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Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations

NHS England commissioning statement

November 2023 Version 4.0

Commissioning Position

NHS England has confirmed that ivacaftor, tezacaftor/ivacaftor and elexacaftor/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 commissioning statement.

These medications will be available to patients with mutations approved and licensed by the UK regulator*, in addition, those named mutations approved by the US Food and Drug Administration (FDA) for which the use of the medications would be off-label in England. This commissioning statement updates access under the licence and supersedes previous relevant clinical commissioning policies: 'Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations: [200810P]'; 'Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: "off - label" use in patients with named rarer mutations: [200809P]' and 'Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off -label use in patients with cystic fibrosis who have named mutations': [210508P].

The treatments in this policy will be available through the access agreement in place between NHS England and Vertex pharmaceuticals.

The Condition

Cystic fibrosis (CF) is the most common, life-limiting, recessively inherited disease in the UK, affecting approximately 10,500 people (8,700 in England). 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 (1). This imbalance leads to thick, sticky mucus in the lungs, pancreas, and other organs.

Complications of CF include increased susceptibility to serious infections, reduced lung function, pancreatic insufficiency and CF related diabetes, liver cirrhosis, 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. Therapeutic treatments for CF include antibiotics to prevent and treat chest infection and medicines to reduce

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the levels of mucous in the body. The latter includes the CFTR modulator therapies ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor, and elexacaftor/tezacaftor/ivacaftor.

*From 1st January 2021 the Medicines and Healthcare Products Agency (MHRA) is the standalone medicine's regulator for the UK.

Licensed use

This commissioning statement updates the licensed indications and supersedes the previous relevant clinical commissioning policy: 'Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations: [200810P]'. Under this new commissioning statement NHS commissions ivacaftor, lumacaftor/ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor in accordance with the UK licence as follows:

- Ivacaftor for patients who are aged 1 month and above for: the R117H mutation and for 9 named gating mutations when heterozygous in the *CFTR* gene.
- Lumacaftor/ivacaftor for patients who are aged 1 year and older who are homozygous for the F508del mutation in the *CFTR* gene.
- Tezacaftor/ivacaftor for the treatment of patients with CF aged 6 years and older who are homozygous for the F508del mutation) or heterozygous in the *CFTR* gene for any one of 14 mutations combined with the F508del mutation.
- Elexacaftor/tezacaftor/ivacaftor for patients aged 2 years and above who have two F508del mutations or one F508del combined with any other mutation.

The look-up table of licensed mutations from the manufacturer can be found here:

<https://www.cfsource.co.uk/hcp/treatments-finder>

For all these CFTR products where the UK licence is amended in the future, eligible patients will automatically have access under those terms. The manufacturer will be responsible for supplying an age-appropriate product within the UK.

Off-label use

This commissioning statement supersedes the previous clinical commissioning policy: 'Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: "off -label" use in patients with named rarer mutations: [200809P]' updated on 21 January 2021 and confirms the circumstances when NHS England will reimburse the off-label use of ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor.

A clinician considering prescribing a medication outside the terms of the licence ('off -label') should do so in accordance with Medicines and Healthcare products Regulatory Agency (MHRA) and General Medical Council (GMC) guidance which apply throughout England and the UK. The GMC guidance states prescribing unlicensed medicines may be necessary where 'there is no suitably licensed medicine that will meet the patient's need'. Should clinicians consider this appropriate for their patients and they have followed local medicines governance arrangements for off-label use, then NHS England will meet these costs as follows:

a) Named CFTR mutations that will not be considered by the UK regulator

Where the UK medicines regulator may not consider the evidence for some named CFTR mutations, NHS England will, however, reimburse the off -label use of ivacaftor, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor in line with the approach to in vitro data taken by the US Food and Drug Administration (FDA) and the approved list of named mutations as follows:

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- Ivacaftor: People with CF aged 1 month and older who are heterozygous in the CFTR gene for any one of 87 named mutations outside the UK licence.
- Tezacaftor/ivacaftor: People with CF aged 6 years and older who have any one of 140 named mutations outside the UK licence. In addition, 14 mutations licensed by the UK regulator for people with CF who have the F508del mutation are included for off-label prescribing when combined with any mutation other than F508del.
- Elexacaftor/tezacaftor/ivacaftor: For people with CF aged 2 years and older who are heterozygous for any one of the 177 named mutations outside the UK licence which can be combined with any other mutation.

In reaching this decision, NHS England has considered the FDA approach using a cell-based in vitro system/study¹ to validate the efficacy of all three drugs for an expanded range of mutations (clinical data were not available or readily feasible due to the rarity of the mutations under consideration).

For further details on prescribing, dosage, monitoring and stopping criteria, please see Appendix 1.

Mechanism for funding

NHS England will fund these treatments through specialised commissioning teams.

Commissioning Statement review date

This is an urgent commissioning statement, which means that 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 NHS England should be contacted at this email address: england.CET@nhs.net.

Links to other policies

Supersedes:

- Clinical Commissioning Urgent Policy Statement 'Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations: [200810P] published May 2023.
- Clinical Commissioning Urgent Policy Statement 'Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations: [200810P] published January 2022.
- Clinical Commissioning Urgent Policy Statement 'Cystic Fibrosis Modulator Therapies Access Agreement for licensed mutations: [200810P] published on 21 January 2021.
- Clinical Commissioning Urgent Policy statement 'Ivacaftor and tezacaftor/ivacaftor for cystic fibrosis: "off-label" use in patients with named rarer mutations: [200809P]' published on 21 January 2021.
- Commissioning Statement 'Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations [210508P] published on 10 May 2021.

¹ 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% above baseline was the designated threshold for determining mutant CFTR channel response to the medications.

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

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2. 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.
3. Advice for clinicians on Cataract Related to CFTR Modifying Drug of Cystic Fibrosis. The Royal College of Ophthalmologists 2019. Available from: <https://www.rcophth.ac.uk/wp-content/uploads/2019/12/Cataract-related-CFTR-for-cystic-fibrosis.pdf>. Accessed 13/08/2020
4. U.S. Food and Drug Administration. Drugs@FDA: FDA-Approved Drugs. Available from : <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&AppINo=210491>
5. Clinical and Functional Translation of CFTR. Available from: <https://cftr2.org>
6. 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

Appendix 1: Prescribing Guidance and Monitoring

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 commissioning statement. 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, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor).

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 or as the triple therapy elexacaftor/tezacaftor/ivacaftor.

As ivacaftor contains lactose, ivacaftor either in monotherapy or in a combination regimen as tezacaftor/ivacaftor or elexacaftor/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 is available to adults, adolescents, and children aged 1 month and older with cystic fibrosis who have at least one copy of 97 named mutations in the *CFTR* gene (4). The other CF mutation can be any mutation.

Eleven of the 97 mutations² are marked as being of ‘varying clinical consequence’³ (VCC) (5). 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 milliequivalents abnormal nasal potential difference or abnormal intestinal current measurement on rectal biopsy (6).

Ivacaftor dosage

Infants aged at least 1 month, toddlers, children, adolescents and adults should be dosed according to the patient’s weight. The dosing for adults and paediatric patients aged 6 years and older and weighing more than 25kg (Table 1).

Table 1:	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 1 month, toddlers and children weighing 3 kg to less than 25 kg: granules are taken mixed with 1 teaspoon (5ml) of soft food or liquid and the dose depends on the weight of the patient (Table 2).

*From 1st January 2021 the Medicines and Healthcare Products Agency (MHRA) is the standalone medicine’s regulator for the UK.

² D74W, S977F, R1070Q, D1152H, D110E, F1052V, R1070W, D1270N, D579G, G1069R, F1074L

³ 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.

Table 2:

Age	Weight	Morning dose	Evening dose
Ivacaftor as monotherapy			
1 month to less than 3 months	≥ 3 kg	One sachet of ivacaftor 13.4 mg granules	One sachet of ivacaftor 13.4 mg granules
3 months to less than 6 months	≥ 3 kg	One sachet of ivacaftor 25 mg granules	One sachet of ivacaftor 25 mg granules
6 months and older	≥ 5 kg to < 7 kg	One sachet of ivacaftor 25 mg granules	One sachet of ivacaftor 25 mg granules
	≥ 7 kg to < 14 kg	One sachet of ivacaftor 50 mg granules	One sachet of ivacaftor 50 mg granules
	≥ 14 kg to < 25 kg	One sachet of ivacaftor 75 mg granules	One sachet of ivacaftor 75 mg granules
	≥ 25 kg	See SmPC for further details.	

Clinicians should refer to the current SmPC before prescribing, and for dose modifications if patients are on other therapies or have co-morbidities. The dose of ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors.

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 3).

Weight	Morning	Evening
< 30kg	50 mg tezacaftor and 75 mg ivacaftor taken orally with fat-containing food	75 mg ivacaftor
≥ 30 kg	100 mg tezacaftor and 150 mg ivacaftor taken orally with fat- containing food	150 mg ivacaftor
≥ 12 years	100 mg tezacaftor and 150 mg ivacaftor taken orally with fat- containing food	150 mg ivacaftor

The dose of tezacaftor/ivacaftor and ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors or if the patient has hepatic impairment, as described in the SmPC.

Lumacaftor / ivacaftor as a combination therapy dosage

For patients aged 1 year and over the recommended dose is age and weight adjusted and taken in the morning and evening, approximately 12 hours apart with fat-containing food (Table 4)

Table 4 Lumacaftor / ivacaftor as a combination therapy: for patients aged 1 year and over

Age	Weight	Dose per sachet	Lumacaftor/ivacaftor dose (every 12 hours)	
			Morning	Evening
1 to <2 years	7 kg to <9 kg	lumacaftor 75 mg/ ivacaftor 94 mg	1 sachet	1 sachet
	9 kg to <14 kg	lumacaftor 100 mg/ ivacaftor 125 mg		
	≥14 kg	lumacaftor 150 mg/ ivacaftor 188 mg		
2 to 5 years	<14 kg	lumacaftor 100 mg/ ivacaftor 125 mg	2 tablets	2 tablets
	≥ 14 kg	lumacaftor 150 mg/ ivacaftor 188 mg		
6 to <12 years		lumacaftor 100 mg/ ivacaftor 125 mg	2 tablets	2 tablets
12 years and older		lumacaftor 200 mg/ ivacaftor 125 mg	2 tablets	2 tablets

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

Elexacaftor/tezacaftor/ivacaftor dosage

The recommended dose is in the form of oral tablets or granules (depending on age) and should be swallowed whole and taken in the morning and evening, approximately 12 hours apart with fat-containing food (Table 5).

Table 5: Elexacaftor/tezacaftor/ivacaftor dosing for patients aged 2 years and older		
Age	Morning	Evening
2-<6y and <14kg	One sachet of ivacaftor 60 mg/tezacaftor 40 mg/elexacaftor 80 mg granules	One sachet of ivacaftor 59.5 mg granules
2-<6y and ≥14kg	One sachet of ivacaftor 75 mg/tezacaftor 50 mg/elexacaftor 100 mg granules	One sachet of ivacaftor 75 mg granules
6-12y and <30kg	Two tablets (each containing elexacaftor 50mg, tezacaftor 25mg and ivacaftor 37.5mg)	One tablet of 75mg ivacaftor

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6-12y and ≥ 30 kg	Two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg)	One tablet of 150 mg ivacaftor
≥ 12 years	Two tablets (each containing elexacaftor 100 mg, tezacaftor 50 mg and ivacaftor 75 mg)	One tablets of 150 mg ivacaftor

The dose of elexacaftor/tezacaftor/ivacaftor and ivacaftor should be adjusted when co-administered with moderate and strong CYP3A inhibitors or if the patient has hepatic impairment, as described in the SPC.

Monitoring criteria

Liver function tests and blood pressure monitoring 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, in a combination regimen with lumacaftor, tezacaftor/ivacaftor or as the triple therapy elexacaftor/tezacaftor/ivacaftor (2).

In line with guidance from the Royal College of Ophthalmologists (3) it is recommended that paediatric patients when starting ivacaftor treatment, either in monotherapy, in a combination regimen with lumacaftor, tezacaftor/ivacaftor or as the triple therapy ivacaftor/tezacaftor/elexacaftor, 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, tezacaftor/ivacaftor or elexacaftor/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, tezacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor. For women who are breast-feeding and taking ivacaftor, tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from ivacaftor, tezacaftor/ivacaftor or elexacaftor/tezacaftor/ivacaftor taking into account the benefit of breast-feeding for the child and the benefit of therapy for the women.

Effective from

The commissioning statement is effective from the date of publication.

Recommendations for data collection

Hospital trusts should submit data on the numbers of patients treated with CFTR modulators to the national Cystic Fibrosis Registry which is hosted by the Cystic Fibrosis Trust.