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HEALTH TECHNOLOGY BRIEFING
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Elexacaftor/tezacaftor/ivacaftor (fixed-dose combination) for cystic fibrosis homozygous for F508del mutation in patients aged 6 to 11 years old

NIHRIO ID	26979	**NICE ID**	10215
Developer/Company	Vertex Pharmaceuticals Inc	**UKPS ID**	Not available

Licensing and market availability plans	The regulatory filing and marketing/launch plans of this technology in the EU/UK could not be established as at the time of producing this briefing.

SUMMARY

The triple fixed-dose combination (FDC), elexacaftor/tezacaftor/ivacaftor-FDC, is in clinical development for cystic fibrosis (CF) that is homozygous for F508del mutation for patients aged 6 to 11 years old. 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.

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 with F508del mutations, who currently have limited options.

PROPOSED INDICATION

Cystic fibrosis (CF) homozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/F), patients aged 6 to 11 years.[1]

TECHNOLOGY

DESCRIPTION

The triple fixed-dose combination (FDC) of elexacaftor, tezacaftor and ivacaftor (elexacaftor /tezacaftor/ivacaftor-FDC) is in clinical development for patients aged 6 to 11 years old who have CF that is homozygous for F508del mutation in the CFTR gene.[1]

Elexacaftor (VX-445) is a next-generation CFTR corrector designed to restore Phe508del CFTR protein function in patients with CF when administered with tezacaftor and ivacaftor.[2]

Tezacaftor is a selective CFTR corrector that binds to the first Membrane Spanning Domain (MSD-1) of CFTR. Tezacaftor facilitates the cellular processing and trafficking of normal or multiple mutant forms of CFTR (including F508del-CFTR) to increase the amount of CFTR protein delivered to the cell surface, resulting in increased chloride transport in vitro.[3]

Ivacaftor is a CFTR potentiator that potentiates the channel-open probability (or gating) of CFTR at the cell surface to increase chloride transport. For ivacaftor to function CFTR protein must be present at the cell surface. Ivacaftor can potentiate the CFTR protein delivered to the cell surface by tezacaftor, leading to a further enhancement of chloride transport than either active substance alone. The combination targets the abnormal CFTR protein by increasing the quantity and function of CFTR at the cell surface and subsequently increasing airway surface liquid height, and ciliary beat frequency in vitro in human bronchial epithelial (HBE) cells from homozygous F508del CF patients. The exact mechanisms by which tezacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.[3]

In the phase III clinical trial NCT03691779, patients were administered the triple FDC tablets of elexacaftor 100mg, tezacaftor 50mg and ivacaftor 75mg in the morning, followed by ivacaftor 75mg single tablet in the evening.[1]

INNOVATION AND/OR ADVANTAGES

Whilst the dual combination of a first-generation CFTR corrector (lumacaftor or tezacaftor) and ivacaftor provides both short-term and long-term benefit to patients with homozygous for F508del mutation, these combinations do not fully restore function to F508del CFTR protein.[4]

It has been shown in vitro that a combination of two correctors with distinct binding sites on CFTR and complementary mechanisms of action can increase the amount of F508del CFTR protein at the cell surface to a greater extent than either corrector alone.[4]

Elexacaftor shares some structural similarities and a mechanism of action with VX-659.[5] VX-659 has been developed for use in combination with tezacaftor and ivacaftor to increase both the amount and function of F508del CFTR protein to a greater extent than a dual combination

of a corrector and a potentiator. Additivity of VX-659 to tezacaftor and ivacaftor in vitro increases F508del CFTR protein processing within the cell and trafficking to the cell surface.[4] Because elexacaftor works through different mechanisms from tezacaftor, it is believed that the combination will increase the amount of F508del CFTR protein at the cell surface more than either compound alone, an effect that could be potentiated by ivacaftor to further increase chloride transport.[5,4]

The use of elexacaftor /tezacaftor/ivacaftor to target F508del CFTR protein has previously resulted in increased CFTR function in vitro and translated to improvements in patients with CF with one or two F508del alleles. This approach has the potential to treat the underlying cause of CF in approximately 90% of patients.[5]

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-FDC was granted orphan drug designation in the EU in December 2018 for the treatment of CF.[6]

The medicinal product tezacaftor/ivacaftor (tezacaftor 100 mg/ ivacaftor 150 mg) 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.[3,7] Very common adverse effects (>10%) in patients treated with tezacaftor/ivacaftor in combination with ivacaftor include nasopharyngitis and headache.[3]

The medicinal product tezacaftor/ivacaftor was designated an orphan drug in the EU in February 2017, and this designation was maintained at the time of Marketing Authorisation.[8]

The medicinal product ivacaftor has been granted Marketing Authorisation in the EU for:[9]

- 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

The medicinal product ivacaftor was designated an orphan drug in the EU in July 2008, and this designation was maintained at the time of Marketing Authorisation.[10] The most common side effects with ivacaftor (which may affect more than 1 in 10 people) are headache, sore throat, upper respiratory tract infection (nose and throat infection), nasal congestion, abdominal (belly) pain, nasopharyngitis (inflammation of the nose and throat), diarrhoea, dizziness, rash, bacteria in sputum (phlegm) and an increase in certain liver enzymes. Serious side effects include abdominal pain and increased liver enzymes.[9]

Elexacaftor/tezacaftor/ivacaftor-FDC is also in phase III clinical development for patients aged 12 years and older with CF that is heterozygous for F508del mutation in the CFTR gene and a minimal function mutation, and for patients aged 6 to 11 years with CF that is homozygous or heterozygous for F508del mutation.[1,11]

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).[12]

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.[12]

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.[12]

CLINICAL NEED AND BURDEN OF DISEASE

The latest annual report from the UK Cystic Fibrosis Registry shows that in 2017:[13]

- 10,469 people in the UK had a diagnosis of CF
- 214 patients were newly-diagnosed, of which 172 were identified by newborn screening
- 132 people with CF died, and the median age at death was 31 years
- 1,599 patients were aged 6 to 11 years (patients with height data recorded)
- 9,818 (99.3%) patients have been genotyped, of which 4,956 (49.1%) were homozygous for F508del mutation

In England in 2017/18 there were 13,592 hospital admissions for all ages with a primary diagnosis of CF (ICD-10 code E84), resulting in 88,098 finished consultant episode (FCE) bed days.[14]

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.[15]

Current treatments for CF manage the symptoms and complications rather than the cause of the disease.[16]

CURRENT TREATMENT OPTIONS

Treatments can be broadly classified as:[16]

- 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

The medicinal product lumacaftor/ivacaftor has a Marketing Authorisation in the UK for the treatment of patients aged 6 years and older with CF who are homozygous for the F508del mutation in the CFTR gene.[17,18]

PLACE OF TECHNOLOGY

If licensed, elexacaftor /tezacaftor/ivacaftor-FDC will offer an additional treatment option for patients aged 6 - 11 years with CF homozygous for the F508del mutation in the CFTR gene, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03691779, **EudraCT-2018-001695-38, VX18-445-106; children aged 6 to 11 years; Fixed dose combination (FDC) tablet (VX-445/TEZ/IVA) in the morning plus IVA as mono tablet in the evening; phase III**
Sponsor	Vertex Pharmaceuticals Incorporated
Status	Ongoing
Source of Information	Trial registry[1]
Location	Various locations across the US
Design	Non-randomised, open label
Participants	n=56 (planned); aged 6 to 11 years; homozygous or heterozygous for F508del mutation (F/F or F/MF genotypes)
Schedule	Participants will receive: • Part A: Triple Combination of 100 mg VX-445/ 50 mg TEZ/ 75 mg IVA as an FDC tablet in the morning and 75 mg IVA as mono tablet in the evening. • Part B: Triple Combination of VX-445/TEZ/IVA as FDC tablet in the morning and IVA as mono tablet in the evening with the dose to be based on the outcome of Part A.
Follow-up	Active treatment for 15 days, overall follow-up (including adverse events) 28 weeks.
Primary Outcomes	• Part A: Observed pre-dose concentration (Ctrough) of VX-445, TEZ, and IVA [Time Frame: Day 1 through 15] • Part A: Maximum Observed Concentration (Cmax) of VX-445, TEZ, and IVA [Time Frame: Day 1 through 15]

	• Part A: Area under the concentration versus time curve during a dosing interval (AUCtau) of VX-445, TEZ, and IVA [Time Frame: Day 1 through 15] • Part B: Safety and tolerability as assessed by number of subjects with adverse events and serious adverse events [Time Frame: from baseline through safety follow-up (28 Weeks)]
Secondary Outcomes	• Part A: Maximum observed concentration (Cmax) of VX-445, TEZ, and IVA metabolites [Time Frame: from Day 1 through 15] • Part A: Observed pre-dose concentration (Ctrough) of VX-445, TEZ, and IVA metabolites [Time Frame: from Day 1 through 15] • Part A: Area under the concentration versus time curve during a dosing interval (AUCtau) of VX-445, TEZ, and IVA metabolites [Time Frame: from Day 1 through 15] • Part A: Safety and tolerability as assessed by number of subjects with adverse events (AEs) and serious adverse events (SAEs) [Time Frame: from baseline through safety follow-up (28 Weeks)] • Part B: Absolute change in percent predicted forced expiratory volume in 1 second (ppFEV1) [Time Frame: from baseline through Weeks 12 and 24] • Part B: Absolute change in sweat chloride [Time Frame: from baseline through Weeks 12 and 24] • Part B: Absolute change in Cystic Fibrosis Questionnaire Revised (CFQ R) respiratory domain score [Time Frame: from baseline through Weeks 12 and 24] • Part B: Absolute change in body mass index (BMI) and BMI for age-z-score [Time Frame: from baseline at Week 24] • Part B: Absolute change in weight and weight for age-z-score [Time Frame: from baseline at Week 24] • Part B: Absolute change in height and height for age-z-score [Time Frame: from baseline at Week 24] • Part B: Absolute change in the Modified Facial Hedonic Scale [Time Frame: from baseline at Week 24] • Parts B: Ctrough of VX-445, TEZ, IVA, and IVA metabolites [Time Frame: Day 1 through Week 24] • Part B: Absolute change in lung clearance index2.5 (LCI2.5) [Time Frame: from baseline through Week 24]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as Jan 2020.

ESTIMATED COST

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

RELEVANT GUIDANCE

NICE GUIDANCE

- 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 in development. Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years old homozygous for the F508del mutation (ID1486). Expected publication date to be confirmed.
- 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. Service Specification: Cystic fibrosis (children). A01/S/b.

OTHER GUIDANCE

- Cystic Fibrosis Trust. Standards for the clinical care of children and adults with cystic fibrosis in the UK. Second ed. December 2011.[12]

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.

REFERENCES

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