Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Tezacaftor and ivacaftor for cystic fibrosis homozygous or heterozygous for F508del mutation in patients aged 12 years and older who discontinued treatment with Orkambi

NIHRIO ID	20370	**NICE ID**	9835
Developer/Company	Vertex Pharmaceuticals Inc	**UKPS ID**	Not Available

Licensing and market availability plans	Licensed for this indication.

SUMMARY

The fixed-dose combination (FDC) tezacaftor/ivacaftor-FDC has received approval for patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and one of a number of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CF is a life-limiting inherited disease that affects about 10,000 people in the UK. Genetic mutations affect the CFTR gene, which is essential for the regulation of salt and water movements across cell membranes. This results in thickened secretions in organs with epithelial cell lining, mainly affecting the lungs and digestive system.

Tezacaftor is 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 combination of tezacaftor and ivacaftor may result in an effective treatment for people with CF and may especially be a treatment option for those who cannot take a combination of ivacaftor and lumacaftor (another cystic fibrosis medicine), due to side effects or interactions with other medicines they are taking.

PROPOSED INDICATION

Cystic fibrosis (CF) homozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/F), or CF heterozygous for F508del mutation and one of another number of listed mutations, patients aged 12 years and older who have discontinued treatment with Orkambi (fixed-dose combination of lumacaftor and ivacaftor) due to respiratory symptoms considered related to treatment.[1,2]

TECHNOLOGY

DESCRIPTION

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 NCT03150719, patients were administered the FDC tablets of tezacaftor 100mg and ivacaftor 150mg in the morning, followed by ivacaftor 150mg single tablet in the evening.[1]

INNOVATION AND/OR ADVANTAGES

Studies suggest that there is a relatively high rate of drug intolerance in patients newly treated with lumacaftor/ivacaftor, with between 17% and 25% of patients being unable to tolerate this treatment.[4,5] Whilst the paediatric population appears to better tolerate drug initiation, adults and patients with severe lung disease (baseline percent predicted forced expiratory volume in one second (FEV1%) ≤40%) have higher rates of adverse effects and discontinue the therapy.[4] In addition, strong cytochrome P-450-3A induction by lumacaftor causes prohibitive drug-drug interactions in some patients and limits the use of lumacaftor/ivacaftor in patients with ivacaftor-responsive mutations.[6,7]

Compared to lumacaftor, tezacaftor has improved pharmacokinetic properties with fewer side effects and drug-drug interaction.[8] In clinical trials, combination therapy with tezacaftor/ivacaftor was comparable to lumacaftor/ivacaftor in terms of clinical efficacy outcomes, including the primary outcome FEV1, and was found to have fewer side effects (including transient bronchoconstriction).[6,8] Unlike lumacaftor, tezacaftor is not an inducer of CYP3A4 enzymes and does not interfere with the metabolism of ivacaftor or many other medications that are frequently used in CF, reducing drug-drug interactions and dosing complexities.[9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The medicinal product Symkevi® (100mg tezacaftor and 150mg ivacaftor) in a combination regimen with Kalydeco® (150mg ivacaftor) has been granted Marketing Authorisation in the EU for patients

aged 12 years and older with CF with F/F genotype or with CF heterozygous for F508del mutation and one of another number of listed mutations.[2] The overview published by the European Medicines Agency states that "Symkevi could especially be a treatment option for those who cannot take a combination of ivacaftor and lumacaftor due to side effects or interactions with other medicines they are taking."[10] Very common adverse effects (>10%) in patients treated with Symkevi in combination with ivacaftor include nasopharyngitis and headache.[3]

The medicinal product Symkevi® (100mg tezacaftor and 150mg ivacaftor) was designated an orphan drug in the EU in February 2017, and this designation was maintained at the time of Marketing Authorisation.[11]

The medicinal product Kalydeco® (150mg ivacaftor) has been granted Marketing Authorisation in the EU for: [12]

- 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 Kalydeco® (150mg ivacaftor) was designated an orphan drug in the EU in July 2008, and this designation was maintained at the time of Marketing Authorisation.[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]

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 severe long-term medical condition.[14]

CLINICAL NEED AND BURDEN OF DISEASE

Cystic fibrosis (CF) is the most common, life-limiting recessively inherited disease in the UK.[14]
The latest annual report from the UK Cystic Fibrosis Registry shows that in 2017:[15]

- 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
- 6,878 patients were aged 12 years and older (69.6% of patients who had annual reviews)
- 9,818 (99.3%) patients have been genotyped, of which 4,956 (49.1%) were homozygous for F508del mutation and 3,990 (40.4%) were heterozygous for F508del mutation

In England in 2017/18 there were 13,592 hospital admissions with a primary diagnosis of CF (ICD-10 code E84), resulting in 88,098 finished consultant episode (FCE) bed days.[16]

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.[17]

Current treatments for CF manage the symptoms and complications rather than the cause of the disease.[18]

CURRENT TREATMENT OPTIONS

Treatments can be broadly classified as:

- 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[18]

NICE recommends mannitol dry powder for inhalation as an option for treating CF in adults who cannot use rhDNase and whose lung function is rapidly declining and for whom other osmotic agents are not considered appropriate.[19]

The medicinal product Orkambi® (lumacaftor and ivacaftor combination regimen) has a Marketing Authorisation in the UK for the treatment of patients aged 12 years and older with CF with F/F genotype, but is not recommended by NICE.[20,21]

PLACE OF TECHNOLOGY

Tezacaftor/ivacaftor-FDC offers an additional treatment option for patients aged 12 years and older with CF with F/F genotype or CF heterozygous for F508del mutation and one of another number of listed mutations who do not respond to treatment with, or cannot tolerate, Orkambi, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

<table>
<tr><td>Trial</td><td>NCT03150719, EudraCT-2017-000540-18, VX16-661-114; tezacaftor–ivacaftor-ivacaftor vs placebo; phase III</td></tr>
<tr><td>Sponsor</td><td>Vertex Pharmaceuticals Inc</td></tr>
<tr><td>Status</td><td>Published</td></tr>
<tr><td>Source of Information</td><td>Trial registry[1,22]</td></tr>
<tr><td>Location</td><td>EU (not UK) and USA</td></tr>
<tr><td>Design</td><td>Randomised, placebo-controlled</td></tr>
<tr><td>Participants</td><td>n=98; aged 12 yrs and older; cystic fibrosis; homozygous for F508del mutation (F/F); prior discontinuation of Orkambi, with at least 1 respiratory sign or symptom considered related to therapy; FEV1 value ≥25% and ≤90% of predicted normal for age, sex and height</td></tr>
<tr><td>Schedule</td><td>Randomised to fixed-dose combination (FDC) of tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening vs triple placebo</td></tr>
<tr><td>Follow-up</td><td>Active treatment for 56 days, follow-up period not reported</td></tr>
<tr><td>Primary Outcomes</td><td>• Incidence of respiratory adverse events (AEs) at day 56</td></tr>
<tr><td>Secondary Outcomes</td><td>Time frame: from baseline to the average of day 28 and day 56 measurements:
• Absolute change in percent predicted FEV1 (ppFEV1)
• Relative change in ppFEV1
• Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score

• Tolerability, defined as number and proportion of study participants who discontinue treatment [Time frame: through day 56]
• Safety assessments based on the number of subjects with AEs and serious AEs (SAEs) [Time frame: day 1 up to safety follow-up (up to 28 days after last dose of study drug)]</td></tr>
<tr><td>Key Results</td><td>Respiratory, thoracic and mediastinal disorder SAEs and AEs
<table>
<tr><th>SAEs and AEs</th><th>Placebo</th><th>TEZ/IVA</th></tr>
<tr><td>SAE - Pleuritic pain</td><td>1/47 (2.13%)</td><td>0/50 (0.00%)</td></tr>
<tr><td>AE - Cough</td><td>8/47 (17.02%)</td><td>9/50 (18.00%)</td></tr>
<tr><td>AE - Dyspnoea</td><td>5/47 (10.64%)</td><td>5/50 (10.00%</td></tr>
<tr><td>AE - Haemoptysis</td><td>2/47 (4.26%)</td><td>3/50 (6.00%)</td></tr>
<tr><td>AE - Respiration abnormal</td><td>1/47 (2.13%)</td><td>3/50 (6.00%)</td></tr>
<tr><td>AE - Oropharyngeal pain</td><td>3/47 (6.38%)</td><td>2/50 (4.00%)</td></tr>
<tr><td>AE - Sputum increased</td><td>5/47 (10.64%)</td><td>2/50 (4.00%)</td></tr>
</table></td></tr>
<tr><td>Adverse effects (AEs)</td><td>Other SAEs</td></tr>
</table>

SAEs	Placebo	TEZ/IVA
Total subjects affected	9/47 (19.15%)	5/50 (10.00%)
Pericardial effusion	1/47 (2.13%)	0/50 (0.00%)
Multiple organ dysfunction syndrome	0/47 (0.00%)	1/50 (2.00%)
Suicidal ideation	0/47 (0.00%)	1/50 (2.00%)
Constipation	0/47 (0.00%)	1/50 (2.00%)
Musculoskeletal chest pain	1/47 (2.13%)	0/50 (0.00%)
Infective pulmonary exacerbation of CF	7/47 (14.89%)	3/50 (6.00%)
Sepsis	0/47 (0.00%)	1/50 (2.00%)
Lower respiratory tract infection	1/47 (2.13%)	0/50 (0.00%)

ESTIMATED COST

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

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation (ID1303). Expected date of issue to be confirmed.
- NICE technology appraisal. Lumacaftor-ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (TA398). July 2016.
- 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. Service Specification: Cystic fibrosis (adults). A01/S/a.
- 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.[14]

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