

**HEALTH TECHNOLOGY BRIEFING  
MARCH 2019**

**Tezacaftor/ivacaftor (fixed-dose combination) for cystic fibrosis homozygous for F508del mutation in patients aged 6 to 11 years**

<b>NIHRI ID</b>	24031	<b>NICE ID</b>	10025
<b>Developer/Company</b>	Vertex Pharmaceuticals Inc	<b>UKPS ID</b>	Not Available

<b>Licensing and market availability plans</b>	The company anticipate submitting an indication extension to the EMA in the second half of 2019. <sup>1</sup>
--	---

**SUMMARY**

The fixed-dose combination (FDC) tezacaftor/ivacaftor-FDC is in clinical development for cystic fibrosis (CF) that is homozygous for F508del 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 this gene mutation. If approved, this licence extension would mean that patients with this gene mutation 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) homozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/F), patients aged 6 to 11 years.<sup>2</sup>

## TECHNOLOGY

### DESCRIPTION

The fixed-dose combination (FDC) of tezacaftor and ivacaftor (tezacaftor/ivacaftor-FDC) is in clinical development for Cystic fibrosis (CF) homozygous for F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene (F/F) in patients aged 6 to 11 years.<sup>2</sup>

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.<sup>3</sup>

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.<sup>3</sup>

In the phase III clinical trial NCT03559062 the dosing regimen is not stated.<sup>2</sup> 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.<sup>4</sup>

### INNOVATION AND/OR ADVANTAGES

The combination regimen of lumacaftor and ivacaftor (Orkambi<sup>®</sup>) has been authorised in the EU for patients aged 6 years and older with CF with F/F genotype.<sup>5</sup> Compared to lumacaftor, tezacaftor has improved pharmacokinetic properties with fewer side effects and drug-drug interaction.<sup>6</sup> In clinical trials, combination therapy with tezacaftor/ivacaftor was comparable to lumacaftor/ivacaftor in terms of clinical efficacy outcomes, including the primary outcome forced expiratory volume in one second (FEV1), and was found to have fewer side effects (including transient bronchoconstriction).<sup>6,7</sup> 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.<sup>8</sup>

The combination regimen of tezacaftor and ivacaftor (Symkevi<sup>®</sup>) 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 with F/F genotype.<sup>9</sup> If approved, this licence extension would mean that patients with this genotype could have access to this treatment regimen at an earlier age.

## DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The medicinal product Symkevi® (100mg tezacaftor and 150mg ivacaftor) in a combination regimen with Kalydeco® (150mg ivacaftor) was granted Marketing Authorisation in the EU in November 2018 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.<sup>10</sup> Very common adverse effects (>10%) in patients treated with Symkevi in combination with ivacaftor include nasopharyngitis and headache.<sup>3</sup> 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.<sup>11</sup>

The medicinal product Kalydeco® (150mg ivacaftor) has been granted Marketing Authorisation in the EU for:<sup>12</sup>

- 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.<sup>13</sup>

## 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).<sup>14</sup>

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.<sup>14</sup>

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.<sup>14</sup>

## CLINICAL NEED AND BURDEN OF DISEASE

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

- 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 with a primary diagnosis of CF (ICD-10 code E84), resulting in 88,098 finished consultant episode (FCE) bed days.<sup>16</sup>

## 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.<sup>17</sup>

Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease.<sup>18</sup>

### 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<sup>18</sup>

The medicinal product Orkambi® (lumacaftor and ivacaftor combination regimen) has a Marketing Authorisation in the UK for the treatment of patients aged 6 years and older with CF with F/F genotype.<sup>5</sup> NICE has published a technology appraisal guidance that does not recommend this treatment for patients aged 12 years and older.<sup>19</sup> A technology appraisal guidance has been proposed by NICE for this treatment regimen in patients aged 2 to 11 years who have CF with F/F genotype.<sup>20</sup>

### 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/F genotype, who currently have few effective therapies available.

## CLINICAL TRIAL INFORMATION

<b>Trial</b>	<a href="#">NCT03559062</a> , 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	<a href="#">NCT03537651</a> , 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
<b>Sponsor</b>	Vertex Pharmaceuticals Inc	Vertex Pharmaceuticals Inc
<b>Status</b>	Complete but unpublished	Ongoing
<b>Source of Information</b>	Trial registry <sup>2</sup> , press release <sup>1</sup>	Trial registry <sup>4</sup>
<b>Location</b>	EU (incl UK) and Australia	EU (incl UK), USA, Canada and Australia
<b>Design</b>	Randomised, placebo-controlled	Single group assignment, open label
<b>Participants</b>	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 index <sub>2.5</sub> (LCI <sub>2.5</sub> ) result ≥7.5; able to swallow tablets	Previously participated in parent studies NCT03559062 or NCT02953314
<b>Schedule</b>	Pts randomised 4:1 based on genotype: <ul style="list-style-type: none"> <li>F/F pts randomised to fixed dose combination (FDC) of tezacaftor-ivacaftor vs matching placebo (dosages not stated)</li> <li>F/RF pts randomised to FDC of tezacaftor-ivacaftor vs ivacaftor and tezacaftor-matching placebo (dosages not stated)</li> </ul>	Fixed dose combination (FDC): <ul style="list-style-type: none"> <li>Pts &lt;40kg receive tezacaftor 50mg / ivacaftor 75mg tablets in the morning, ivacaftor 75mg tablet in the evening</li> <li>Pts ≥40kg receive tezacaftor 100mg / ivacaftor 150mg tablets in the morning, ivacaftor 150mg tablet in the evening</li> </ul>
<b>Follow-up</b>	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
<b>Primary Outcomes</b>	Absolute change in LCI <sub>2.5</sub> [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)]
<b>Secondary Outcomes</b>	<ul style="list-style-type: none"> <li>Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score [Time frame: from baseline through wk 8]</li> </ul>	Time frame: from baseline through 96 wks: <ul style="list-style-type: none"> <li>Absolute change in LCI<sub>2.5</sub></li> <li>Absolute change in sweat chloride</li> </ul>

	<ul style="list-style-type: none"> <li>Safety and tolerability as measured by adverse events (AEs) and serious adverse events (SAEs) [Time frame: from baseline through safety follow-up (16 wks)]</li> </ul>	<ul style="list-style-type: none"> <li>Absolute change in CFQ-R respiratory domain score</li> <li>Absolute change in body mass index (BMI)</li> </ul>
<b>Key Results</b>	Pts treated with tezacaftor/ivacaftor experienced a mean within-group absolute improvement in LCI2.5 of -0.51 through 8 wks (p < 0.0001).	-
<b>Adverse effects (AEs)</b>	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.	-
<b>Expected reporting date</b>	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. Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years homozygous for the F508del mutation (ID1486). Expected date of issue to be confirmed.
- 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.<sup>14</sup>

## REFERENCES

- 1 Vertex Pharmaceuticals Inc. *Positive Phase 3 Study for Tezacaftor/Ivacaftor Combination in Children Aged 6-11 Years with Cystic Fibrosis Supports European Medicines Agency Submission*. 14 February 2019. Available from: <https://investors.vrtx.com/news-releases/news-release-details/positive-phase-3-study-tezacaftorivacaftor-combination-children> [Accessed 20 March 2019].
- 2 ClinicalTrials.gov. *A Study to Evaluate Efficacy and Safety of TEZ/IVA in Subjects Aged 6 Through 11 Years With Cystic Fibrosis*. Trial ID: NCT03559062. Status: Completed. Available from: <https://www.clinicaltrials.gov/ct2/show/NCT03559062> [Accessed 20 March 2019].
- 3 Electronic Medicines Compendium. *Symkevi 100 mg/150 mg film coated tablets*. Available from: <https://www.medicines.org.uk/emc/product/9634/smpc> [Accessed 27 February 2019].
- 4 ClinicalTrials.gov. *A Study to Evaluate the Safety and Efficacy of Long-term Treatment With TEZ/IVA in CF Subjects With an F508del CFTR Mutation*. Trial ID: NCT03537651. Status: Active, not recruiting. Available from: <https://www.clinicaltrials.gov/ct2/show/study/NCT03537651> [Accessed 20 March 2019].
- 5 Electronic Medicines Compendium. *Orkambi 100 mg/125 mg film coated tablets*. Available from: <https://www.medicines.org.uk/emc/product/8952/smpc> [Accessed 6 March 2019].
- 6 Gentsch M, Mall MA. Ion Channel Modulators in Cystic Fibrosis. *Chest*. 2018;154(2):383-93. Available from: <http://www.sciencedirect.com/science/article/pii/S0012369218306640> <https://doi.org/10.1016/j.chest.2018.04.036>.
- 7 Taylor-Cousar JL, Munck A, McKone EF, van der Ent CK, Moeller A, Simard C, et al. Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del. *New England Journal of Medicine*. 2017;377(21):2013-23. Available from: <https://www.nejm.org/doi/full/10.1056/NEJMoa1709846> 10.1056/NEJMoa1709846.
- 8 Donaldson SH, Pilewski JM, Griese M, Cooke J, Viswanathan L, Tullis E, et al. Tezacaftor/Ivacaftor in Subjects with Cystic Fibrosis and F508del/F508del-CFTR or F508del/G551D-CFTR. *American Journal of Respiratory and Critical Care Medicine*. 2018;197(2):214-24. Available from: <https://www.atsjournals.org/doi/abs/10.1164/rccm.201704-0717OC> 10.1164/rccm.201704-0717OC.
- 9 European Medicines Agency (EMA). *Symkevi (tezacaftor / ivacaftor)*. Available from: [https://www.ema.europa.eu/en/documents/overview/symkevi-epar-medicine-overview\\_en.pdf](https://www.ema.europa.eu/en/documents/overview/symkevi-epar-medicine-overview_en.pdf) [Accessed 20 March 2019].
- 10 European Commission. *Union Register of medicinal products for human use*. Available from: <http://ec.europa.eu/health/documents/community-register/html/h1306.htm> [Accessed 27 February 2019].
- 11 European Medicines Agency (EMA). *EU/3/17/1828*. Available from: <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3171828> [Accessed 20 March 2019].
- 12 Electronic Medicines Compendium. *Kalydeco 150 mg film-coated tablets*. Available from: <https://www.medicines.org.uk/emc/product/3040/smpc> [Accessed 20 March 2019].
- 13 European Medicines Agency (EMA). *EU/3/08/556*. Available from: <https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu308556> [Accessed 20 March 2019].
- 14 Cystic Fibrosis Trust. *Standards for the clinical care of children and adults with cystic fibrosis in the UK*. 2011. Available from: [https://www.cysticfibrosis.org.uk/~/\\_/media/documents/the-](https://www.cysticfibrosis.org.uk/~/_/media/documents/the-)

- [work-we-do/care/consensus-docs-with-new-address/cystic-fibrosis-trust-standards-of-care.ashx?la=en](https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/care/consensus-docs-with-new-address/cystic-fibrosis-trust-standards-of-care.ashx?la=en).
- 15 UK Cystic Fibrosis Registry. *Cystic Fibrosis: Strength in Numbers. Annual Data Report 2017*. August 2018. Available from: <https://www.cysticfibrosis.org.uk/~media/documents/the-work-we-do/uk-cf-registry/2017-registry-annual-data-report-interactive.ashx?la=en>.
- 16 NHS Digital. *Hospital Admitted Patient Care Activity, 2017-18: Diagnosis*. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2017-18> [Downloaded 27 November 2018].
- 17 National Institute for Health and Care Excellence. *Cystic fibrosis: diagnosis and management (NG78)*. Last Update Date: October 2017. Available from: <https://www.nice.org.uk/guidance/ng78> [Accessed 27 February 2019].
- 18 National Institute for Health and Care Excellence. *Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation. Final scope*. May 2018. Available from: <https://www.nice.org.uk/guidance/gid-ta10277/documents/final-scope>.
- 19 National Institute for Health and Care Excellence. *Lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation (TA398)*. Last Update Date: July 2016. Available from: <https://www.nice.org.uk/guidance/ta398> [Accessed 27 February 2019].
- 20 National Institute for Health and Care Excellence. *Lumacaftor with ivacaftor for treating cystic fibrosis in children aged 2 to 11 years old homozygous for the F508del mutation. Draft scope (pre-referral)*. September 2018. Available from: <https://www.nice.org.uk/guidance/gid-ta10390/documents/draft-scope-pre-referral>.

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