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HEALTH TECHNOLOGY BRIEFING
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Elexacaftor/tezacaftor/ivacaftor (fixed-dose combination) for cystic fibrosis heterozygous for F508del mutation in patients aged 12 years old and older

NIHRIO ID	28436	**NICE ID**	10356
Developer/Company	Vertex Pharmaceuticals Inc.	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase III development.

SUMMARY

The triple fixed-dose combination (FDC), elexacaftor/tezacaftor/ivacaftor, is in clinical development for cystic fibrosis (CF) that is heterozygous for F508del mutation for patients aged 12 years and older. CF is the most common, life-limiting recessively inherited (a faulty gene inherited from both parents) disease in the UK. Genetic mutations affect the CF transmembrane conductance regulator (CFTR) gene, which is essential for the regulation of salt and water movements across cell membranes. These mutations mean that the CFTR protein is not processed and moved through the cells normally, resulting in little to no CFTR protein at the cell surface. This results in thickened secretions in organs with epithelial cell lining, mainly affecting the lungs and digestive system, leading to chronic infections and difficulty digesting food.

Elexacaftor and tezacaftor are designed to increase the amount of mature protein at the cell surface by targeting the processing and trafficking defect of the F508del CFTR protein. Ivacaftor is designed to enhance the function of the CFTR protein once it reaches the cell surface. The triple therapy of elexacaftor/tezacaftor/ivacaftor-FDC may result in an effective therapeutic option for people with CF heterozygous for F508del mutations, who currently have limited options.

PROPOSED INDICATION

Cystic Fibrosis (CF) patients heterozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and a gating or residual function mutation (F/G and G/RF genotypes) in patients aged 12 years and older.[1]

TECHNOLOGY

DESCRIPTION

Elexacaftor/tezacaftor/ivacaftor - FDC (Trikafta™) is a combination therapy combining three CFTR modulators. Elexacaftor and tezacaftor are CFTR correctors, a type of modulator designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. Ivacaftor is a potentiator. Once CFTR protein reaches the cell surface, potentiators help facilitate the opening of the chloride channel to allow chloride and sodium (salt) to move in and out of the cell.[2]

In phase III clinical trials for cystic fibrosis (NCT04058353, NCT04058366) patients receive a fixed-dose combination oral tablet of 100-mg elexacaftor/ 50-mg tezacaftor/ 75-mg ivacaftor in the morning and a 150mg oral tablet of ivacaftor in the evening.[1,3,4]

INNOVATION AND/OR ADVANTAGES

There are currently no treatment options available in the NHS that specifically target F508del mutations in the CFTR gene.[5]

In vitro, the triple combination therapy significantly improved Phe508del CFTR protein processing, trafficking and chloride transport to a greater extent than any two of these agents in dual combination. In patients with cystic fibrosis, elexacaftor/tezacaftor/ivacaftor had an acceptable safety and side effect profile. The use of the triple combination therapy to target Phe508del CFTR protein resulted in increased CFTR function in vitro and translated to improvements in patients with cystic fibrosis with one or two Phe508del alleles. This approach has the potential to treat the underlying cause of cystic fibrosis in approximately 90% of patients.[6]

Specific to this indication, the drug ivacaftor helps people with gating mutations and residual function mutations by forcing the gate on the CFTR channel to stay open longer. This enables chloride to move through the channel and reduces the symptoms of CF.[7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Elexacaftor/tezacaftor/ivacaftor -FDC does not currently have Marketing Authorisation in the EU/UK for any indication.

The treatment regimen of elexacaftor + tezacaftor + ivacaftor was granted orphan drug designation in the EU in December 2018 for the treatment of CF.[8]

Tezacaftor/ivacaftor (tezacaftor 100mg/ ivacaftor 150mg) in a combination regimen with ivacaftor(150mg) has been granted Marketing Authorisation in the EU for patients aged 12 years and older with CF homozygous for F508del mutation or with CF heterozygous for F508del mutation and have one of another number of listed mutations.[9]

Very common adverse effects (>10%) in patients treated with tezacaftor/ivacaftor in combination with ivacaftor include nasopharyngitis and headache.[9]

Tezacaftor/ivacaftor was designated an orphan drug in the EU in February 2017, and this designation was maintained at the time of Marketing Authorisation.[10]

The medicinal product ivacaftor has been granted Marketing Authorisation in the EU for:[11]

- the treatment of patients with cystic fibrosis (CF) aged 6 years and older and weighing 25 kg or more who have one of the following gating (class III) mutations in the CFTR gene: G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R
- the treatment of patients with cystic fibrosis (CF) aged 18 years and older who have an R117H mutation in the CFTR gene

Ivacaftor was designated an orphan drug in the EU in July 2008, and this designation was maintained at the time of Marketing Authorisation.[12]

Elexacaftor/tezacaftor/ivacaftor is also in phase III clinical development for patients aged 12 years and older with CF that is homozygous for F508del mutation in the CFTR gene, and for patients aged 6 to 11 years with CF that is homozygous or heterozygous for F508del mutation.[13]

PATIENT GROUP

DISEASE BACKGROUND

CF results from mutations affecting a gene that encodes for the CFTR (a chloride channel) which is essential for the regulation of salt and water movements across cell membranes. Absent or reduced function of CFTR results in thickened secretions in organs with epithelial cell lining, hence it is multi-system, although mainly affects the lungs, digestive system and vas deferens (part of the male reproductive system).[14]

The most common CF mutation, F508del, is primarily considered to be a processing mutation. The F508del mutation removes a single amino acid from the CFTR protein. Without this building block, the CFTR protein cannot stay in the correct 3-D shape. The cell recognizes that the protein is not the right shape and disposes of it. The CFTR protein is shaped like a tunnel, or channel, with a gate. Gating mutations lock the gate in the closed position so that chloride cannot get through.[7] More than 2,000 variants of CFTR have been described, and these mutations are largely categorized based on the mechanism of impairment. Loss-of-function mutations (class I–III) result in little to no functional CFTR protein and are associated with a classic CF phenotype. Although there is a high degree of individual variation, people with at least one residual function mutation (class IV–VI) have some functional CFTR and more often have a clinical phenotype characterized by preserved pancreatic function and mild lung disease.[15]

In CF, the airways become clogged with thick sticky mucus, which impairs the clearance of microorganisms. This leads to recurrent infection, inflammation, bronchial damage, bronchiectasis and eventually death from respiratory failure. Patients are often infected with S. aureus and P. aeruginosa, but also by a number of other organisms, some of which are resistant to many antibiotics.[14]

In about 85% of cases, the pancreatic exocrine ducts become sufficiently blocked to cause maldigestion and intestinal malabsorption (pancreatic insufficiency). Infants may fail to thrive, and older children and adults may become under-nourished. Appetite is often adversely

affected which is a problem as there is an underlying increase in metabolic demands leading to a need for an increased energy intake. Other complications include male infertility, CF related diabetes, chronic liver disease and portal hypertension, joints affected by CF arthropathy, bones affected by reduced bone mineral density, and behavioural and psychological problems associated with a sever long-term medical condition.[14]

CLINICAL NEED AND BURDEN OF DISEASE

CF is one of the UK's most common life-threatening inherited diseases and affects around 1 in every 2,500 live births in the UK.[14]

The latest annual report from the UK Cystic Fibrosis Registry shows that in 2018:[16]

- 10,509 people in the UK had a diagnosis of CF (96% had an annual review)
- 222 patients were newly-diagnosed, of which 151 were identified by newborn screening
- 137 people with CF died, and the median age at death was 32 years
- 6,855 (69.6%of patients who had annual reviews) patients were aged 12 years and older
- 9,757 (99.1%) patients have been genotyped, of which 3,991 (40.5%) were heterozygous for F508del mutation.

In England in 2018/19 there were 17,171 Finished Consultant Episodes (FCE) and 13,991 hospital admissions for all ages with a primary diagnosis of CF (ICD-10 code E84), resulting in 91,101 FCE bed days. 13,206 of the FCEs were patients aged over 14 years.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Care for people with CF should be provided by a specialist CF multidisciplinary team (MDT) based at a specialist CF centre. The MDT should include specialist paediatricians or adult physicians, nurses, physiotherapists, dietitians, pharmacists and clinical psychologists. Patients should have a comprehensive annual review, and routine reviews at regular intervals.[18]

Current treatments for CF manage the symptoms and complications rather than the cause of the disease.[19]

CURRENT TREATMENT OPTIONS

Treatments can be broadly classified as:[5]

- nutritional repletion (for example, pancreatic enzymes and nutritional supplements)
- relief of airway obstruction (for example, physiotherapy, drugs to improve clearance of mucus such as dornase alfa [rhDNase], hypertonic saline, and bronchodilators)
- treatment of acute infections
- suppression of chronic infection
- suppression of inflammation (for example, steroids, high dose ibuprofen)
- lung transplantation

NICE recommends mannitol dry powder for inhalation as an option for some people with cystic fibrosis in adults and colistimethate sodium and tobramycin dry powders for inhalation for treating chronic lung infections in some people with cystic fibrosis.[5]

PLACE OF TECHNOLOGY

If licenced, the triple fixed-dose combination of elexacaftor/tezacaftor/ivacaftor would provide a treatment option for cystic fibrosis patients heterozygous for F508del and a gating or residual function mutation in patients aged 12 years and older, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**VX18-445-110,** NCT04058366, 2019-000833-37; A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes) **Phase III extension** **Location:** EU countries (inc UK), United States, Canada and Australia.
Trial design	Single Group Assignment, Open Label
Population	N=250. Completed study drug treatment in parent study (VX18-445-104); or had study drug interruption(s) in parent study but completed study visits up to the last scheduled visit of the treatment period in the parent study.
Intervention(s)	Elexacaftor/tezacaftor/ivacaftor fixed-dose combination (FDC) tablet for oral administration in the morning and ivacaftor 150-mg tablet for oral administration in the evening.
Comparator(s)	None
Outcome(s)	Primary outcomes: • Safety and tolerability as assessed by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From Baseline up to Week 100] See trial for full list.
Results (efficacy)	-
Results (safety)	-

Trial	**VX18-445-104,** NCT04058353, 2018-002835-76; A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445 Combination Therapy in Subjects With Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes) **Phase III** **Location:** EU countries (inc UK), United States, Canada and other countries.
Trial design	Randomised, double blind, parallel assignment.
Population	N=250 (planned), aged 12 years and older, confirmed diagnosis of CF and is heterozygous for F508del and either a gating or residual function mutation (F/G and F/RF genotypes)
Intervention(s)	Elexacaftor/tezacaftor/ivacaftor fixed-dose combination (FDC) tablet for oral administration in the morning and ivacaftor 150-mg tablet for oral administration in the evening.

Comparator(s)	Subjects will receive either ivacaftor as mono tablet OR tezacaftor/ivacaftor as FDC in the morning and ivacaftor as mono tablet in the evening.
Outcome(s)	Primary Outcome(s): • Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) for ELX/TEZ/IVA group [Time Frame: From Baseline through Week 8] See trial for full list.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of the treatment regimen of VX-445/tezacaftor/ivacaftor-FDC is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Elexacaftor, tezacaftor and ivacaftor fixed dose combination therapy for treating cystic fibrosis with the F508del mutation (ID1661). Expected date of issue December 2020.
- NICE technology appraisal in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation (ID1303). Suspended. Expected date of issue to be confirmed.
- NICE technology appraisal. Mannitol dry powder for inhalation for treating cystic fibrosis (TA266). November 2012.
- NICE guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard. Cystic fibrosis (QS168). May 2018.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Specialised Respiratory Service Specification: Cystic Fibrosis (Adults). A01/S/a.
- NHS England. 2013/14 NHS Specialised Respiratory Service Specification: Cystic Fibrosis (Children). A01/S/b
- NHS England. Clinical Commissioning Policy for Inhaled therapies for Adults and Children with Cystic Fibrosis. NHS England A01/P/b. January 2015

OTHER GUIDANCE

- Cystic Fibrosis Trust. Standards of care and good clinical practice for the physiotherapy management of cystic fibrosis. April 2017.[20]

ADDITIONAL INFORMATION

Vertex did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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