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HEALTH TECHNOLOGY BRIEFING
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Lumacafor/ivacaftor (fixed-dose combination) for cystic fibrosis homozygous for F508del mutation in patients aged 12 to 23 months

NIHRIO ID	26527	**NICE ID**	10131
Developer/Company	Vertex Pharmaceuticals Inc	**UKPS ID**	Not Available

Licensing and market availability plans	The regulatory filing and marketing/launch plans of this drug combination for this population could not be established at the time of producing this briefing.

SUMMARY

The fixed-dose combination (FDC) lumacaftor/ivacaftor-FDC is in clinical development for cystic fibrosis (CF) that is homozygous for F508del mutation for patients aged 12 to 23 months. 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.

Lumacaftor 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 lumacaftor/ivacaftor-FDC may result in an effective therapeutic option for young children 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 - patients aged 12 to 23 months[1]

TECHNOLOGY

DESCRIPTION

Lumacaftor/ivacaftor-FDC (Orkambi®) is in clinical development for the treatment of CF homozygous for F508del mutation in CFTR gene in patients aged 12 to 23 months.[1] Lumacaftor is a CFTR corrector that acts directly on F508del-CFTR to improve its cellular processing and trafficking, thereby increasing the quantity of functional CFTR at the cell surface.[2]

Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface. The combined effect of lumacaftor and ivacaftor is increased quantity and function of F508del-CFTR at the cell surface, resulting in increased chloride ion transport. The exact mechanisms by which lumacaftor improves cellular processing and trafficking of F508del-CFTR and ivacaftor potentiates F508del-CFTR are not known.[2]

In the phase III clinical trial NCT03601637, patients receive lumacaftor/ivacaftor-FDC dependent upon weight at day 1. The dosing regimen is not reported.[1]

INNOVATION AND/OR ADVANTAGES

Lumacaftor/ivacaftor-FDC has been authorised in the EU for patients aged 2 years and older with CF who are homozygous for F508del mutation in the CFTR gene.[3] The benefits of this treatment include:[4]

- Improved lung function and lung ventilation in CF patients aged 6 years and older
- Reduction in the number of exacerbations requiring hospital admission or antibiotic therapy in patients aged 12 years and older
- Decrease in the amount of chloride in sweat in children aged 2 to 5 years
- Improvement in growth (body mass index, weight and height) in children aged 2 to 5 years

If licensed, patients with CF who are homozygous for F508del mutation in the CFTR gene could have access to this treatment regimen at an earlier age.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

The medicinal product lumacaftor/ivacaftor-FDC (Orkambi®) has been granted Marketing Authorisation in the EU:

- In tablet formulation for the treatment of patients with CF aged 6 years and older with CF who are homozygous for F508del mutation in the CFTR gene (100mg lumacaftor and 125mg ivacaftor, or 200mg lumacaftor and 125mg ivacaftor)[3]
- In granule formulation for the treatment of patients with CF aged 2 years and older with CF who are homozygous for F508del mutation in the CFTR gene (100mg lumacaftor and 125mg ivacaftor, or 150mg lumacaftor and 188mg ivacaftor)[2]

Very common adverse effects (≥10%) in patients treated with lumacaftor/ivacaftor-FDC include headache, nasal congestion, dyspnoea, productive cough, increased sputum, upper abdominal pain, diarrhoea and nausea.[2]

The medicinal product lumacaftor/ivacaftor-FDC was designated an orphan drug in the EU in August 2014, and this designation was withdrawn at the time of Marketing Authorisation upon request of the marketing authorisation holder.[5]

The medicinal product ivacaftor (150mg ivacaftor) has been granted Marketing Authorisation in the EU for:[6]

- the treatment of patients with 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 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.[7]

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).[8]

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.[8]

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.[8]

CLINICAL NEED AND BURDEN OF DISEASE

CF is the most common, life-limiting recessively inherited disease in the UK.[8]

The latest annual report from the UK Cystic Fibrosis Registry shows that in 2017:[9]

- 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

- 723 patients were aged 1 to 2 years (patients with height data recorded, newly diagnosed)
- 9,818 (99.3%) patients have been genotyped, of which 4,856 (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.[10]

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.[11]

Current treatments for cystic fibrosis manage the symptoms and complications rather than the cause of the disease.[12]

CURRENT TREATMENT OPTIONS

Treatments can be broadly classified as:[12]

- 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 has published a technology appraisal guidance for Orkambi® (lumacaftor/ivacaftor-FDC) that does not recommend this treatment for patients aged 12 years and older.[13] A technology appraisal guidance has been proposed by NICE for this treatment regimen in patients aged 2 to 11 years who have CF homozygous for the F508del mutation.[14] There is currently no published guidance for patients aged 2 years and under.

PLACE OF TECHNOLOGY

If licensed, lumacaftor/ivacaftor-FDC will offer an additional treatment option for patients aged 12 to 23 months with CF, homozygous for the F508del mutation, who currently have few effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	NCT03601637, **VX16-809-122; homozygous for F508del mutation (F/F); lumacaftor/ivacaftor FDC; phase III**
Sponsor	Vertex Pharmaceuticals Inc

Status	Ongoing
Source of Information	Trial registry[1]
Location	USA and Canada
Design	Non-randomised, open-label
Participants	n=40 (planned); aged 12 to 23 mths; cystic fibrosis; homozygous for F508del mutation (F/F)
Schedule	Pts receive lumacaftor/ivacaftor as FDC granules dependent upon weight at day 1
Follow-up	Active treatment period not reported, safety follow-up up to 10 days after the last dose for Part A, up to 2 wks after the last dose for Part B
Primary Outcomes	• Part A: area under the concentration versus time curve during a dosing interval (AUCtau) of lumacaftor and ivacaftor [Time Frame: from baseline through safety follow-up (up to 10 days after the last dose)] • Part B: 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 (up to 2 wks after the last dose)]
Secondary Outcomes	Part A: • Safety and tolerability as assessed by number of subjects with AEs and SAEs [Time Frame: from baseline through safety follow-up (up to 10 days after the last dose)] • Average observed pre-dose concentrations (Ctrough) of lumacaftor and ivacaftor metabolites [Time Frame: from baseline through safety follow-up (up to 10 days after the last dose)] Part B: • Absolute change in sweat chloride [Time Frame: from baseline at wk 24] • Average observed pre-dose concentration (Ctrough) of lumacaftor, ivacaftor, and their respective metabolites [Time Frame: from baseline through safety follow-up (up to 2 wks after the last dose)]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Sep 2020.

ESTIMATED COST

The cost of the treatment regimen lumacaftor/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). 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.[8]

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

1 ClinicalTrials.gov. *Safety and Pharmacokinetic Study of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age With Cystic Fibrosis, Homozygous for F508del. Trial ID: NCT03601637*. Status: Recruiting. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03601637 [Accessed 4 April 2019].

2 Electronic Medicines Compendium. *Orkambi 100 mg/125 mg and150 mg/188 mg granules in sachet*. Available from: https://www.medicines.org.uk/emc/product/9845/smpc [Accessed 4 April 2019].

3 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].

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5 European Medicines Agency (EMA). *EU/3/14/1333*. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3141333 [Accessed 4 April 2019].

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7 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].

8 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-work-we-do/care/consensus-docs-with-new-address/cystic-fibrosis-trust-standards-of-care.ashx?la=en.

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10 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].

11 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].

12 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.

13 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].

14 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.

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