Health Technology Briefing
February 2023

Elexacaftor/tezacaftor/ivacaftor and ivacaftor for treating cystic fibrosis without an F508del mutation and with an ELX/TEZ/IVA-responsive mutation in the CFTR gene in patients aged 6 years and older

Company/Developer	Vertex Pharmaceuticals Inc

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 34886	NICE ID: 11847	UKPS ID: 667905

Licensing and Market Availability Plans

Currently in phase III trials

Summary

Elexacaftor(ELX)/tezacaftor(TEZ)/ivacaftor(IVA) is a triple combination drug that is under investigation in a combination regime with ivacaftor for cystic fibrosis (CF) patients without an F508del mutation and with an ELX/TEZ/IVA-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is an inherited disease, caused by CFTR mutations in the DNA, that progressively affects the lungs and digestive system causing breathing difficulties and problems absorbing nutrients from food. There are currently few licensed medications that treat patients with non-F508del, but ELX/TEZ/IVA responsive mutations in CF, resulting in an unmet need for these patients.

ELX/TEZ/IVA changes proteins on the surface of cells to make them function more normally and improve the quantity, making the mucus in the lungs and digestive system less thick, reducing symptoms in the patient and limiting the inflammation and damage caused by the mucus. ELX/TEZ/IVA is administered orally once a day in the morning followed by an oral administration of IVA alone in the evening to maintain its effectiveness.

Proposed Indication

For the treatment of cystic fibrosis (CF) patients aged 6 years and older without an F508del mutation and with an ELX/TEZ/IVA-responsive mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.[1]

Technology

Description

Elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor(IVA) (Trikafta, Kaftrio) is a fixed dose combination medicine.[1] ELX/TEZ/IVA acts as a CF transmembrane conductance regulator (CFTR) modulating therapy that contains two correctors (TEZ and ELX) that work by facilitating correct folding and presentation of the mature CFTR protein on a cells surface, and a potentiator of the CFTR channel (IVA) allowing for an increase in chloride ion flow.[2] These actions are expected to make mucus and digestive juices less thick, thereby helping to relieve symptoms of the disease.[3] Although ELX and TEZ are administered once a day with IVA in the oral fixed dose combination, IVA requires twice daily dosing with a 12 hour gap as its metabolite only maintains 1/6th of the non-metabolised potency unlike ELX and TEZ.[2]

ELX/TEZ/IVA is in development for the treatment of CF in patients aged 6 years and older without an F508del mutation and with an ELX/TEZ/IVA-responsive mutation in the CFTR gene. In the phase III clinical trial (NCT05274269), the fixed-dose combination ELX/TEZ/IVA was administered orally in the morning, followed by oral IVA in the evening.[1]

Key Innovation

ELX/TEZ/IVA is currently licensed in a combination regimen with IVA for use in CF patients aged 6 years and older with at least one F508del mutation in CFTR gene.[4] The F508del mutation is found in approximately 90% of CF patients. [5] There are currently no treatments that treat the underlying cause of the disease in patients who do not have the f508del mutation leaving a treatment gap and unmet need for patients who do not have this mutation.[6] Treatment with ELX/TEZ/IVA and IVA has been demonstrated to improve Quality of Life (QoL) respiratory scores and lung function in patients, with slower damage to the lungs and digestive system, lowering mortality, pulmonary exacerbations, and lung transplants.[7,8] If licensed ELX/TEZ/IVA and IVA will become the first CFTR modulator therapy available to CF patients aged 6 years and older that do not have an F508del mutation in the CFTR gene.

Regulatory & Development Status

ELX/TEZ/IVA in combination regimen with IVA, has Marketing Authorisation in the UK for the treatment of CF patients aged 6 years and older who have at least one F508del mutation in the CFTR gene.[4]

ELX/TEZ/IVA has the following regulatory designations/ awards:

- Orphan drug in the EU in 2019 for the treatment of cystic fibrosis.[3]
- Breakthrough therapy designation by the US FDA for cystic fibrosis 2019.[9]
- Fast track status by the US FDA for the treatment of cystic fibrosis in 2019.[10]

Patient Group

Disease Area and Clinical Need

CF is an inherited autosomal recessive disorder that is caused by mutations in a gene that makes the CFTR protein, which is involved in regulating the production of mucus and digestive juices.[3] There are more than

2000 gene variants of the disease that have been identified with the most predominant being the class II mutation in F508del.[2] Mutations in the CFTR gene cause the CFTR protein to malfunction or not be made at all, leading to a build-up of thick mucus, which in turn leads to persistent lung infections, destruction of the pancreas, and complications in other organs.[11] Symptoms of CF usually start early in childhood and severity gradually increasing through the patient's lifetime with progressive damage to the lungs and digestive system, reducing overall life expectancy. Symptoms include recurring chest infections, wheezing and breathlessness, difficulty gaining weight and growing, jaundice, bowel obstructions in new born babies, osteoporosis, and diabetes.[12]

CF is a rare disease with a prevalence of 1 in 2000 at birth in Northern Europeans and varying prevalence in other populations depending on ethnic composition.[8] In the UK in 2021, 10,908 patients were registered as having CF, of those 188 were newly diagnosed that year.[13] 30 out of every 100,000 babies born in the UK have CF (2021).[13,14] The median age of death for CF patients that died in 2021 (UK) was 38 years, with 66 deaths reported in 2021. In the five-year period 2017-21 (UK), the mean predicted survival age was 53.5 years.[13] In England (2021-22), there were 8,127 finished consultant episodes (FCE) for CF (ICD-10 code: E84), with 6,939 hospital admissions of which 3,524 were day cases and 35,502 FCE bed days.[15]

Recommended Treatment Options

There is no cure for CF, but a range of treatments that can help to control the symptoms, prevent, or reduce complications, and improve quality of life. Medications taken by patients with CF include:[16]

- Antibiotics to fight chest infections
- Medications to thin the mucus within the lungs e.g. dornase alfa, hypertonic saline and mannitol dry powder
- Medications to help reduce the levels of mucus in the body e.g. ivacaftor or lumacaftor
- Bronchodilators
- Steroid medications
- Medications to treat the root cause of CF e.g. ELX/TEZ/IVA

There are no NICE recommended treatments to treat the underlying cause of the disease specifically for CF patients without an F508del mutation and with an ELX/TEZ/IVA-responsive mutation in the CFTR gene.

Clinical Trial Information

Trial	NCT05274269, 2021-005320-38; A Phase 3 Double-blind, Randomized, Placebo-controlled Study Evaluating the Efficacy and Safety of ELX/TEZ/IVA in Cystic Fibrosis Subjects 6 Years of Age and Older With a Non-F508del ELX/TEZ/IVA-responsive CFTR Mutation **Phase III** – Active, not recruiting **Location(s):** 14 European countries and Canada **Primary completion date:** April 2023
Trial Design	Randomised, parallel assignment, quadruple-masked, placebo-controlled
Population	N=307 patients with cystic fibrosis that do not have an F508del mutation in the CFTR gene; aged 6 years and older
Intervention(s)	ELX/TEZ/IVA in the morning and IVA in the evening, oral administration
Comparator(s)	Matched placebo

Outcome(s)	Primary outcome measure: - Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) [Time frame: from baseline through week 24] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	NCT05331183, 2021-005914-33; A Phase 3 Open-label Study Evaluating the Long-term Safety and Efficacy of Elexacaftor/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects With Non-F508del CFTR Genotypes **Phase III –** Recruiting **Location(s):** Belgium, France, Germany, Netherlands, and Spain **Primary completion date:** April 2025
Trial Design	Single group assignment, open label
Population	N=270; patients with cystic fibrosis that do not have an F508del mutation in the CFTR gene; aged 6 years and older
Intervention(s)	ELX/TEZ/IVA in the morning and IVA in the evening, oral administration
Comparator(s)	No comparator used
Outcome(s)	Primary outcome measure: - Safety and tolerability as assessed by number of participants with adverse events (AEs) and serious adverse events (SAEs) [Time frame: day 1 up to week 100]
Results (efficacy)	-
Results (safety)	-

Estimated Cost

ELX/TEZ/IVA is already marketed in the UK for the treatment of CF in patients; a pack of 56 tablets of ELX/TEZ/IVA (of 50mg, 25mg, 37.5mg strength or 100mg, 50mg, 75mg strength) costs £8,346.30 at List Price.[17]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard. Cystic fibrosis (QS168). May 2018.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor and elexacaftor/tezacaftor/ivacaftor for licensed and off-label use in patients with cystic fibrosis who have named mutations. 210508/P. January 2022.

- NHS England. Standard Contract for Cystic Fibrosis (adults). A01/S/a. August 2018.
- NHS England. Standard Contract for Cystic Fibrosis (children). A01/S/b. July 2018.
- NHS England. Clinical Commissioning Policy: Continuous Aztreonam Lysine for Cystic Fibrosis (all ages). 16001/P. July 2016.
- NHS England. Clinical Commissioning Policy: Inhaled Therapy for Adults and Children with Cystic Fibrosis. A01/P/b. January 2015.

Other Guidance

- Welsh Health Specialised Services Committee (WHSSC). Specialised services specification: PP198 Cystic fibrosis Modular Therapies. 2022.[18]
- European Cystic Fibrosis Society (ECFS). ECFS Standards of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis. 2022.[19]
- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. 2011.[20]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.