GIG CYMRU NHS WALES
Cyd-bwyllgor Comisiynu
Joint Commissioning Committee

Cystic Fibrosis Modulator Therapies

Policy Position Statement: PPS198

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Document Name	Cystic Fibrosis Modulator Therapies
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Target Audience	Chief Executives, Medical Directors, Directors of Finance, Directors of Planning, Medicine Management, Cystic Fibrosis Consultants, Cystic Fibrosis Centre Managers, Medicines Manufacturer
Description	NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy
Document Update Information	References added and updated Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek®) added to section 1.1 Section 1.1 updated to indicate that there are now 5 rather than 4 CFTR modulators available. Updated survival data included. Population data for UK and Wales updated. Section 1.2 equality impact assessment added for Vanzacaftor/tezacaftor/deutivacaftor Section 2.1 inclusion criteria – Inclusion criteria updated to include vanzacaftor-tezacaftor-deutivacaftor and to include a statement to inform For all these CFTR products where the MHRA license is updated to include gene mutations in the future, eligible patients will automatically have access under those terms. Section 2.7 updated to include vanzacaftor-tezacaftor-deutivacaftor.

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Policy Statement

NHS Wales Joint Commissioning Committee (NWJCC) will commission Cystic Fibrosis Modulator Therapies for people with Cystic Fibrosis (CF) in accordance with the criteria outlined in this document.

Welsh Language

NWJCC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience, the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this, NWJCC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation

NWJCC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the NWJCC commitment.

Disclaimer

NWJCC assumes that healthcare professionals will use their clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply this document.

This document may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.
NWJCC disclaims any responsibility for damages arising out of the use or non-use of this policy.

1. Introduction

This Policy Position Statement has been developed for the planning and delivery of Cystic Fibrosis Modulator Therapies for people with Cystic Fibrosis (CF) resident in Wales. This service will only be commissioned by the NHS Wales Joint Commissioning Committee (NWJCC) and applies to residents of all seven Health Boards in Wales.

In creating this document NWJCC has reviewed the relevant guidance issued by the National Institute of Health and Care Excellence (NICE)[1] and has concluded that Cystic Fibrosis Modulator Therapies should be made available.

1.1 Background

Cystic fibrosis is an inherited, multi-system, genetic condition that causes a build-up of sticky mucus in the lungs, digestive system and many other organs. People with CF can experience a range of problems throughout the body. In the lungs, the build-up of mucus can cause chronic infections, and in the digestive system excess mucus can cause a difficulty in digesting food[2].

Cystic fibrosis is caused by variants in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that result in the absence or dysfunction of the CFTR protein. The CFTR protein regulates the proper flow of water and salt in and out of cells lining the lungs and other organs[3]. This leads to the build-up of thick, sticky mucus, which can lead to infections in the lungs and damage to the pancreas. It can also lead to problems in many other parts of the body[2]. Mathematical predictions in the UK cystic fibrosis registry annual data report suggests that half of people born in 2022 are predicted to live to at least 66.2 years[4].

Many different gene variants are responsible for cystic fibrosis. The commonest variant is F508del, nearly 9 in 10 patients carry at least one copy of this type of mutation[5]. Disease severity generally correlates with the severity of the loss of chloride transport. Variants in the CFTR gene result in the absence or dysfunction of the CFTR protein, a cell-surface localised chloride channel that regulates salt and water absorption and secretion across epithelia in multiple organs. Cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies are designed to correct the malfunctioning protein by the CFTR gene. Because different variants cause different defects in the protein, the medications developed so far are effective only in people with specific gene variants.

[1] 1 Recommendations | Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis | Guidance | NICE
[2] Spread the word What is CF factsheet Jan 2020.pdf
[3] Sweat chloride as a biomarker of CFTR activity: Proof of concept and ivacaftor clinical trial data
[4] UK Cystic Fibrosis Registry 2024 Annual Data Report (amended Nov 2025)
[5] Types of CFTR Mutations | Cystic Fibrosis News Today

Two classes of modulators have been developed - "correctors" that facilitate processing and trafficking of the protein to the cell surface, and "potentiators" that increase the opening ability of the channel once at the apical membrane. For some variants a potentiator alone might be enough to significantly improve ion channel function. However, for Phe508del, a combination is required of a corrector to facilitate trafficking of the misfolded and prematurely degraded protein to the cell membrane, and also a potentiator to rectify the defective ion channel function when it reaches the cell membrane.

There are five CFTR modulator therapies with market authorisation that act as either potentiators or correctors.

- **Ivacaftor (Kalydeco®)**
  Ivacaftor is a CFTR potentiator, meaning it increases the activity of the defective CFTR protein. This means that ivacaftor increases the chances that the defective channel will open on the cell surface and let chloride and sodium ions pass through.
- **Tezacaftor/Ivacaftor (Symkevi®)**
  Ivacaftor/Tezacaftor (used in combination with Ivacaftor). Tezacaftor is a corrector designed to move the defective CFTR protein to the correct position in the cell while ivacaftor increases the activity of the defective CFTR protein.
- **Lumacaftor/Ivacaftor (Orkambi®)**
  Lumacaftor/Ivacaftor. Lumacaftor is a corrector of the CFTR working in combination with ivacaftor as a potentiator of the CFTR.
- **Elexacaftor/tezacaftor/ivacaftor (Kaftrio®)**
  Elexacaftor/tezacaftor/ivacaftor (used in combination with ivacaftor). Elexacaftor and tezacaftor are both correctors designed to move the defective CFTR protein to the correct position in the cell while ivacaftor increases the activity of the defective CFTR protein.
- **Vanzacaftor/tezacaftor/deutivacaftor (Alyftrek®)**
  Vanzacaftor and tezacaftor are CFTR correctors that bind to different sites on the CFTR protein facilitating increased amount of CFTR protein being delivered to cell surface. Deutivacaftor potentiates the channel opening.

There are approximately 11,381 people with cystic fibrosis registered within the UK including 483 registered in Wales[4].

1.2 Equality Impact Assessment

The Equality Impact Assessment (EIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable NHS Wales Joint Commissioning Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race,

gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

An EIA was carried out by NICE during the evaluation of Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis and vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis. For further details, please refer to the NICE website at: NICE EIA 1 and NICE EIA 2.

2. Recommendations

The recommendations below represent the views of NICE, arrived at after careful consideration of the evidence available. Health professionals are expected to take into account the relevant NICE guidance[1], alongside the individual needs, preferences and values of the patient.

2.1 Inclusion Criteria

Drug Treatment	Recommendations
Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis.	**NICE TA988** 1.1 Ivacaftor–tezacaftor–elexacaftor (IVA–TEZ–ELX) plus ivacaftor (IVA) alone is recommended within its marketing authorisation, as an option for treating cystic fibrosis in people 2 years and over who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. 1.2 Tezacaftor-ivacaftor (TEZ-IVA) plus IVA alone is recommended, within its marketing authorisation, for treating cystic fibrosis in people aged 6 years and over who have: • 2 copies of the CFTR gene with F508del mutations, or • a copy of the CFTR gene with a F508del mutation and a copy of the CFTR gene with 1 of the following mutations P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T'. 1.3 Lumacaftor-ivacaftor (LUM-IVA) is recommended, within its marketing authorisation, for treating cystic fibrosis in people 1 year and over

	who have 2 copies of the CFTR gene with F508del mutations.
Vanzacaftor-tezacaftor-deutivacaftor for treating cystic fibrosis with 1 or more F508del mutations in the CFTR gene in people 6 years and over.	**NICE TA1085** 1.1 Vanzacaftor-tezacaftor-deutivacaftor (Vnz-Tez-Diva) can be used as an option to treat cystic fibrosis in people aged 6 years and over who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Vnz-Tez-Diva can only be used if the company provides it according to the commercial arrangement. 1.2 Use the least expensive option for the suitable treatments (including Vnz-Tez-Diva and Iva-Tez-Elx), having discussed the advantages and disadvantages of the available treatments with the person with the condition. Take account of administration costs, dosages, price per dose and commercial arrangements. 1.3 This recommendation is not intended to affect treatment with Vnz-Tez-Diva that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS healthcare professional consider it appropriate to stop. For children or young people, this decision should be made jointly by the healthcare professional, the child or young person, and their parents or carers.

For all these CFTR products where the MHRA licence is updated to include gene mutations in the future, eligible patients will automatically have access under those terms. It is also important to note that different formulations of the same drug may have different marketing authorisations.

NWJCC will reimburse the off-label use of CFTR modulators where the UK medicines regulator has not considered the evidence for the named CFTR mutations, such as the approach taken by the EMA. The commissioning policy and associated risk sharing agreement with the company makes provision to support the cost of treatment for small numbers of patients who are at the margins of patient eligibility according to current licensed indications.

Any patients who fall into the off-label group for CFTR modulators, please contact nwjcc.medical@wales.nhs.uk prior to prescribing.

Please ensure (off-label) prescribing is done in accordance with the national and local guidance.

2.2 Continuation of Treatment

Healthcare professionals are expected to review a patient's health at regular intervals to ensure they are demonstrating an improvement to their health due to the treatment being given.

If no improvement to a patient's health has been recorded then clinical judgement on the continuation of treatment must be made by the treating healthcare professional.

2.3 Acceptance Criteria

The service outlined in this specification is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.4 Transition arrangements

Transition arrangements should be in line with Transition from children's to adults' services for young people using health or social care services, NICE guidance NG43 and the Welsh Government Transition and Handover Guidance

Transition involves a process of preparation for young people and their families for their transition to adulthood and their transition to adult services. This preparation should start from early adolescence 12-13 year olds. The exact timing of this will ideally be

dependent on the wishes of the young person but will need to comply with local resources and arrangements.

The transition process should be a flexible and collaborative process involving the young person and their family as appropriate and the service.

The manner in which this process is managed will vary on an individual case basis with multidisciplinary input often required and patient and family choice taken into account together with individual health board and environmental circumstances factored in.

For the specialised paediatric services it commissions, the JCC will routinely commission treatment up until a patient is 16 years old. The JCC does not commission specialised paediatric services for patients aged 18 years and older. For patients aged 16 or 17 years of age, the JCC will continue to commission ongoing specialised treatment initiated before the patient's 16th birthday and under the ongoing care of a specialised paediatric team.

2.5 Designated Providers

Adults and young people in South Wales have access to:
The All Wales Cystic Fibrosis Centre based at:
University Hospital Llandough
Penlan Road
Llandough
CF64 2XX

People also have access to:

Bristol Royal Infirmary
Marlborough Street
Bristol
BS2 8HW

Royal Brompton Hospital
Sydney Street
Chelsea
London
SW3 6NP

Adults and young people in North Wales and Powys have access to:

Liverpool Heart and Chest Hospital.
Thomas Drive
Liverpool
L14 3PE

West Midlands Adult Cystic Fibrosis Centre based at:
Birmingham Heartlands Hospital
Bordesley Green East
Birmingham
B9 5SS

Manchester Adult Cystic Fibrosis Centre based at:
Wythenshawe Hospital
Manchester Adult CF Centre
South Moor Road
Manchester
M23 9LT

Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
ST4 6QG

Infants, Toddlers and children have access to:

The Children's Hospital for Wales
Heath Park
Cardiff
CF14 4XW

Alder Hey Children's Hospital
E Prescott Road
Liverpool
L14 5AB

Birmingham Children's Hospital
Steelhouse Lane
Birmingham
B4 6NH

Royal Manchester Children's Hospital
Oxford Road
Manchester
M13 9WL

2.6 Patient Pathway (Annex i)

Patients should be referred to one of the designated providers listed in section 2.5 for assessment of eligibility for treatment included in this policy. See annex i for the patient pathway.

2.7 Mechanism for funding

If a non-contracted provider wishes to treat a patient that meets the criteria they should contact NWJCC at NWJCC.IPC@wales.nhs.uk. They will be asked to demonstrate they have an appropriate MDT in place.

Funding is approved on the basis that Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor, lumacaftor–ivacaftor and vanzacaftor-tezacaftor-deutivacaftor is prescribed and administered in accordance with its marketing authorisation. The following products are available. Summaries of Product Characteristics (SmPC) for each product can be accessed from The Electronic Medicines Compendium (EMC) website:

Ivacaftor-tezacaftor-elexacaftor	25mg/50mg/37.5mg tablets (Kaftrio®)
	40mg/80mg/60mg granules (Kaftrio®)
	50mg/100mg/75mg granules (Kaftrio®)
	50mg/100mg/75mg tablets (Kaftrio®)
Ivacaftor	13.4mg granules (Kalydeco®)
	25mg granules (Kalydeco®)
	50mg granules (Kalydeco®)
	59.5mg granules (Kalydeco®)
	75mg granules (Kalydeco®)
	150mg tablets (Kalydeco®)
	75mg tablets (Kalydeco®)
Tezacaftor-ivacaftor	150mg/100mg tablets (Symkevi®)
	75mg/50mg tablets (Symkevi®)
Lumacaftor-ivacaftor	125mg/100mg tablets (Orkambi®)

	125mg/100mg granules (Orkambi®)
	188mg/150mg granules (Orkambi®)
	125mg/200mg tablets (Orkambi®)
	94mg/75mg granules (Orkambi®)
Vanzacaftor-tezacaftor-deutivacaftor	10mg/50mg/125mg tablets (Alyftrek®)
	4mg/20mg/50mg tablets (Alyftrek®)

The company has a commercial arrangement. This makes the cystic fibrosis modulators available to the NHS with a discount. The size of the discount is commercial in confidence. Health Boards in Wales should refer to the AWTTC Commercial Medicines Access References Tool (CMART) for further information on the Patient Access Scheme (PAS) price.

2.8 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner. (These standards can include clinical outcomes, PROMS, Quality of Life etc).

The centre must enable the patient's, carer's and advocate's informed participation and to be able to demonstrate this. Provision should be made for patients with communication difficulties and for children, teenagers and young adults.

2.9 Action to be taken

- Health Boards and NWJCC are to circulate this Policy Position Statement to all Hospitals/MDTs to inform them of the conditions under which the technology will be commissioned.
- The providers are to ensure that they are purchasing cystic fibrosis modulator therapies at the agreed discounted price.
- Providers are to ensure the need to approve all cystic fibrosis modulator therapies at the appropriate MDT.
- The Provider should work to written quality standards and provide monitoring information to NWJCC on request.

3. Listening to People

3.1 Complaints, Incidents and Redress Process

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to Listening to People, The NHS Wales Complaints, Incidents and Redress Process – People's Guidance 2026. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to NWJCC.

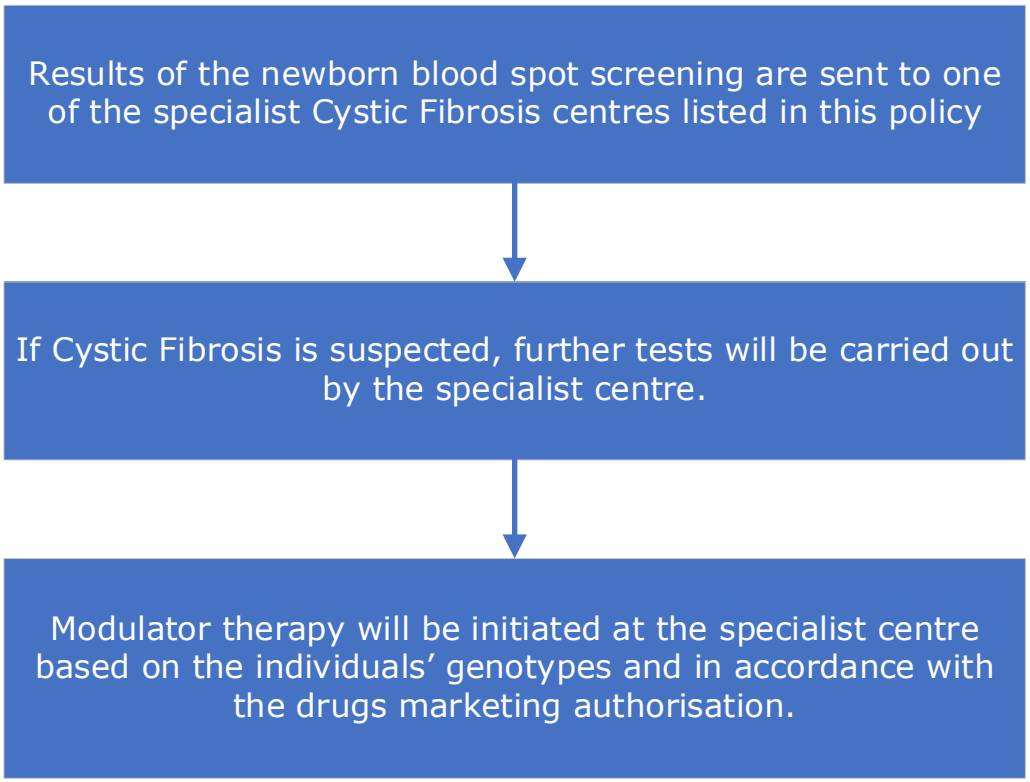
3.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Individual Patient Funding Requests

Annex i Patient Pathway



Annex ii Codes

The list of ICD codes below is indicative and is not exhaustive. The ICD10 codes have been provided and verified by the Information Standards Team at Digital Health and Care Wales (DCHW). Additional codes may be used for contract monitoring purposes, furthermore some codes may cover indications not included within this policy.

Code Category	Code	Description
ICD-10	E84	Cystic Fibrosis Incl: mucoviscidosis
	E84.0	Cystic Fibrosis with pulmonary manifestations
	E84.1	Cystic Fibrosis with intestinal manifestations • Distal intestinal obstruction syndrome • Meconium ileus in cystic fibrosis† (P75*)
	E84.8	Cystic Fibrosis with other manifestations
	E84.9	Cystic Fibrosis, unspecified
National Clinical Coding Standard	DCS.IV.6	Cystic Fibrosis with Manifestations (E84)

Contact Us

If you have a question related to this document you can contact us using one of the methods outlined below.

If you would like this document in an alternative format and/or language, please contact us for assistance.

Email:

NWJCC consultation mailbox NWJCC.Consultation@wales.nhs.uk

Telephone:

General Enquiries – 01443 433112

Website:

Contact us - NHS Wales Joint Commissioning Committee

Writing:

If you wish to contact the NHS Wales Joint Commissioning Committee, you can write to us at one of our locations below, we welcome correspondence in Welsh or English:

South Wales Offices
Unit 1, Charnwood Court, Heol Billingsley, Nantgarw, CF15 7QZ
Unit G1 The Willowford, Main Avenue, Treforest Industrial Estate, Pontypridd, CF37 5YL

North Wales Offices
Unit 3, Media Point - Unit 3, Mold Business Park, Mold, CH7 1XY
Preswylfa, Hendy Road, Mold, CH7 1PZ