Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING MARCH 2019

Tezacaftor/ivacaftor (fixed-dose combination) for cystic fibrosis heterozygous for F508del mutation and one residual mutation in patients aged 6 to 11 years

NIHRIO ID	27095	**NICE ID**	TBC
Developer/Company	Vertex Pharmaceuticals Inc	**UKPS ID**	Not Available

Licensing and market availability plans	The company anticipate submitting an indication extension to the EMA in the second half of 2019.[1]

SUMMARY

The fixed-dose combination (FDC) tezacaftor/ivacaftor-FDC is in clinical development for cystic fibrosis (CF) that is heterozygous for F508del mutation and a residual mutation for patients aged 6 to 11 years. CF is a life-limiting inherited disease that affects about 10,000 people 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.

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 therapy of tezacaftor/ivacaftor-FDC (Symkevi®) has been approved in the EU for patients aged 12 years and older with CF that have one of these gene mutations. If approved, this licence extension would mean that patients with these gene mutations could have access to this treatment regimen at an earlier age.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was unavailable to comment.

PROPOSED INDICATION

Cystic fibrosis (CF) heterozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and a residual function (RF) mutation (F/RF), patients aged 6 to 11 years.[2]

TECHNOLOGY

DESCRIPTION

The fixed-dose combination (FDC) of tezacaftor and ivacaftor (tezacaftor/ivacaftor-FDC) is in clinical development for cystic fibrosis (CF) heterozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and a residual function (RF) mutation (F/RF) in patients aged 6 to 11 years.[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 NCT03559062 the dosing regimen is not stated.[2] However, in the phase III extension study NCT03537651, patients weighing <40kg were administered the FDC tablets of tezacaftor 50mg and ivacaftor 75mg in the morning, followed by ivacaftor 75mg single tablet in the evening, and patients weighing ≥40kg were administered the FDC tablets of tezacaftor 100mg and ivacaftor 150mg in the morning, followed by ivacaftor 150mg single tablet in the evening.[4]

INNOVATION AND/OR ADVANTAGES

Ivacaftor monotherapy (Kalydeco®) has been authorised in the EU for patients aged 6 years and older weighing 25kg or more with CF heterozygous for F508del mutation and one of another number of listed mutations. Clinical trials of patients with CF with F/RF genotype aged 12 years and older have shown that treatment with tezacaftor–ivacaftor and ivacaftor alone resulted in significant benefits with respect to the primary end point, the absolute change in the percentage of predicted FEV1, as compared with placebo, but difference was significant in favour of tezacaftor-ivacaftor. The least-squares mean difference versus placebo from the baseline value to the average of the week 4 and week 8 measurements was 6.8 percentage points (95% confidence interval [CI], 5.7 to 7.8) for tezacaftor–ivacaftor and 4.7 percentage points (95% CI, 3.7 to 5.8) for ivacaftor alone (P<0.001 for both comparisons).[5]

The combination regimen of tezacaftor and ivacaftor (Symkevi®) has been authorised in the EU as it has been shown to be an effective at improving lung function for patients aged 12 years and older with CF heterozygous for F508del mutation and one of another number of listed mutations.[6] If

approved, this licence extension would mean that patients with CF heterozygous for F508del mutation and these listed mutations could have access to this treatment regimen at an earlier age.

It has not been possible to identify the R/F mutations included in the phase III trial NCT03559062, and so it is not known if the licence extension would include the same RF mutations as the current EU Marketing Authorisations for ivacaftor monotherapy (Kalydeco®) or tezacaftor and ivacaftor (Symkevi®).

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.[7] 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.[8]

The medicinal product Kalydeco® (150mg 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 25kg 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.[10]

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).[11]

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.[11]

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.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Cystic fibrosis (CF) is the most common, life-limiting recessively inherited disease in the UK.[11]
The latest annual report from the UK Cystic Fibrosis Registry shows that in 2017:[12]

- 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 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.[13]

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, nurses, physiotherapists, dietitians, pharmacists and clinical psychologists. Patients should have a comprehensive annual review, and routine reviews at regular intervals.[14]

Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease.[15]

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[15]

PLACE OF TECHNOLOGY

If approved, this licence extension for tezacaftor/ivacaftor-FDC will offer an additional treatment option for patients aged 6 to 11 years with CF with F/RF genotype, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03559062, EudraCT-2016-004479-35, VX16-661-115; homozygous for F508del mutation (F/F) or heterozygous for F508del mutation with an eligible residual function mutation (F/RF); tezacaftor–ivacaftor vs placebo or ivacaftor; phase III	NCT03537651, EudraCT-2017-002968-40, VX17-661-116; homozygous for F508del mutation (F/F) or heterozygous for F508del mutation with an eligible residual function mutation (F/RF); tezacaftor–ivacaftor; phase III extension
Sponsor	Vertex Pharmaceuticals Inc	Vertex Pharmaceuticals Inc
Status	Complete but unpublished	Ongoing
Source of Information	Trial registry[2], press release[1]	Trial registry[4]
Location	EU (incl UK) and Australia	EU (incl UK), USA, Canada and Australia
Design	Randomised, placebo-controlled	Single group assignment, open label
Participants	n=69; aged 6 to 11 years; cystic fibrosis; homozygous for F508del mutation (F/F) or heterozygous for F508del mutation with an eligible residual function mutation (F/RF); percent predicted forced expiratory volume in 1 second (ppFEV1) value ≥70% adjusted for age, sex and height; screening lung clearance index2.5 (LCI2.5) result ≥7.5; able to swallow tablets	Previously participated in parent studies NCT03559062 or NCT02953314
Schedule	Pts randomised 4:1 based on genotype: • F/F pts randomised to fixed dose combination (FDC) of tezacaftor-ivacaftor vs matching placebo (dosages not stated) • F/RF pts randomised to FDC of tezacaftor-ivacaftor vs ivacaftor and tezacaftor-matching placebo (dosages not stated)	Fixed dose combination (FDC): • Pts <40kg receive tezacaftor 50mg / ivacaftor 75mg tablets in the morning, ivacaftor 75mg tablet in the evening • Pts ≥40kg receive tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening
Follow-up	Active treatment for 8 wks, safety follow-up for 8 wks	Active treatment up to 96 wks, safety follow-up for up to 100 wks
Primary Outcomes	Absolute change in LCI2.5 [Time frame: from baseline at wk 8]	Safety and tolerability of long-term treatment based on adverse events (AEs) and serious adverse events (SAEs) [Time frame: from baseline through safety follow-up (up to 28 days after last dose at wk 96)]
Secondary Outcomes	• Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score [Time	Time frame: from baseline through 96 wks): • Absolute change in LCI2.5

	frame: from baseline through wk 8] • Safety and tolerability as measured by adverse events (AEs) and serious adverse events (SAEs) [Time frame: from baseline through safety follow-up (16 wks)]	• Absolute change in sweat chloride • Absolute change in CFQ-R respiratory domain score • Absolute change in body mass index (BMI)
Key Results	Pts treated with tezacaftor/ivacaftor experienced a mean within-group absolute improvement in LCI2.5 of -0.51 through 8 wks ($p < 0.0001$).	-
Adverse effects (AEs)	Safety data were similar to those observed in previous studies of tezacaftor/ivacaftor. The most common AEs (≥10%) among pts receiving tezacaftor/ivacaftor were cough, headache, and productive cough. No SAEs or AEs leading to treatment discontinuation or interruption were observed.	-
Expected reporting date	Study completion date reported as December 2018. Key data announced in press release February 2019.	Study completion date reported as December 2020.

ESTIMATED COST

The cost of the treatment regimen 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 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.[11]

REFERENCES

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