Michael; Munck, Anne; Gelfond, Daniel; Bodewes, Frank; Schwarzenberg, Sarah Jane. Nutritional Status Improved in Cystic Fibrosis Patients with the G551D Mutation After Treatment with Ivacaftor. Dig. Dis. Sci. 2015;0(0):0.	None declared	Yes	The authors of this multicentre randomised double blind, placebo controlled trial have demonstrated that nutritional status i.e. both weight gain and BMI of both children and younger adults in the range of ≤ 20 years of age and > 20years respectively with CF and the G551D mutation benefited from treatment with Ivacaftor 150mg twice a day for 48 weeks relative to the placebo group. Although there is no direct correlation between improvements in nutritional status and lung function or sweat chloride concentration.
1-	RCT	Follow on study from previous STRIVE and ENVISION study. Data pooled, n= 209	Ivacaftor 150mg twice a day	STRIVE ≥ 12 yrs. ENVISION 6-11 yrs. of age. As pooled together mean age 22.1 SD 11.4yrs	CF and G551 mutation	-	To better understand the effect of Ivacaftor treatment across the distribution of individual FEV1 responses, data from the STRIVE & ENVISION studies.	Patients were assigned to a category (lower, middle and upper) based on absolute change from baseline through week 48 in percent predicted FEV1. Across all categories there was improvements in FEV1, sweat chloride concentration and CFQ-R in the Ivacaftor treatment group compared with the placebo group. There was a statistical significance for all outcomes in the upper and some in the middle lower categories. NNT for a ≥ 5% improvement in % predicted FEV1 was 1.90, for a ≥5% body weight increase aws 5.74 and to prevent pulmonary exacerbation was 3.85.	-	-	Konstan, Michael W.; Plant, Barry J.; Elborn, J. Stuart; Rodriguez, Sally; Munck, Anne; Ahrens, Richard; Johnson, Charles. Efficacy response in CF patients treated with ivacaftor: post-hoc analysis. Pediatr. Pulmonol. 2015;50(5):447-455.	Serious adverse events were similar in the treatment and placebo group. Frequent adverse events observed in the treatment group were, headache, upper respiratory tract infection, abdominal pain, diarrhoea. Adverse events varied according to the tertiles of FEV1 responses, but generally equally distributed.	Yes	The authors of this follow on study have demonstrated that across all FEV1 response tertiles patients treated with Ivacaftor had a greater change from baseline in FEV1 % predicted than the placebo group. Concluding patients with similar clinical characteristics as the STRIVE and ENVISION RCTs have the potential of benefiting from Ivacaftor treatment. In view of potential bias this evidence has been downgraded.

1-	Systematic	1st RCT n= 19, 2nd RCT in adults n =167, 3rd RCT peads n = 52 (26 placebo and 26 intervention) and 4th RCT n=140	150mg of Ivacaftor twice a day for 48 weeks.	6-11 years of age. Mean age 8.9 years	CF patients with G551D mutation. FEV1 40-50% predicted	-	Absolute change from baseline through to week 24 in % predicted FEV1	Davies et al RCT has already been discussed in detail, to outline main evidence only as follows: Improvement in relative change from baseline FEV1 at 24 weeks mean difference 17.4% (p<0.0001). No data recorded at week 48. BMI for age z scores in the treatment group compared to placebo at 24 weeks, mean difference(MD) 0.34 (p<0.001) and 48 weeks MD 0.45 (p<0.001). Reduction in sweat chloride concentration day 15 , MD -50mmol/L	-	-	Patel, Sanjay; Sinha, Ian P.; Dwan, Kerry; Echevarria, Carlos; Schechter, Michael; Southern, Kevin W.. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. Cochrane Database Syst Rev 2015;3(0):CD009841.	(4 patients out of 52) required interruption 3 from placebo group and 1 patient from treatment group. More mild adverse events were experienced in the placebo group than treatment group. One patient from the placebo group withdrew completely due to anxiety and psychological issues.	Yes	The authors conclude after reviewing the evidence from both G551D RCTs, Ivacaftor is clinically effective at 24 and 48 weeks in treating CF patients ≥ 6 years old with the G551D mutation. There is no evidence to support the cost effectiveness of this lifelong treatment. There is a study bias in view of this the evidence has been downgraded.
1-	Systematic	RCT 1 in adults n=167 (≥ 12 years) RCT 2 n =52 (patient aged 6-11 yrs. old) open label study extension two include both RCTs	150mg of Ivacaftor twice a day for 48 weeks for both RCTs, extension study 96 weeks in total	Peads study i.e. RCT 2 aged 6-11 yrs. old. Mean age 9 SD 1.9	CF patients with G551D mutation. FEV1 40-50% predicted	-	To review the clinical effectiveness of Ivacaftor in terms lung function measure as efficacy outcome in patients aged≥ 6 with a G551D mutation.	Adult RCT disregarded. Ivacaftor improved lung function in both RCTs. In children mean difference in change in percentage predicted FEV1 was 10% at 48 weeks, this was maintained during the follow up study at 72 weeks. Pulmonary exacerbations were uncommon in both treatment and placebo group. Children treated with Ivacaftor gained weight compared with the placebo at 48 weeks, treatment effect of 2.8kg (95% CI 1.3 to 4.2). Sweat chloride concentration treatment effect -53.5mmol/l (95% CI -60.9to -46.0).	Cost effectiveness of Ivacaftor for CF patients with the G551D mutation.	The incremental cost effectiveness ratio (ICER) varied between £335,000 and £1,274,000 per QALY. Total additional lifetime cost for all eligible CF patients in England ranged from £438M to £479M the lifetime cost for standard care was only £72M.	Whiting, Penny; Al, Maiwenn; Burgers, Laura; Westwood, Marie; Ryder, Steve; Hoogendoorn, Martine; Armstrong, Nigel; Allen, Alex; Severens, Hans; Kleijnen, Jos. 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.	Adverse events were minor and no differences found between the treatment and placebo group. Most common ones cough, headache, upper respiratory tract infection and pulmonary exacerbation. No withdrawal from treatment. In both RCT and extension study.	Yes	The authors conclude after reviewing the evidence from two good quality RCTs and an extension study that Ivacaftor is effective in treating CF patients ≥ 6 years old with the G551D mutation. Improvements in lung function, sweat chloride concentration and nutritional status were seen at 48 weeks and maintained in the extension study. However its potential to affect children in a younger age cohort is unclear at this stage. The high cost of Ivacaftor may prove to be a challenge in its uptake unless data become available on the long term use of Ivacaftor. In view of possible bias in the study the evidence has been downgraded.

1-	Systematic	Variable depending on study chosen, here looking at study by Ramsey (2011) n =161 and Aherns (2011) n =52	Administering oral Ivacaftor 150mg twice a day for 48 weeks	Patients older than 6 years of age. Ramsey (2011) age 12-53 yrs., Aherns (2011) age 6-11 yrs.	CF patients with G551D mutation.	Clinical effectiveness of the intervention	To evaluate the clinical effectiveness of Ivacaftor in terms I) Changes in lung function. II) Changes in sweat chloride concentration and III) Change in nutritional status in patients with CF and G551D mutation.	Study by Accurso et al (2010), n= 39 is excluded here as it looked at the adult cohort(18-51 yrs.). Ramsey (2011) study showed a significant increase in FEV1 (p<0.0001), a decrease in sweat chloride (p <0.0001), a decrease in pulmonary exacerbation rate (p=0.0003), an increase in CFQ-R score (p<0.001) and increase in weight (p<0.0001) from baseline. Some sweat chloride values in the treatment group were lowered below the diagnostic threshold of 60mEq/L. Study by Aherns et al (2011),showed a statistically significant increase in FEV1 (p<0.0001), a decrease in sweat chloride (p<0.0001) and an increase in weight gain (p=0.0004) with Ivacaftor. No statistically significant change in the CFQ-R scores. Patients who completed this study had the option to continue in an open label study, on going still however results to date shown significant weight gain with on going treatment.	-	-	Pettit, Rebecca S.. Cystic fibrosis transmembrane conductance regulator-modifying medications: the future of cystic fibrosis treatment. Ann Pharmacother 2012;46(42223):1065-1075.	The Ivacaftor group had a higher rate of adverse events compared to the placebo (13% vs 6%). Events that led to discontinuation of Ivacaftor; Increased levels of hepatic enzymes, AV block, panic attack and respiratory failure. The adverse effects that occurred frequently in the treatment group were URTI, rash, headache, nasal congestion and dizziness. Pulmonary exacerbation, cough and haemoptysis occurred less frequently in the treatment group than the placebo group. 2 patients experienced hypoglycaemia in the treatment group. Generally well tolerated. In the Aherns et al (2011) study adverse events were similar between the two groups, most common being cough, headache, pulmonary exacerbation, vomiting and throat pain. In conclusion study showed Ivacaftor was safe and effective in the 6-11 year old group.	Yes	The author concludes the evidence demonstrated by the good quality RCTs is that Ivacaftor is clinically effective as an oral potentiator. Both studies by Aherns et al (2011) and Ramsey et al (2011) highlight the decrease in sweat chloride concentration, improvement in FEV1 and weight gain in patients who has CF with a G551D CFTR mutation. However the evidence is limited to two double blinded RCTs, with a small paediatric sample size. The evidence has been downgraded in view of this.
2-	Case-control	Follow up data from 2 RCTs generating a cohort of 189 patients with G551D mutation receiving ivacaftor and matched cohort of 886 patients from US CF registry homozygous for F508del mutation	Ivacaftor (dose not specified)	Over 6 years old. Mean G551D age 22.6 ± 11.3; Mean F508del age 21.3 ± 10.5	CF patients with G551D mutation and CF patients with non gating mutation (F508del mutation)	Clinical effectiveness of the intervention	To estimate the annual rate of decline in lung function as measured by FEV1	Patients with G551D mutation treated with ivacaftor had a significant acute benefit in lung function that persists over time, confirming earlier studies. Rate of lung function decline in G551D ivacaftor-treated patients was slower by nearly half when compared to matched F508del control patients	To measure improvement in nutritional status by measuring BMA and Weight-for-age	Treatment with ivacaftor was shown to improve BMI and WFA z scores for G551D patients both acutely and ove rthe 3-year analysis period. Hpowwer there was no difference in rate of improvement between the ivacaftor treated patients and the matched control group.	Sawicki, Gregory S.; McKone, Edward F.; Pasta, David J.; Millar, Stefanie J.; Wagener, Jeffrey S.; Johnson, Charles A.; Konstan, Michael W.. Sustained Benefit from Ivacaftor Demonstrated by Combining Clinical Trial and Cystic Fibrosis Patient Registry Data. Am. J. Respir. Crit. Care Med. 2015;192(7):836-842.	None noted	Lung function declined more slowly in patients on Ivacaftor therapy than matched patients with mutations where the drug is not indicated, for up to 3 years.	The authors conclude that it is possible to use clinical trial data matched with observational patient registry data to compare longer-term outcomes in patients with CF. Overall they identified a slower rate of lung function decline and improvements in nutrition for G551D patients who were treated with ivacaftor in clinical trials for up to 3 years. The authors propose that these findings suggest that ivacaftor is a disease-modifying therapy of CF. However, the comparator group of patients with CF had a different underlying genotype which may have different disease progression. There was a selection bias where G551D patients drawn from clinical studies compared to F508del control patients drawn from the CF registry..

Appendix Two

Literature search terms

Assumptions / limits applied to search:	
Original search terms:	n/a
Updated search terms - Population	cystic fibrosis OR gating mutation OR gating mutations OR CFTR mutation OR CFTR mutations OR G551D OR G178R OT S549N OR S549R OR G551S OR G1244E OR S1251N OR S1255P OR G1349D
Updated search terms - Intervention	ivacaftor OR kalydeco OR VX-770
Updated search terms - Comparator	n/a
Updated search terms - Outcome	n/a

Inclusion criteria	**General inclusion criteria**
	In order of decreasing priority, articles will be selected based on the following criteria. 1.All relevant systematic reviews and meta-analysis in the last 5 years and those in 5-10 years period which are still relevant (e.g. no further updated systematic review available) 2.All relevant RCTs and those in the 5-10 years period which are still relevant (e.g. not superseded by a next phase of the trial/ the RCT is one of the few or only high quality clinical trials available) >>>> If studies included reaches 30, inclusion stops here 3.All relevant case control and cohort studies, that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here 4.All relevant non analytical studies (case series/ reports etc.) that qualify after exclusion criteria >>>> If studies included reaches 30, inclusion stops here
	Specific inclusion criteria
	Requested by PWG and manually included J Davies et al. An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2 to 5 years with cystic fibrosis and a CFTR gating mutation: The KIWI study. J of Cystic Fibrosis 2015, Volume 14, Supplement 1, Page S2. Requested by PWG and manually included J VanDevanter, Donald R., et al. "Cystic fibrosis in young children: A review of disease manifestation, progression, and response to early treatment." Journal of Cystic Fibrosis (2015).
Exclusion criteria	**General exclusion criteria**
	Studies with the following characteristics will be excluded: 1. Does not answer a PICO research question 2. Comparator differs from the PICO 3. < 50 subjects (where studies with >50 subjects exist) 4. No relevant outcomes 5. Incorrect study type 6. Inclusion of outcomes for only one surgeon/doctor or only one clinical site (where studies with > one surgeon/doctor or one clinical site exist)
	Specific exclusion criteria
	n/a