Clinical Commissioning Urgent Policy Statement
Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: “off-label” use in patients with named rarer mutations [200809P]

Commissioning position

Summary

NHS England has confirmed ivacaftor and tezacaftor/ivacaftor will be made available as treatment options for people with cystic fibrosis who have one of an expanded range of cystic fibrosis transmembrane conductance regulator (CFTR) mutations within the criteria set out in this policy. These treatments are “off-label” for use in the named rarer mutations and hence outside those commissioned by Clinical Commissioning Urgent Policy for licensed Cystic Fibrosis Modulator Therapies NHS England: [200810P]. The treatments in this policy will be made available through the access agreement in place between NHS England and Vertex pharmaceuticals.

Information about expanded range of eligible patients with rarer mutations

The intervention

NHS England’s urgent policy statement for licensed Cystic Fibrosis Modulator Therapies [200810P] approves the use of ivacaftor and tezacaftor/ivacaftor in line with the current EMA marketing authorisations.

The interventions under consideration are ivacaftor, and the combination therapy, tezacaftor with ivacaftor. Both medications are licensed to treat patients with cystic fibrosis who have one of a specified range of mutations and who are above specified ages. This policy expands access to treatments for named rarer CFTR mutations for which these drugs are indicated but “off-label”, having considered the evidence reviewed by the United States Food and Drug Administration (FDA) in 2017 for ivacaftor (1) and in 2018 for tezacaftor/ivacaftor. NHS England has considered the FDA approach using a cell-based in vitro system/study to validate the efficacy of these drugs for some of the mutations in the expanded range of mutations (clinical data were not available or readily feasible due to the rarity of the mutations under consideration). The in vitro system allowed for the assessment of changes in CFTR mediated chloride transport in response to ivacaftor and tezacaftor/ivacaftor in Fischer rat thyroid (FRT) cells expressing mutant CFTR channels. A shift in “percentage normal” CFTR chloride transport of at least 10% was the designated threshold for determining mutant CFTR channel response to ivacaftor. A 10% of normal shift in chloride transport was believed to be reasonable to define a population with disease-causing mutations that may be amenable to treatment with ivacaftor and unlikely to exclude patients with CF mutations that would respond clinically.

Ivacaftor

Ivacaftor is a CFTR potentiator which increases the probability that a defective CFTR channel, when correctly situated on the cell surface, will open and let chloride and bicarbonate ions pass through. This reduces the viscosity of mucous and digestive juices, thereby helping to relieve symptoms of the disease. The overall level of ivacaftor-mediated CFTR chloride transport is dependent on both the number of CFTR channels at the cell surface and how responsive a CFTR channel is to ivacaftor. NHS England currently commissions ivacaftor for R117H and 9

named gating mutations[1] when heterozygous in the CFTR gene for patients who are aged 4 months and above.

Having considered the in vitro data and the relevant clinical evidence, the policy expands the range of mutations for which ivacaftor as a monotherapy is made available to include people aged 4 months and over who are heterozygous for the CFTR mutations listed under the eligibility criteria for ivacaftor in **Table 2**.

Tezacaftor/ivacaftor

Tezacaftor is designed to move the defective CFTR protein to the correct position in the cell, thereby facilitating the passage of chloride and sodium ions and reducing the viscosity of mucous and digestive secretions. Incorrect location of the protein is the major defect in the commonest CFTR mutation worldwide, F508del. ivacaftor will then act to further potentiate CFTR function, enhancing efficacy. tezacaftor combined with ivacaftor (tezacaftor/ivacaftor) has marketing authorisation for the treatment of patients with CF aged 6 years and older who are homozygous for the F508del mutation or heterozygous for the F508del mutation combined with one of the following mutations in the CFTR gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T. NHS England currently commissions tezacaftor/ivacaftor in accordance with its EMA marketing authorisation.

Having considered the in vitro data and the relevant clinical evidence, the policy expands the range of mutations for which treatment with tezacaftor/ivacaftor for CF patients is available to include two groups of people who have at least one copy of any of the named mutations in the *CFTR* gene responsive to tezacaftor/ivacaftor. The mutations are listed in **Table 6.**

The group listed above no longer require F508del to be combined with these mutations.

Access will also be expanded to tezacaftor/ivacaftor to the following group of people with CF who have at least one copy of the following mutations: E56K, R74W, D110E, D110H, E193K, R347H, E831X, F1052V, K1060T, A1067T, F1074L, D1270N.

The condition

Cystic Fibrosis (CF) is caused by mutations in the CFTR gene that affect the production of the CFTR protein. CF is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately 10,500 people (8,700 in England). New-born screening for CF has been undertaken routinely in the whole of the UK since mid-2007 leading to early diagnosis in most cases. A defect in the CFTR protein results in a reduction in quantity of the CFTR channels and/or a reduction in function of the CFTR channels resulting in a reduction in the passage of chloride ions through the open channel pore. This affects the balance of salt ions and fluids inside and outside of the cell (2). This imbalance leads to thick, sticky mucus in the lungs, pancreas, and other organs.

Approximately 2,000 mutations have been identified in the CFTR gene with about 300 proven to be definitively associated with CF. A minority of CFTR mutations have residual ion transport and affect about 5% of the population with CF. The commonest genetic mutation is the F508del mutation which causes CF when combined with another CF causing variant. F508del results in fewer than the normal number of CFTR channels at the cell surface.

Due to the genetic nature of the disease, incidence of CF varies depending on how often the mutation occurs in the population. CF is found most commonly in populations of white ethnicity.

[1] G551D, G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, G1349D

Current treatments

People with CF are susceptible to a range of infections as well as reduced lung function. The symptoms of a lung infection can include increased coughing and wheezing, getting out of breath more easily and the production of more sputum. These infections are so serious that it is common for people with CF to spend weeks in hospital several times a year for intravenous antibiotic treatment and monitoring. Pancreatic enzymes of people with CF build up in the pancreas instead of reaching the digestive system causing the pancreas to become inflamed and resulting in pancreatic insufficiency. Problems with the pancreas can also cause CF-related diabetes, which affects around a third of people with CF. Scarring, or fibrosis, can develop in the livers of people with CF. In severe cases, this can lead to cirrhosis. CF is also associated with low bone mineral density which may lead to osteoporosis and osteopenia.

There is no cure for CF. In severe cases of CF, when the lungs stop working properly and all medical treatments have failed to help, a lung transplant may be recommended. A range of treatments can help control the symptoms, prevent or reduce complications, and make the condition easier to live with. Medicinal treatments for CF include antibiotics to prevent and treat chest infection and medicines to reduce the levels of mucous in the body. The latter includes ivacaftor and tezacaftor/ivacaftor for people with CFTR mutations. Bronchodilators can be used to widen the airways and make breathing easier and steroid medicine can be used to treat nasal polyps. The influenza vaccination should be given annually. Physical activity and physiotherapy techniques can help clear mucus from the lungs and improve physical strength and overall health. Dietary advice on how to take in extra calories and nutrients is important to avoid malnutrition.

Clinical trial evidence

A 3-paper evidence review was commissioned by NHS England and undertaken by Solutions for Public Health (SPH). The 3-paper review provides an assessment of three chosen published papers of central importance to the topic: the assessment is a summary of the evidence rather than a full critical appraisal and extended review of all available evidence. For this evidence review there was no formal summary provided by the reviewers. Therefore, the whole evidence review is provided below:

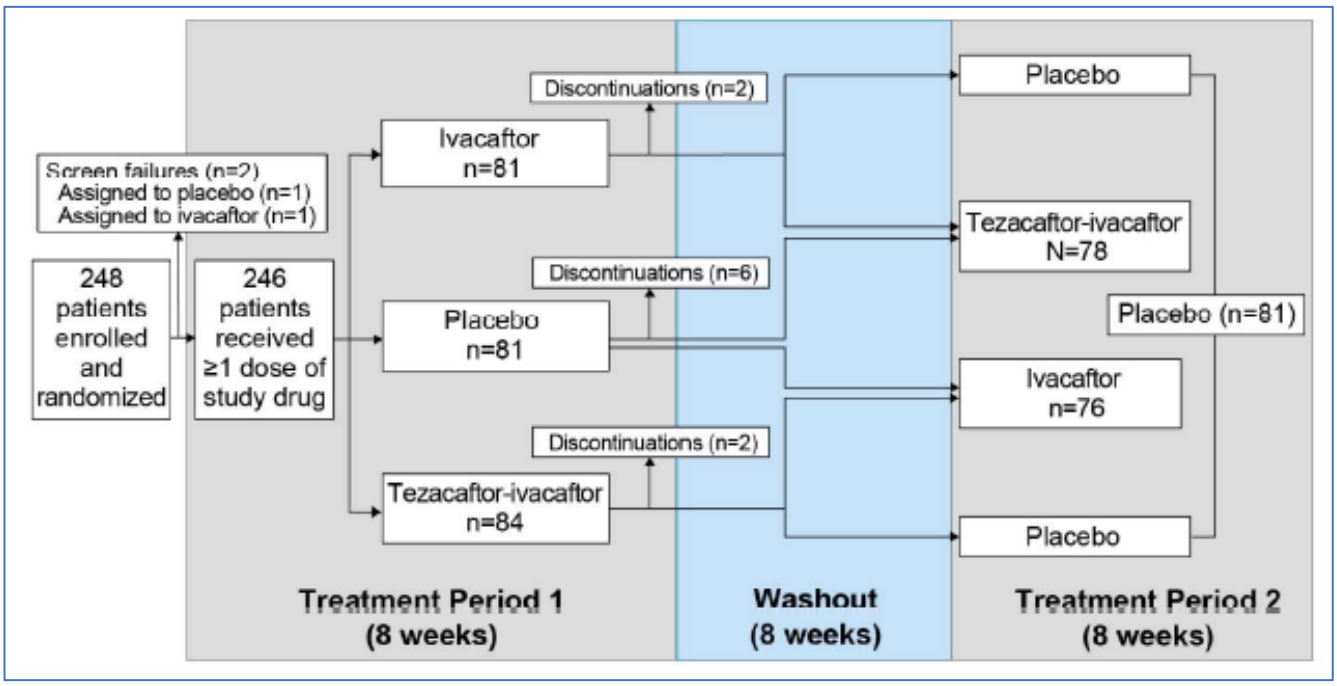
Three papers were presented for review by NHS England. Paper 1 is an international, multicentre phase III RCT comparing the effectiveness of tezacaftor/ivacaftor and ivacaftor monotherapy with placebo in patients with CF. Paper 2 is a phase II RCT comparing the effectiveness of ivacaftor[2] with placebo in patients with cystic fibrosis (CF) in the USA. Both RCTs were crossover studies. Paper 3 is an in vitro study designed to evaluate the effect of ivacaftor on rat cells expressing mutant CFTR protein forms with defects other than channel gating.

Paper 1: Rowe et al 2017. tezacaftor–ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis

This was an international phase III, randomized, double-blind, placebo-controlled, two period, three intervention crossover trial. 246 patients aged ≥12 years with CF and heterozygous for the Phe508del mutation and a CFTR mutation with residual CFTR function[3] were recruited from 86 sites[4]. The three interventions were tezacaftor–ivacaftor (n=162), ivacaftor monotherapy (n=157), or placebo (n=162). Patients were randomly assigned (1:1:1:1:1:1) to one of six sequences, each involving two 8-week intervention periods separated by an 8-week washout

[2] Ivacaftor is a Cystic Fibrosis Transmembrane Conductance regulator (CFTR) potentiator which facilitates chloride transport by increasing the channel open probability of the CFTR protein.
[3] Noncanonical splice mutations 2789+5G→A, 3849+10kbC→T,3272-26A→G, 711+3A→G. Missense mutations E56K, P67L, E831X, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, R1070W, A455E, F1074L, D579G,D1152H, S945L, D1270N,S977F,F1052V, K1060T
[4] 86 sites in Australia, Europe, Israel and North America

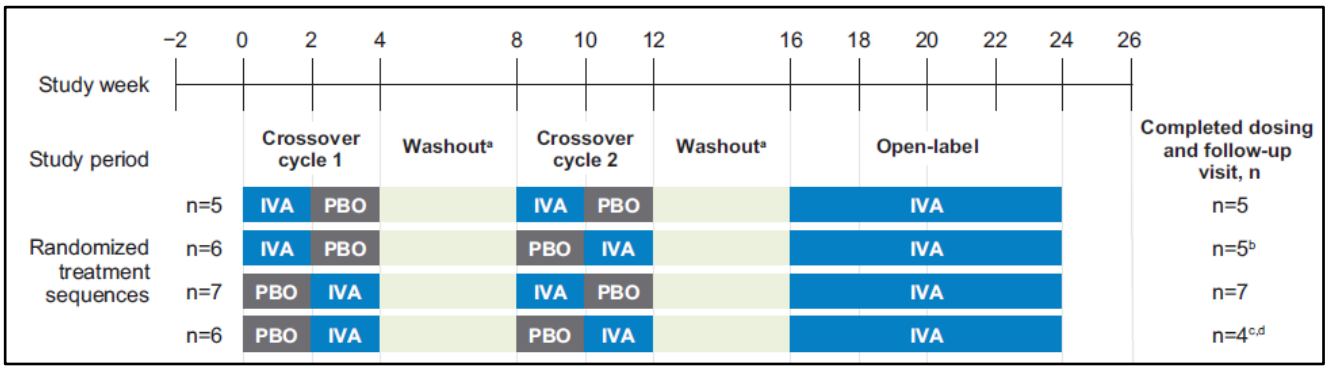
period. Ten patients discontinued participation in the trial; three of these were due to adverse events (7).



Source: Rowe et al 2017

Paper 2: Nick et al 2019. ivacaftor in cystic fibrosis with residual lung function: Lung function results from an N-of-1 study

This was a phase II, randomised, double-blind, placebo-controlled, within patient, crossover study conducted by a single centre in the USA. Twenty-four patients aged ≥12 years with CF non 'gating' mutations[5] with clinical or molecular evidence of residual CFTR function were randomized to one of four treatment sequences for two 4-week, double-blind crossover cycles (each divided into two weeks of ivacaftor treatment (150mg every 12 hours) and placebo). These were followed by a 4-8-week washout period before 21/24 patients received eight weeks of ivacaftor treatment in the open label phase of the study. Two patients discontinued due to nonadherence (n=2) and one patient had an adverse event (8).



Source: Nick et al 2019

[5] Excluding the gating mutations for which ivacaftor is already licensed. The mutations included were missense mutations (R117H, E56K, P67L, D110E, D110H, R117C, R347H, R352Q, A455E, D579G, S945L, L206W, R1070W, F1074L, D1152H, S1235R, D1270N) and defective mRNA mutations(2789+5G→A, 3849+10kbC→T, 3272-26A→G, 711+5G→A, 3120G→A, 1811+1.6kbA→G, 711+3A→G, 1898+3A→G, 1898+1G→A, 1717-1G→A, 1717-8G→A, 1342-2A→C, 405+3A→C, 1716G/A, 1811+1G→C, 1898+5G→T, 3850-3T→G, IVS14b+5G→A, 1898+1G→T, 4005+2T→C, 621+3A→G, 621+1G→T).

Paper 3: Van Goor et al 2014. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function

This was an in vitro study designed to evaluate the effect of ivacaftor on mutant CFTR protein forms with defects other than channel gating. Electrophysiological tests measured chloride transport in a panel of Fischer rat thyroid (FRT) cell lines engineered to express one of 54 mutant CFTR forms associated with CF or CFTR-related disorders (9).

Effectiveness:

Lung function (measured by percentage of predicted forced expiratory volume in 1 second (ppFEV)

Rowe et al 2017 showed a statistically significant improvement in lung function measured by absolute change in the ppFEV for tezacaftor-ivacaftor and ivacaftor monotherapy compared to placebo (p<0.001) (7). Treatment with tezacaftor-ivacaftor was superior to ivacaftor alone (p<0.001). The least-squares mean difference from the baseline value to the average of the week 4 and week 8 measurements was:

- tezacaftor-ivacaftor (n=161) vs placebo (n=161): 6.8 % (95% Confidence Interval (CI) 5.7 to 7.8), p<0.001
- ivacaftor (n=156) vs placebo (n=161): 4.7% (95% CI 3.7 to 5.8), p<0.001
- tezacaftor-ivacaftor (n=161) vs ivacaftor alone (n=156): 2.1% (96% CI 1.2 to 2.9), p<0.001

Nick et al 2019 reported improved lung function with 2 weeks of treatment with ivacaftor compared to placebo; the absolute change from cycle baseline in ppFEV favoured ivacaftor over placebo by 2.3 (SD 1.0, 95% CI 0.4 to 4.1) percentage points (8).

In the open label phase of the study with ivacaftor monotherapy, the absolute mean change in $ppFEV_1$ at 2 weeks, 4 weeks and 8 weeks from open label baseline was 3.7 (SD 3.7%), 4.3 (SD 5.1%) and 4.7 (SD 4.2%) percentage points respectively (p<0.0001). Two weeks after treatment with ivacaftor had stopped, the change from open label baseline had decreased to 2.1 (SD 0.6%) percentage points.

Lung function (measured by Lung Clearance Index at 2.5% (LCI 2.5)

Nick et al 2019 reported improved lung function following treatment with ivacaftor. After 2 weeks of treatment with ivacaftor relative to placebo, the posterior mean difference between ivacaftor and placebo was −0.42 (SD 0.22). Mixed-effects modelling showed an estimated treatment effect of −0.2 (95% CI −1.3 to 0.9, p=0.686) indicating that the effect of ivacaftor on LCI 2.5 was not statistically significant.

In the open label phase of the study with ivacaftor monotherapy, the absolute mean difference from open label baseline in $LCI_{2.5}$ at 2 weeks, 4 weeks and week 8 was −1.1 (SD 2.6), −0.8 (SD 2.8) and −1.6 (SD 2.3) respectively. At follow up (2 weeks after 8 weeks of treatment with ivacaftor had stopped), the change from open label baseline was -2.0 (SD 3.7) (n=20). The differences from baseline were not tested.

Sweat chloride

Rowe et al 2017 reported that compared to placebo, both tezacaftor-ivacaftor and ivacaftor monotherapy resulted in lower sweat chloride concentration (mmol/L) indicating better CFTR function[6]. No p-values were reported.

- tezacaftor-ivacaftor (n=161) vs placebo (n=161): -9.5 (95% CI -11.7 to -7.3)
- ivacaftor (n=156) vs placebo (n=161): -4.5 (95% CI -6.7 to -2.3)

[6] The $LCI_{2.5}$ is the turnovers required to reduce the concentration of nitrogen to 2.5% of its starting concentration

- tezacaftor-ivacaftor (n=161) vs ivacaftor alone (n=156): -5.1 (95% CI -7.0 to -3.1)

Nick et al 2019 reported lower sweat chloride concentration following open label treatment with ivacaftor. The mean absolute difference from baseline at week 2 and week 8 of the open label phase of ivacaftor monotherapy treatment was −15.4 (13.0) mmol/L and −15.7 (14.8) mmol/L (n=19) respectively. The differences from baseline were not tested.

Body weight (measured by body mass index (BMI)

Rowe et al 2017 reported an increase in mean BMI from baseline to week 8, for all treatment groups (tezacaftor-ivacaftor 0.34 kg/m^2, ivacaftor 0.47kg/m^2, placebo 0.18kg/m^2). No between group statistical analysis was reported. Increased BMI is associated with improved chloride ion transport and management of CF symptoms.

Nick et al 2019 reported an increase in mean BMI after 8 weeks of treatment with ivacaftor in the open label period of the trial. The mean BMI (kg/m^2) at baseline was 24.2(SD 4.8, range 18.5 to 34.8) (n=24). At 8 weeks the mean absolute difference in BMI from open label baseline was +0.5 (SD 0.7) kg/m^2 which equated to a mean increase in weight (+1.8 (SD 1.9) kg) (n=21). The differences from baseline were not tested.

Quality of life (measured by absolute change in the Cystic Fibrosis Questionnaire–Revised (CFQ-R)[7] respiratory domain score

In Rowe et al 2017, compared to placebo, there was a statistically significant difference in the least-squares mean difference from the baseline value to the average of week 4 and week 8 in favour of both the tezacaftor-ivacaftor and ivacaftor monotherapy treatment groups for quality of life[8]**.**

- tezacaftor-ivacaftor (n=161) vs placebo (n=161): 11.1 (95% CI 8.7 to 13.6) points, p<0.001
- ivacaftor (n=156) vs placebo (n=161): 9.7 (95% CI 7.2 to 12.2) points, p<0.001
- tezacaftor-ivacaftor (n=161) vs ivacaftor alone (n=156): 1.4 (95% CI -1.0 to 3.9) points, p=0.26 (no statistically significant difference)

Patients treated with tezacaftor-ivacaftor or ivacaftor were more likely to experience a clinically important difference of ≥4/100 points (tezacaftor-ivacaftor 65%, ivacaftor 58%, placebo 33%).

Pulmonary exacerbations

Rowe et al 2017 reported pulmonary exacerbations in all three treatment groups. Fewer pulmonary exacerbations are associated with improved management of CF.

- tezacaftor-ivacaftor: 11 events, 0.34 event rate per year, rate ratio vs placebo 0.54 (95%CI 0.26 to 1.13)
- ivacaftor: 9 events, 0.29 event rate per year, rate ratio vs placebo 0.46 (95%CI 0.21 to 1.01)
- placebo: 20 events, 0.63 event rate per year

Chloride transport in Fischer rat thyroid (FRT) cell lines

In this in vitro study, Van Goor et al (2014) reported a statistically significant response in favour of ivacaftor in FRT cells expressing 35 out of 54 missense CFTR mutations[9]:

[7] Scores range from 0 to 100 points, with higher scores indicating a higher patient-reported quality of life with respect to respiratory status

8 From baseline value to the average of the week 4 and week 8 measurements in each intervention period.

[9] F1052V, S1235R, D1152H, D1270N, R668C, K1060T, R74W, R117H, E193K, A1067T, L997F, R1070Q, D110E, D579G, D110H, R1070W, E56K, P67L, F1074L, A455E, S945L, S977F, R347H, L206W, R117C, R352Q, R1066H, T338I, R334W, I336K, H1054D, F508del, M1V, E92K, L927P.

- increased chloride transport over baseline ($p<0.05$). The net increase over baseline chloride transport by ivacaftor reached maximum sustained levels of 2.1% to 200.7% of normal CFTR. This equated to a 1.6 to 52.0-fold increase[10] over baseline chloride transport
- the concentration of ivacaftor that gave a half maximal response (EC50) ranged from 123 ± 33 to 735 ± 204 nM

The remaining 19 mutant CFTR forms tested had no statistically significant response to ivacaftor ($p>0.05$).

Adverse events

No deaths were reported in either of the human studies (Nick et al 2019, Rowe et al 2017).

Rowe et al 2017 reported Grade 3 (severe) or Grade 4 (life-threatening) adverse events in 21 patients; 4 patients (2%) in the tezacaftor-ivacaftor group, 8 (5%) in the ivacaftor group and 9 (6%) in the placebo group.

Rowe et al (2017) reported that the proportion of patients experiencing any AE was similar across all three treatment groups: tezacaftor-ivacaftor (72%), ivacaftor (73%), placebo (78%).

This is consistent with the similar proportion of patients experiencing AEs in the RCT by Nick et al 2019 comparing ivacaftor (75%) and placebo (70%).

The most common AEs (any severity) reported by Rowe et al were:

- cough: tezacaftor-ivacaftor (14%), ivacaftor (11%), placebo (19%)
- infective pulmonary exacerbation of CF: tezacaftor-ivacaftor (13%), ivacaftor (13%), placebo (19%)
- headache: tezacaftor-ivacaftor (12%), ivacaftor (7%), placebo (8%)
- haemoptysis. tezacaftor-ivacaftor (7%) vs ivacaftor (11%) vs placebo (9%)

Following 8 weeks of treatment with ivacaftor monotherapy, the most common AEs (any severity) reported by Nick et al 2019 were cough (33%), upper respiratory tract infections (33%) and fatigue (16.7%).

[10] The fold increase over baseline was determined by dividing the level of chloride transport (% normal) in the presence of ivacaftor by the baseline chloride transport

Implementation

It is estimated that around 253 additional patients in England with CF will become eligible for treatment with Ivacaftor or with tezacaftor/ivacaftor within the expanded range of eligible mutations and age ranges (Table 1).

Table 1: Estimated numbers of people with cystic fibrosis who will become eligible for treatment with ivacaftor or tezacaftor/ivacaftor if the eligibility criteria are expanded

Tier	Drug	Description	Number	Totals
1	tezacaftor/ ivacafator	>=12 years and expanded list mutations	23	
		>=12 years and expanded list mutations without F508del as the other mutation	103	
		Sub-Total		126
2	ivacaftor	>=6 years and expanded list mutations	99	
		6 months to < 6 yrs and expanded list mutations	80	
		Sub-total		179
		Total estimated number of people eligible for treatment in the UK		305
		Total estimated number of people eligible for treatment in the England (83%)		253

It is recognised that subsequent age extensions to the licenses have increased the number of patients who may be eligible.

Criteria

The CFTR therapies must only be prescribed by physicians with experience in the treatment of cystic fibrosis working within NHS England commissioned CF services in line with this policy. For patients whose genotype is unknown, an accurate and validated genotyping method will be performed before starting treatment to confirm the presence of an indicated mutation in the *CFTR* gene (see below under ivacaftor and tezacaftor/ivacaftor). A “look up” Table is provided on the FutureNHS website

Moderate transaminase (alanine transaminase [ALT] or aspartate transaminase [AST]) elevations are common in subjects with CF. Liver function tests will be done for all patients prior to initiating ivacaftor either in monotherapy or in a combination regimen as tezacaftor/ivacaftor after considering potential risk of hospital attendance [(8)].

As ivacaftor contains lactose, Ivacaftor either in monotherapy or in a combination regimen as tezacaftor/ivacaftor will not be prescribed to patients with rare hereditary problems of galactose intolerance, total lactase deficiency or congenital glucose-galactose malabsorption.

Ivacaftor

Treatment with ivacaftor as a monotherapy will be extended to adults, adolescents, and children aged 4 months and older with cystic fibrosis who have at least one copy of the following named mutations in the *CFTR* gene. The other mutation can be any mutation.

Table 2 ivacaftor as a monotherapy: for patients aged 4 months and over			
Named mutations	E56K	P67L	D110H
	R117C	E193K	R347H
	L206W	R352Q	A455E
	711+3A->G	E831X	S945L
	K1060T	A1067T	2789+5G>A
	3272-26A>G	3849+10kbC>T	
Mutations with 'varying clinical consequence' (VCC)	R74W*	D110E*	D579G*
	S977F*	F1052V*	G1069R*
	R1070Q*	R1070W*	F1074L*
	D1152H*	D1270N*	

Ivacaftor dosage

Infants aged at least 4 months, toddlers, children, adolescents and adults should be dosed according to the patient's weight.

Table 3:	**Dosage for adults and paediatric patients age 6 years and older weighing more than 25kg**
Patients ≥ 25 kg	one 150 mg tablet is taken orally every 12 hours with fat-containing food.

Dosing recommendations for Infants aged at least 4 months, toddlers, children weighing less than 25kg should be dosed according to Table 4.

For paediatric patients aged 4 months to 6 years granules are taken mixed with 1 teaspoon (5ml) of soft food or liquid and the dose depends on the weight of the patient.

Table 4:		**Dosage for infants aged at least 4 months, toddlers, children weighing less than 25kg**	
Age	Weight	Dose	Total daily dose
4 months to less than 6 months	≥5 kg	25 mg granules taken orally every 12 hours with fat-containing food	50 mg
6 months and older	≥5 kg to < 7 kg	25 mg granules taken orally every 12 hours with fat-containing food	50 mg
	≥ 7 kg to < 14 kg	50 mg granules taken orally every 12 hours with fat-containing food	100 mg
	≥ 14 kg to < 25 kg	75 mg granules taken orally every 12 hours with fat-containing food	150 mg
	>25 kg	See SmPC	

Clinicians should refer to the current Summary of Product Characteristics before prescribing and for dose modifications if patients are on other therapies or have co-morbidities.

Tezacaftor/ivacaftor

The eligibility criteria already approved in the NHS England policy 190137P will be extended to include people who do not have F508del as the other mutation but are heterozygous (have at least one copy) for any of the mutations listed in **Table 6**. Where the patent has a named mutation the other mutation can be any mutation.

The policy provides access to tezacaftor/ivacaftor for patients 6 years and above in line with the age-related formulations available within the UK and Europe. Paediatric formulations will be made available in line with any future age-related extensions within the UK and Europe and will then be included within the policy criteria.

Tezacaftor/ivacaftor dosage

For people aged 6 years and above the recommended dose is age and weight adjusted and taken in the morning and evening, approximately 12 hours apart with fat-containing food.

Table 5: tezacaftor/ivacaftor Dosing recommendations for patients aged 6 years and older		
Weight	Morning	Evening
< 30kg	50 mg tezacaftor and 75 mg ivacaftor taken orally every 12 hours with fat-containing food	75 mg ivacaftor
≥ 30 kg	100 mg tezacaftor and 150 mg ivacaftor taken orally every 12 hours with fat-containing food	150 mg ivacaftor
≥ 12 years	100 mg tezacaftor and 150 mg ivacaftor taken orally every 12 hours with fat-containing food	150 mg ivacaftor

The dose of Symkevi and ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors or hepatic impairment as described in the SPC.

Table 6: tezacaftor/ivacaftor as a combination therapy: for patients aged 6 years and over			
Named mutations	E56K	P67L	D110H
	R117C	E193K	R347H
	L206W	R352Q	A455E
	711+3A->G	E831X	S945L
	K1060T	A1067T	2789+5G>A
	3272-26A>G	3849+10kbC>T	
Mutations with ‘varying clinical consequence’ (VCC)	R74W*	D110E*	D579G*
	S977F*	F1052V*	R1070W*
	F1074L*	D1152H*	D1270N*

The mutations marked with an asterix are defined as being of ‘varying clinical consequence[11] (VCC) (3). It is therefore important that supportive diagnostic criteria are used in addition to the presence of the mutation. In these cases, a definitive CF diagnosis requires sweat chloride >60

[11] This means that some patients with this gene change, combined with another CF causing mutation, have CF. Other patients with this gene change, combined with another CF causing mutation, do not have CF.

milliequivalents abnormal nasal potential difference or abnormal intestinal current measurement on rectal biopsy (4).

Monitoring criteria

Where the benefits of testing outweigh the risks of potential exposure to COVID-19, liver function tests will be done at least every 3 months during the first year of treatment and annually thereafter for all patients taking ivacaftor treatment, either in monotherapy or in a combination regimen with tezacaftor/ivacaftor (5).

In line with guidance from the Royal College of Ophthalmologists (6) it is recommended that paediatric patients when starting ivacaftor treatment, either in monotherapy or in a combination regimen with tezacaftor/ivacaftor, should be seen on a regular basis by their local optometrist to detect any significant visual difficulties which may prompt referral to hospital eye services for further assessment.

Stopping criteria

In the event of significant elevations of transaminases (e.g. patients with ALT or AST > 5 x the upper limit of normal (ULN), or ALT or AST > 3 x ULN with bilirubin > 2 x ULN), dosing with ivacaftor or tezacaftor/ivacaftor will be interrupted and laboratory tests closely followed until the abnormalities resolve.

Consideration will be given to delaying or discontinuing therapy if hepatotoxicity or renal toxicity occurs.

During pregnancy it is preferable to avoid the use of ivacaftor and tezacaftor/ivacaftor. For women who are breast-feeding and taking ivacaftor or tezacaftor/ivacaftor, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ivacaftor or tezacaftor/ivacaftor taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women.

These products have market authorisation for the treatment of CF but are “off-label” for use with patients with these named rarer mutations in the UK and Europe, any provider organisation treating patients with these interventions will be required to assure themselves that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the Trust’s Drugs and Therapeutics committee (or similar) and NHS England may ask for assurance of this process.

Effective from

The policy is effective from the date of publication.

Recommendations for data collection

NICE will provide an amended data collection agreement to include the therapies within this policy. Hospital trusts currently submit data on the numbers of patients treated with ivacaftor and tezacaftor/ivacaftor to the national cystic fibrosis registry which is hosted by the Cystic Fibrosis Trust.

Mechanism for funding

NHS England will fund these treatments through specialised commissioning teams.

Policy review date

This is an urgent policy statement, which means that the full process of policy production has been abridged: a full independent evidence review has not been conducted; and public consultation has not been undertaken. If a review is needed due to a new evidence base, then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Links to other policies

Clinical Commissioning Urgent Policy for licensed Cystic Fibrosis Modulator Therapies.

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and

- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities

Definitions

CFTR gene	Refers to the cystic fibrosis transmembrane conductance regulator (CFTR) gene which contains the instructions for making the CFTR protein.
COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus.
In-vitro system/study	This refers to a study performed or taking place in a test tube, culture dish, or elsewhere outside a living organism.
Mutation	In this context 'mutation' refers to the changing of the structure of a gene, resulting in a variant form that may be transmitted to subsequent generations
Osteoporosis	A medical condition in which the bones become brittle and fragile, typically as a result of hormonal changes, or deficiency of calcium or vitamin D.
Osteopenia	A medical condition in which the protein and mineral content of bone tissue is reduced, but less severely than in osteoporosis.

References

1. Durmowicz, A., Lim, R., Rogers, H., Rosebraugh, C., Chowdhury, B. The U.S. Food and Drug Administration's Experience with Ivacaftor in Cystic Fibrosis. Establishing Efficacy Using In Vitro Data in Lieu of a Clinical Trial. Annals 2018. 15(1) pp. 1-2. Available from: https://pubmed.ncbi.nlm.nih.gov/29020455/
2. Cystic Fibrosis Trust. How does CF affect the body, Available from https://www.cysticfibrosis.org.uk/
3. Clinical and Functional Translation of CFTR. Available from: https://cftr2.org
4. Farrell, P., White, T., Clement L., Hempstead, S., Accurso, F.Derichs, N. Diagnosis of Cystic Fibrosis: Consensus Guidelines from the Cystic Fibrosis Foundation. The Journal of Paediatrics (2017). 181S: S4-S15.e1
5. COVID-19 rapid guideline: cystic fibrosis. NICE 2020. Available from : https://www.nice.org.uk/guidance/ng170/chapter/3-Modifications-to-usual-care-and-service-delivery. Accessed 13/08/2020.
6. Advice for clinicians on Cataract Related to CFTER Modifying Drug of Cystic Fibrosis. The Royal College of Opthalmologists 2019. Available from: https://www.rcophth.ac.uk/wp-content/uploads/2019/12/Cataract-related-CFTER-for-cystic-fibrosis.pdf. Accessed 13/08/2020

Evidence Summary References:

7. Rowe S, Daines C, Ringshausen F, Kerem E, Wilson J, Tullis E, tezacaftor–ivacaftor in Residual-Function Heterozygotes with Cystic Fibrosis. New England Journal of Medicine 2017. 377(21):2024-2035. Available from: https://www.ncbi.nlm.nih.gov/pubmed/29099333
   This paper has a supplementary appendix with more details about the results.

8. Nick J, Clair C, Jones M, Lan L, Higgins M. ivacaftor in cystic fibrosis with residual function: Lung function results from an N-of-1 study. Journal of Cystic Fibrosis. 2019. 19:31:1-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31784217
   This paper has a supplementary appendix with more details about the results.

9. Van Goor F, Yu H, Burton B, Hoffman B. Effect of ivacaftor on CFTR forms with missense mutations associated with defects in protein processing or function. Journal of

Cystic Fibrosis. 2014 13:29-36. Available from:
https://www.ncbi.nlm.nih.gov/pubmed/23891399