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Lumacaftor and ivacaftor (Orkambi) for cystic fibrosis homozygous for the F508del mutation in patients aged 6-11 years

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LAY SUMMARY

Cystic fibrosis is an inherited disease that has severe effects on the lungs and the digestive system. It affects the cells that produce mucus and digestive juices. In cystic fibrosis, the secretions become thick and cause blockage within the tissues and organs (mostly within the lungs). Build-up of thick and sticky secretions in the lungs causes inflammation and long-term infection. In the gut, blockage of the tubes from the pancreas slows down the digestion of food and causes poor growth. People with cystic fibrosis are also at a higher risk of developing a number of related conditions such as diabetes, thin, weakened bones (osteoporosis) and liver problems, leading to a poor quality of life.

Lumacaftor and ivacaftor (Orkambi) is a medicine used to treat cystic fibrosis in patients aged 6 years and above who have a genetic mutation called the F508del mutation. This mutation affects the gene for a protein called cystic fibrosis transmembrane conductance regulator (CFTR) which is involved in regulating the production of mucus and digestive juices. Orkambi is used in patients who have inherited the mutation from both parents and therefore have the mutation in both copies of the CFTR gene. Orkambi is taken orally as tablets twice a day. It offers a new treatment option for patients with cystic fibrosis with the advantage of targeting the actual disease process rather than just the symptoms.

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TARGET GROUP

Cystic fibrosis in patients aged 6 to 11 years homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

TECHNOLOGY

DESCRIPTION

Lumacaftor with ivacaftor (Orkambi; lumacaftor/ivacaftor) is a fixed dose combination of two systemic protein modulators. Lumacaftor (VX809) is a cystic fibrosis transmembrane conductance regulator (CFTR) corrector and ivacaftor (VX770) is a CFTR potentiator. 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.[1] It is formulated as film coated tablets for oral route of administration.[2]

Lumacaftor/ivacaftor is indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene. Recently, lumacaftor/ivacaftor has been granted market authorisation for use in children with cystic fibrosis (CF) ages 6 through 11 who have two copies of the F508del mutation.[3]

Paediatric patients age 6 through 11 years should take two tablets (each containing lumacaftor 100 mg/ivacaftor 125 mg) orally every 12 hours.[3] Treatment duration is not reported. Very common adverse reactions identified from the 24-week, placebo-controlled phase III study in patients 6 to 11 years (NCT01897233) include nasopharyngitis, headache, dizziness, nasal congestion, dyspnoea, productive cough, sputum increased, (upper) abdominal pain, diarrhoea, nausea and bacteria in sputum.[1]

INNOVATION and/or ADVANTAGES

Lumacaftor/ivacaftor has been shown to improve lung function and lung ventilation in patients with cystic fibrosis aged 6 years and above due to combined actions of the two active substances. Whilst one of the active substances, lumacaftor, increases the number of CFTR protein on the cell surface, the other, ivacaftor, increases the activity of the defective CFTR protein. These actions make mucus and digestive juices less thick.[4]

DEVELOPER

Vertex Pharmaceuticals

PATIENT GROUP

BACKGROUND

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population and is considered an orphan disease.[5] Lack of properly functioning CFTR ion channel is responsible for the clinical sequelae of CF, including malabsorption of

nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 2,000 mutations in the CFTR gene, some of which, when present in one or both CFTR alleles, result in the clinical constellation that is CF.[6]

Symptoms of cystic fibrosis tend to start in early childhood, although they can sometimes develop very soon after birth, or may not be obvious until adulthood. Some of the main symptoms of cystic fibrosis can include:

- recurring chest infections
- difficulty putting on weight
- frequent, wet-sounding coughs
- diarrhoea
- occasional wheezing and shortness of breath.

People with the condition can also develop a number of related conditions, including diabetes, thin, weakened bones (osteoporosis), liver problems, and fertility problems, especially in men.[7, 8]

Cystic fibrosis is a progressive condition, which means it tends to get worse over time. Eventually the condition can be fatal if it leads to a serious infection or the lungs stop working properly.[7]

The outlook for cystic fibrosis has improved considerably in recent years because of advancements in treatment, although most people with cystic fibrosis will have a shorter-than-average life expectancy. Currently, about half of the people with cystic fibrosis will live past the age of 40. Children born with the condition nowadays are likely to live longer.[7]

CLINICAL NEED and BURDEN OF DISEASE

The incidence of CF varies between populations: the condition is considerably less common in Asian and African populations than in the white populations of Europe and North America, with variations within each country. The exact prevalence in Europe is unknown, but estimates range between 1 in 8,000 and 1 in 10,000 individuals.[5]

In the UK, cystic fibrosis is estimated to occur in around 1 in 2,500 live births with approximately 200 to 300 new diagnosis annually.[9] The latest UK Cystic Fibrosis Registry registers a total of 10,461 people living with cystic fibrosis in the UK in 2016, of which 247 were newly diagnosed.[10] Approximately 40% of this total are children under 16 years of age of which 20.6% correspond with the age bracket between 4 and 11 years.[10]

Median survival ages for people with one or two copies of F508del, diagnosed at birth, were 46 years for males and 41 for females. This represents around 95% of the UK CF population. For those with two copies of F508del (around 40-50% of that group), the median survival age for those who live to age 30 rises to 52 for men and 49 for females.[11]

The 2016/17 Hospital Episodes Statistics for England recorded 16,287 finished consultant episodes (FCE), 13,879 admissions and 5,435 days cases for cystic fibrosis (ICD-10 code: E.84).[12]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Tezacaftor and ivacaftor combination therapy for treating cystic fibrosis with the F508del mutation (GID-TA10277). 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 clinical guideline. Cystic fibrosis: diagnosis and management (NG78). October 2017.
- NICE quality standard in development. Cystic fibrosis (GID-QS10052). Publication anticipated May 2018.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Respiratory Services: Cystic Fibrosis Children. A01/S/b.

OTHER GUIDANCE

- Standard for the clinical care of children and adults with cystic fibrosis in the UK. Second ed. December 2011.[13]

CURRENT TREATMENT OPTIONS

There are currently no treatment options available that specifically target the F508del mutation. Current treatments for cystic fibrosis generally manage the complications rather than the cause of the disease.[14]

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) and lung transplantation.

NICE technology appraisal guidance 266 recommends mannitol dry powder for inhalation as an option for treating cystic fibrosis in adults who cannot use rhDNase because of ineligibility, intolerance or inadequate response to rhDNase and, whose lung function is rapidly declining (forced expiratory volume in 1 second decline greater than 2% annually) and for whom other osmotic agents are not considered appropriate.[14, 15]

EFFICACY and SAFETY

Trial	NCT01897233, **VX13-809-011; children aged 6-11 years homozygous for the F508del-CFTR mutation; lumacaftor/ivacaftor; phase III**
Sponsor	Vertex Pharmaceuticals Incorporated
Status	Completed
Source of Information	Trial registry,[16] publication[17]
Location	Canada and United States
Design	Open-label
Participants	n=(62); aged 6 to 11 years; diagnosis of CF defined as: with 2 CF-causing mutations, chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities, weight ≥15 kg, homozygous for the F508del-CFTR mutation.
Schedule	Part A Cohort 1: Participants aged 6 through 8 years will receive lumacaftor (LUM) 200 milligram (mg) in fixed-dose combination with ivacaftor (IVA) 250 mg orally every 12 hours (q12h) for 14 days. Part A Cohort 2: Participants aged 9 through 11 years will receive LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 14 days. Part B: Participants aged 6 through 11 years will receive LUM 200 mg in fixed-dose combination with IVA 250 mg orally q12h for 24 weeks.
Follow-up	Active treatment minimum of 14 days, maximum of 24 weeks.
Primary Outcomes	• Part A: Observed plasma concentration of LUM and IVA at hour 4 post-dose (C4h) on day 1 [Time Frame: 4 hours post-morning dose on day 1] • Part A: Observed plasma concentration of LUM and IVA at hour 4 post-dose (C4h) on day 14 [Time Frame: 4 hours post-morning dose on day 14] • Part A: Area under the plasma concentration-time curve from time 0 to end of dosing interval (AUCtau) of LUM and IVA [Time Frame: Day 14 (pre-morning dose, 4, 6, 12, and 24 hours post-morning dose for LUM; pre-morning dose, 2, 4, 6, 12 hours post-morning dose for IVA)] • Part B: Number of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Day 1 up to week 26]
Secondary Outcomes	• Part A: Observed plasma concentration of Lumacaftor Metabolite (M28-LUM) and Ivacaftor Metabolites (M1-IVA and M6-IVA) at hour 4 post-dose (C4h) on day 1 and 14 [Time Frame: Day 1, day 14] • Part A: Number of participants with treatment-emergent adverse events (AEs) and serious adverse events (SAEs) [Time Frame: Day 1 up to day 28] • Part B: Average absolute change from baseline in sweat chloride at day 15 and at week 4 [Time Frame: Baseline, day 15 and week 4] • Part B: Absolute change in sweat chloride from week 24 at week 26 [Time Frame: Week 24, week 26] • Part B: Absolute change from baseline in body mass index (BMI) at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute change from baseline in BMI-for-age Z-score at week 24 [Time Frame: Baseline, week 24]

	• Part B: Absolute change from baseline in weight at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute change from baseline in weight-for-age Z-score at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute Change from baseline in height at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute change from baseline in height-for-age Z-score at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute change from baseline in cystic fibrosis questionnaire-revised (CFQ-R) respiratory domain score at week 24 [Time Frame: Baseline, week 24] • Part B: Absolute change rrom baseline in treatment satisfaction questionnaire for medication (TSQM) domains at week 24 [Time Frame: Baseline, week 24] • Part B: Pre-dose concentration (Ctrough) and 3 to 6 hours post-dose doncentration (C3-6hr) of Lumacaftor, Lumacaftor Metabolite (M28-LUM), Ivacaftor and Ivacaftor Metabolites (M1-IVA and M6-IVA) [Time Frame: For Ctrough: pre-morning dose on week 4, week 6 and week 24; For C3-6hr: 3 to 6 hours post-morning dose on day 1, 15 and week 4]
Key Results	Lumacaftor/ivacaftor was well tolerated; the safety profile was generally similar to that observed in larger lumacaftor/ivacaftor trials with older patients. Four patients discontinued (two because of drug-related adverse events: elevated liver transaminases, n = 1; rash, n = 1). No safety concerns were associated with spirometry. No significant changes in percent predicted FEV_1 were observed (change from baseline at week 24, +2.5 percentage points; 95% confidence interval [CI], -0.2 to 5.2; P = 0.0671). At week 24, significant improvements from baseline were observed in sweat chloride (-24.8 mmol/L; 95% CI, -29.1 to -20.5; P < 0.0001), body mass index z score (+0.15; 95% CI, 0.08 to 0.22; P < 0.0001), Cystic Fibrosis Questionnaire-Revised respiratory domain score (+5.4; 95% CI, 1.4 to 9.4; P = 0.0085), and lung clearance index based on lung volume turnover required to reach 2.5% of starting N_2 concentration (-0.88; 95% CI, -1.40 to -0.37; P = 0.0018).
Adverse effects (AEs)	Reported above
Expected reporting date	-

ESTIMATED COST and IMPACT

COST

Lumacaftor/ivacaftor is already marketed in the UK for the treatment of cystic fibrosis in patients who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene; a packet of 112 tablets (200mg/125mg tablets) costs £8,000.00.[2]

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☐ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced use of secondary care/specialist services, reduced need for interventional procedures*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

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