NICE National Institute for Health and Care Excellence

NICE guidance

Ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor for treating cystic fibrosis

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces TA398.

1 Recommendations

1.1 Ivacaftor–tezacaftor–elexacaftor (IVA–TEZ–ELX) plus ivacaftor (IVA) alone is recommended within its marketing authorisation, as an option for treating cystic fibrosis in people 2 years and over who have at least 1 F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

1.2 Tezacaftor–ivacaftor (TEZ–IVA) plus IVA alone is recommended, within its marketing authorisation, for treating cystic fibrosis in people 6 years and over who have:

- 2 copies of the CFTR gene with F508del mutations, or
- a copy of the CFTR gene with an F508del mutation and a copy of the CFTR gene with 1 of the mutations listed in section 2.2.

1.3 Lumacaftor–ivacaftor (LUM–IVA) is recommended, within its marketing authorisation, for treating cystic fibrosis in people 1 year and over who have 2 copies of the CFTR gene with F508del mutations.

1.4 IVA–TEZ–ELX, TEZ–IVA and LUM–IVA are only recommended if the company provides them according to the commercial arrangement.

Why the committee made these recommendations

Cystic fibrosis causes a range of challenging symptoms that affect the lungs, digestive system and liver. People with cystic fibrosis have a shortened life expectancy and a greatly reduced quality of life. Usual treatment aims to manage the symptoms and includes several intensive treatments and physical therapies. Treatment is very physically demanding and time consuming for people with cystic fibrosis and their families and carers.

Clinical trial evidence shows that IVA–TEZ–ELX improves lung function, growth and weight gain and reduces the number of lung infections more than standard treatment. It is likely that these benefits last while people are having treatment.

Clinical trial evidence shows that TEZ–IVA and LUM–IVA also improve lung function, growth and weight gain and reduce the number of lung infections more than standard treatment. But the short- and long-term improvements are smaller than with IVA–TEZ–ELX.

When considering the condition's severity, and its effect on quality and length of life, the most likely cost-effectiveness estimates for IVA–TEZ–ELX, LUM–IVA and TEZ–IVA are within what NICE considers an acceptable use of NHS resources. So, they are recommended.

2 Information about ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor

Marketing authorisations

2.1 Ivacaftor–tezacaftor–elexacaftor (IVA–TEZ–ELX; Kaftrio, Vertex) is indicated 'in a combination regimen with ivacaftor for the treatment of cystic fibrosis (CF) in patients aged 2 years and older who have at least one F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene'.

2.2 Tezacaftor–ivacaftor (TEZ–IVA; Symkevi, Vertex) is indicated 'in a combination regimen with ivacaftor tablets for the treatment of patients with cystic fibrosis (CF) aged 6 years and older who are homozygous for the F508del mutation or who are heterozygous for the F508del mutation and have one of the following mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene: P67L, R117C, L206W, R352Q, A455E, D579G, 711+3A→G, S945L, S977F, R1070W, D1152H, 2789+5G→A, 3272-26A→G, and 3849+10kbC→T'.

2.3 Lumacaftor–ivacaftor (LUM–IVA; Orkambi, Vertex) is indicated 'for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene'.

Dosage in the marketing authorisation

2.4 IVA–TEZ–ELX is available as tablets or sachets. The dosage schedules are available in the following:

- summary of product characteristics (SPC) for IVA 37.5 mg, TEZ 25 mg and ELX 50 mg tablets

- SPC for IVA 75 mg, TEZ 50 mg and ELX 100 mg tablets
- SPC for IVA 60 mg, TEZ 40 mg and ELX 80 mg sachets
- SPC for IVA 75 mg, TEZ 50 mg and ELX 100 mg sachets.

2.5 The dosage schedule for TEZ–IVA is available in the following:

- SPC for TEZ 50 mg, IVA 75 mg tablets
- SPC for TEZ 100 mg, IVA 150 mg tablets.

2.6 LUM–IVA is available as tablets or sachets. The dosage schedules are available in the following:

- SPC for LUM 100 mg, IVA 125 mg tablets
- SPC for LUM 200 mg, IVA 125 mg tablets
- SPC for LUM 75 mg, IVA 94 mg sachets
- SPC for LUM 100 mg, IVA 125 mg sachets
- SPC for LUM 150 mg, IVA 188 mg sachets.

Price

2.7 The list price for IVA–TEZ–ELX tablets is £8,346.30 (excluding VAT; BNF online, accessed April 2024) per 56-tablet pack of:

- IVA 37.5 mg, TEZ 25 mg and ELX 50 mg, or
- IVA 75 mg, TEZ 50 mg and ELX 100 mg.

2.8 The list price for IVA–TEZ–ELX sachets is £8,346.30 (excluding VAT; dictionary of medicines and devices, accessed April 2024) per 28-sachet pack of:

- IVA 60 mg, TEZ 40 mg and ELX 80 mg, or
- IVA 75 mg, TEZ 50 mg and ELX 100 mg

2.9 The list price for TEZ–IVA is £6,293.91 (excluding VAT; BNF online, accessed April 2024) per 28-tablet pack of:

- TEZ 50 mg and IVA 75 mg, or
- TEZ 100 mg and IVA 150 mg.

2.10 The list price for LUM–IVA tablets is £8,000 (excluding VAT; BNF online, accessed April 2024) per 112-tablet pack of:

- LUM 100 mg and IVA 125 mg, or
- LUM 200 mg and IVA 125 mg.

2.11 The list price for LUM–IVA sachets is £8,000 (excluding VAT; dictionary of medicines and devices, accessed April 2024) per 56-sachet pack of:

- LUM 75 mg and IVA 94 mg, or
- LUM 100 mg and IVA 125 mg, or
- LUM 150 mg and IVA 188 mg.

2.12 The list price for IVA tablets is:

- £7,000 (excluding VAT; BNF online, accessed April 2024) per 28-tablet pack of:
  - IVA 75 mg, or
  - IVA 150 mg
- £14,000 (excluding VAT; BNF online, accessed April 2024) per 56-tablet pack of IVA 150 mg.

2.13 The list price for IVA sachets is:

- £7,000 (excluding VAT; BNF for children online, accessed April 2024) per 28-sachet pack of:
  - IVA 59.5 mg, or

  - IVA 75 mg

- £14,000 (excluding VAT; BNF for children online, accessed April 2024) per 56-sachet pack of:
  - IVA 25 mg, or
  - IVA 50 mg, or
  - IVA 75 mg.

2.14 The company has a commercial arrangement for IVA–TEZ–ELX in combination with IVA, TEZ–IVA in combination with IVA, and LUM–IVA. These make the treatments available to the NHS with a discount. The sizes of the discounts are commercial in confidence.

3 Committee discussion

The evaluation committee considered evidence from a number of sources. See the committee papers for full details of the evidence.

The condition

Cystic fibrosis

3.1 Cystic fibrosis is a genetic condition. It is usually caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene, called the F508del mutation. This causes the loss of phenylalanine at position 508 in the CFTR protein. There are about 9,500 people with cystic fibrosis in England and Wales, around 90% of whom have the F508del mutation. Impaired function of the CFTR protein affects salt and fluid transport. This causes a build-up of thick mucus in the lungs, the digestive system and the tubes that transport enzymes out of the pancreas. Before CFTR modulators were available, people with cystic fibrosis experienced a wide range of challenging symptoms affecting the whole body. Patient submissions explained how the build-up of thick mucus in the lungs leads to difficulty breathing, inflammation and severe infections that require hospitalisation for intravenous antibiotics. Bacteria can also colonise the lungs, leading to inflammation, tissue damage, repeated infections and permanent scarring. People with cystic fibrosis experience progressive lung function loss and are particularly vulnerable to antimicrobial resistance. Pancreatic enzyme supplements are needed to help digest food. Not taking these causes abdominal pain, bloating, excess wind, and difficulty gaining weight. Scarring of the pancreas can lead to cystic fibrosis-related diabetes. Cystic fibrosis significantly shortens people's lives, with a median age of death in 2021 of 38 years. Cystic fibrosis substantially impacts people's mental and emotional wellbeing and can have a large financial burden. Patient submissions also described the substantial impact on carers because of the chronic and severe nature of cystic fibrosis. Caring for someone with cystic fibrosis is physically demanding and involves daily activities such as manual physiotherapy, administration of medicines, sterilising medical equipment and facilitating hospital visits. Parents also described the difficulty of ensuring their children are a healthy weight and managing the high-

calorie diet needed. As well as being physically demanding, caring for someone with cystic fibrosis has a psychological and financial impact. Many carers experience anxiety, depression and fear about the future. Poor mental health can lead to physical health problems. Carers also report decreases in productivity, ability to work and job satisfaction. Because cystic fibrosis is a lifelong condition, carers can experience these effects over a long period of time. As well as the impact on the primary carer, there is an impact on the whole family including siblings and grandparents. Patient experts at the first committee meeting found it difficult and distressing to think back to a world before CFTR modulators, having experienced their transformative effects. One patient expert described the constant anxiety, depression and long-term pessimism of caring for a child with a terminal illness. Another patient expert described how life with cystic fibrosis was severely curtailed, and the considerable mental toll of living with the condition. The committee acknowledged the substantial difficulties faced by people with cystic fibrosis. It recognised that cystic fibrosis is a chronic and severe condition that affects the body across multiple organ systems, and can impact the mental wellbeing of people with the condition and their carers. It also acknowledged that cystic fibrosis is associated with considerable morbidity and can substantially shorten the lives of people with the condition.

Clinical management

Standard care without CFTR modulators

3.2 Clinical experts at the first committee meeting explained that cystic fibrosis is a multi-system condition. Standard care involves daily airway clearance, physiotherapy and nebulised mucolytics and antibiotics. There is also a daily need for pancreatic enzymes to help digestion. Complications such as liver disease and cystic fibrosis-related diabetes are common, and additional medicine is needed to manage these. Patient experts at the first committee meeting described the high treatment burden of standard care and how time-consuming adhering to it can be. They explained that airway clearance and exercise, as well as taking all the necessary medicine, takes around 2.5 hours per day. They added that there is also a need for vitamins and supplements to meet the high nutritional requirements. Despite the high treatment burden, it is not enough to

prevent exacerbations, and many people with cystic fibrosis are regularly admitted to hospital for intravenous antibiotics. The committee agreed that cystic fibrosis has a substantial treatment burden and there is a need for targeted and effective treatments.

CFTR modulators

3.3 In 2019, an agreement was reached between NHS England and Vertex to make lumacaftor–ivacaftor (LUM–IVA) and tezacaftor–ivacaftor (TEZ–IVA) available on the NHS while more evidence was collected. In 2020, the agreement was updated to include ivacaftor–tezacaftor–elexacaftor (IVA–TEZ–ELX). Based on 2021 data from the UK Cystic Fibrosis Registry (UKCFR), 72.6% of people with cystic fibrosis were taking a CFTR modulator and, of those, 72.1% were taking IVA–TEZ–ELX. The proportion taking IVA–TEZ–ELX had increased to 86% by December 2022. Patient submissions explained how the availability of CFTR modulators had changed the nature of cystic fibrosis from a progressive and life-limiting illness to a manageable chronic condition. They described extensive, meaningful benefits of these treatments, including:

- better physical health and mental wellbeing
- increased energy levels
- dramatically improved lung function and less coughing
- fewer medical interventions and less time in hospital
- less treatment burden because of more stable health
- more opportunities for education and employment, and
- the ability to plan for the future.

In addition, patient expert submissions explained how CFTR modulators have had hugely positive effects on carers as well as patients. Submissions from carers detailed the immense psychological benefits, now that their futures appear vastly different. Other submissions described the substantial improvement in family life. Patient experts at the committee meeting agreed,

and described how life had changed for them since CFTR modulators became available. They described the role IVA–TEZ–ELX has had in stabilising health and dramatically improving lung function. One patient expert described how they have felt like a different person since starting IVA–TEZ–ELX. They also described how they have reduced their use of other prescribed treatments for cystic fibrosis. This has resulted in a reduction of the troublesome side effects associated with those other treatments. The patient expert added that increased health stability has given them the ability to enjoy life and even to think about starting a family, which previously they did not consider an option.

Clinical effectiveness

Acute data

3.4 The external assessment group (EAG) did a systematic review to identify clinical evidence for CFTR modulators. The EAG identified 21 trials across a range of age groups and the following cystic fibrosis genotypes:

- the homozygous F508del (F/F) genotype, which has 2 copies of the CFTR gene with F508del mutations
- the minimal function (F/MF) genotype, which has 1 copy of the CFTR gene with an F508del mutation and 1 copy with a minimal function mutation
- the residual function (F/RF) genotype, which has 1 copy of the CFTR gene with an F508del mutation and 1 copy with residual CFTR protein activity
- the gating (F/Gating) genotype, which has 1 copy of the CFTR gene with an F508del mutation and 1 copy with a protein-channel gating mutation.

Commonly reported outcomes were:

- percent-predicted forced expiratory volume in 1 second (ppFEV1)
- number of pulmonary exacerbations (PEx), and

- measures of nutritional status, such as weight-for-age z scores.

When multiple treatments were available for a particular age group or genotype, but no direct data was available, the EAG used network meta-analysis to estimate treatment effects. Full details of the clinical trial evidence and network meta-analyses are provided in the committee papers. The committee concluded that there is a large and robust evidence base for the acute benefits of CFTR modulators. It noted that comparisons of CFTR modulators with standard care alone show modest effectiveness for LUM–IVA and TEZ–IVA and substantial effectiveness for IVA–TEZ–ELX.

Longer-term data

3.5 As part of the interim access agreement (see section 3.3), a data collection agreement was created between NHS England and NHS Improvement, NICE, UK Cystic Fibrosis Trust and Vertex. It aimed to collect longer-term data for CFTR modulators to help resolve key uncertainties in the evidence base. A key source of data was the UKCFR. It included data from all care centres and clinics in the UK, covering 99% of the UK cystic fibrosis population. Other sources of data included pharmacy home-delivery data, patient and carer quality-of-life studies, clinical trials and open-label extension studies.

Long-term rate of ppFEV1 decline with standard care

3.6 To inform the long-term rate of lung function (ppFEV1) decline for people with cystic fibrosis on standard care, the EAG used data from Szczesniak et al. (2023). This was a natural history cohort of 35,252 people aged 6 years and over included in the US Cystic Fibrosis Foundation Patient Registry (CFFPR). Data included in the study was from between 2003 and 2016, before CFTR modulators were widely available. The study provided curves for rate of change in ppFEV1 with age for people with the F/F genotype and the overall cystic fibrosis population. The study compared different methods to model ppFEV1 decline and concluded that the best fitting model was a non-linear stochastic mixed-effects model. This showed that the rate of decline decreased with age. The EAG applied

digitised values for the F/F population to the F/F, F/MF and F/Gating populations. For people with the F/RF genotype, the EAG applied digitised values for the overall cystic fibrosis population because this group has a slower rate of ppFEV1 decline. The company preferred to model the long-term decline in ppFEV1 based on Sawicki et al. (2022). This was a retrospective study of lung function decline across different age groups in people with CFTR modulator-untreated cystic fibrosis. The study used data from the US CFFPR from between 2006 and 2014. Separate linear rates of decline were reported for ages 6 years to 12 years, 13 years to 17 years, 18 years to 24 years, and 25 years and over. The study also reported separate rates according to genotype (F/RF compared with all remaining). After age 25, the same constant annual rate of decline was applied, equal to -1.06 for the F/RF genotype and -1.86 for all remaining genotypes. Clinical experts at the first committee meeting explained that the rate of decline in cystic fibrosis changes with age. Adolescents and females experience particularly high rates of decline, which slow over time. They added that there are also differences between countries, which are based on access to different treatments. Below a ppFEV1 of around 30%, people may have a lung transplant, which restores lung function if successful. But the decision to have a transplant is complex and does not depend on a ppFEV1 cut-off alone. The committee noted that the EAG and company's approaches were broadly in alignment until the age of 25 years. But the EAG's model predicted a slower rate of decline than the company's after the age of 25 years. The committee noted clinical expert testimony that the rate of ppFEV1 decline slows over time and concluded that a non-linear decline in ppFEV1 based on Szczesniak et al. (2023) was appropriate for decision making.

Long-term relative reduction in ppFEV1 decline with IVA–TEZ–ELX

3.7 The company preferred to assume no greater decline in lung function for people on IVA–TEZ–ELX than that seen in people without cystic fibrosis. That is, the long-term changes in ppFEV1 reflect only those related to age, sex and height, with no adjustment for cystic fibrosis or its treatment (a relative reduction in ppFEV1 decline of 100%). This was based on data from the open-label extension study of IVA–TEZ–ELX (study 445-105) and another study comparing this data with a control group who had not had treatment (Lee et al. 2023). The EAG

considered a range of data sources to inform the long-term relative reduction in ppFEV1 decline for IVA–TEZ–ELX. These included study 445-105 and the company's analysis of data collected in the UKCFR. But the EAG considered that all sources were at high risk of overestimating the treatment benefit for IVA–TEZ–ELX. This was because data was collected during the COVID-19 pandemic, when there was shielding and other pandemic precautions, which may have reduced the rate of respiratory infections that cause lung function decline. The studies did not include a control arm, so it was difficult to assess the impact of this. The EAG also cautioned that the acute treatment effect may not have been adequately removed. So, the EAG estimated the rate of lung function decline for IVA–TEZ–ELX based on a study by Newsome et al. (2022) that was done before the COVID-19 pandemic. The study used UKCFR data from 2008 to 2016 to estimate the treatment effect of IVA monotherapy compared with historical and current controls. The treatment effect from Newsome et al. (2022) was adjusted based on the acute treatment effect between IVA monotherapy and IVA–TEZ–ELX. It was then applied for a lifetime in the EAG base case. This predicted a long-term relative reduction in ppFEV1 decline for IVA–TEZ–ELX of 61%. Patient experts at the first committee meeting described how the benefits of IVA–TEZ–ELX treatment had been maintained over time. Clinical experts agreed, but they noted that there may be differences between how children and adults respond to treatment. For example, in some children, lung function returned to normal and remained normal for the duration of treatment. In adults, although CFTR modulators treat the underlying cause of cystic fibrosis, there may still be a decline in lung function over time because of existing lung damage. Considering the effects of the COVID-19 pandemic on longer-term data, patient experts at the first committee meeting explained that many people with cystic fibrosis had no choice but to continue to make essential journeys and go to work. They added that this would have lessened the impact of viral shielding. At the first meeting, the committee considered that COVID-19 infection may have worsened lung function decline but noted that no data on this was collected. The committee noted that neither the company nor the EAG had used data from the UKCFR in their base case. This data was specifically collected as part of the data collection agreement to inform this appraisal. The committee noted that the registry included about 2,000 people with cystic fibrosis in the UK, and so was a large and robust real-world dataset with high external validity. The relative reduction in ppFEV1 decline from the UKCFR is considered confidential by the company and cannot be reported here. The committee recognised that COVID-19

was likely to have contributed to some confounding, but it noted that there may have been some positive and some negative effects. So, the overall impact of COVID-19 on lung function decline is unknown. At the first meeting, the committee concluded that additional analyses investigating the effect of COVID-19 confounding would be helpful in exploring this uncertainty.

In response to the draft guidance consultation, the company submitted 2 new analyses to support the assumption of a relative reduction in ppFEV1 decline of 100%. These included an analysis of study 445-105 excluding data collected during the COVID-19 pandemic and an analysis of data from the US CFFPR comparing people having IVA–TEZ–ELX with a cohort who did not have treatment, over the same time period. At the second meeting, the committee noted several limitations of the company's new analyses including missing outcome data and no sensitivity analyses. The committee found it implausible to assume a relative reduction in ppFEV1 decline of 100% in the population covered by the marketing authorisation, because this implies that progression of cystic fibrosis will stop in all people having treatment. The committee noted that there are likely to be discontinuations and less than perfect adherence (see section 3.10). Also, adults with existing lung damage may continue to experience symptoms and a decline in lung function beyond that associated with age. This means the long-term relative reduction in ppFEV1 decline would be below 100% in the population covered by the marketing authorisation. At the second meeting, the committee still considered the UKCFR to be the most robust and generalisable data set. It also noted that the interim access agreement specified that this data set would be used to inform the appraisal. The committee recognised that ppFEV1 readings based on the UKCFR may have been underestimated because people took these readings at home. It also recognised the extensive comments received in response to the draft guidance consultation supporting a higher relative reduction in ppFEV1 decline than that from the UKCFR. The committee considered the available evidence from the UKCFR, US CFFPR and open-label extension studies, consultation comments on the draft guidance and the biological plausibility for the effect of IVA–TEZ–ELX on ppFEV1. The committee concluded that the long-term relative reduction in ppFEV1 decline with IVA–TEZ–ELX was likely to be greater than the estimate from the UKCFR but less than 100%.

Long-term relative reduction in ppFEV1 decline with TEZ–IVA and

LUM–IVA

3.8 The company estimated the long-term relative reduction in ppFEV1 decline for TEZ–IVA and LUM–IVA using data from open-label extension studies by Flume et al. (2021) and Konstan et al. (2017), respectively. It then did propensity score matching to compare these with historical US controls. This resulted in an estimated 61.5% reduction in ppFEV1 decline for TEZ–IVA and 42% reduction for LUM–IVA. The EAG considered that the company's analyses were at high risk of underestimating the rate of ppFEV1 decline for both treatments. This was because it is unlikely that all confounding will have been adjusted for. Additionally, as with IVA–TEZ–ELX, the EAG added that there may have been inadequate removal of the acute treatment effect. The EAG observed that the company only excluded data from the first 21 to 25 days of treatment. This was likely not long enough to exclude the acute treatment effect because lung function continues to improve after this point. The committee noted that data from the UKCFR was not available to inform long-term efficacy for TEZ–IVA and LUM–IVA. This was because most people on these treatments switched to IVA–TEZ–ELX once it became available. The EAG preferred to assume a relative reduction in long-term ppFEV1 decline for TEZ–IVA based on the ratio of acute treatment effect between TEZ–IVA and IVA–TEZ–ELX. The EAG also preferred to assume no reduction in the rate of long-term ppFEV1 decline for LUM–IVA. The committee disagreed with the EAG on the extent of the impact of confounding. It concluded that the comparison of data from the open-label extension studies with historical controls was more appropriate than making assumptions based on the ratio of acute treatment effect between IVA–TEZ–ELX and TEZ–IVA. The committee concluded that in the absence of registry data, the most appropriate source of data was the company's open-label extension studies. These estimated a 61.5% reduction in decline for TEZ–IVA and 42% reduction in decline for LUM–IVA. The committee noted these estimates may be optimistic because they may include some of the acute treatment effect. The company did not provide scenario analyses that extended the acute treatment-effect window up to week 24 in response to consultation. Without these scenario analyses, the committee concluded there is substantial uncertainty about the reduction in ppFEV1 decline for TEZ–IVA and LUM–IVA.

PEx treatment-effect duration

3.9 Data from the clinical trials show that people who have CFTR modulators have lower rates of PEx compared with people who have standard care. Because the rate of PEx is related to a person's ppFEV1 score, the company and the EAG both used calibration techniques to adjust the rate ratios to avoid double counting. The EAG applied the calibrated rate ratios for the acute trial duration only, because of uncertainty about the long-term benefit. The company preferred to apply rate ratios for a lifetime. The company noted that the open-label extension study for IVA–TEZ–ELX showed a 78% and 71% reduction in annualised PEx requiring antibiotics or leading to hospitalisation, respectively. Patient experts at the first committee meeting explained that since starting on IVA–TEZ–ELX, their rate of PEx has fallen substantially. One expert added that even if they do have an exacerbation, it can be easily treated with oral antibiotics rather than needing hospitalisation for intravenous antibiotics. Clinical experts at the first committee meeting explained that CFTR modulators have a beneficial effect on airway homeostasis, improve mucus clearance and reduce sputum production, all of which help to prevent infections. One clinical expert explained they had seen a large reduction in the need for intravenous antibiotics and hospitalisation in children having IVA–TEZ–ELX, which has been maintained over time. Another expert described how, in adults, reductions in hospitalisations that were seen during the COVID-19 pandemic have been maintained. They added that hospital wards that previously had a waiting list now have capacity and flexibility to accept patients at short notice. The committee concluded that CFTR modulators have a substantial impact on reducing PEx, leading to reductions in hospitalisations and intravenous antibiotics. The committee further concluded that it was reasonable to assume that this effect would be sustained while people remained on treatment.

Adherence to CFTR modulators

3.10 Adherence (referred to as 'compliance' in the committee papers) to CFTR modulator treatment during the acute period was based on the key clinical trials for each genotype and age group. The EAG assumed 100% adherence beyond the acute period for the lifetime of a person with cystic fibrosis in the model. The EAG explained that adherence only impacts costs in the model. So, assuming a

lower rate of adherence would reduce costs but would not account for differences in efficacy that result from lower adherence in the long term. The company preferred to assume a lower adherence rate after the acute period based on pharmacy home-delivery data collected for IVA–TEZ–ELX during the data collection agreement. The exact rate is considered confidential by the company and cannot be reported here. A patient expert at the first committee meeting doubted that adherence would ever be perfect. But they agreed that adherence would remain high because the effect of stopping treatment is quickly apparent. They added that they took IVA–TEZ–ELX more consistently than other prescribed medicines. Clinical experts explained that the dose of CFTR modulators is sometimes reduced if people experience side effects, but the aim is for people to have the highest possible dose. Clinical experts explained that wastage would be minimal in clinical practice because hospitals only order what people need. The committee noted that the reasons for missed doses were unclear but considered that these were likely to translate into cost savings for the NHS rather than medicines wastage. The committee considered that ideally, data on long-term adherence should come from the same source as long-term efficacy. But the committee concluded that the company's preferred rate of adherence from the data collection agreement was the most appropriate for estimating adherence to CFTR modulators.

Adherence to non-CFTR modulator treatments

3.11 Lung function and PEx can be affected by preventative non-CFTR modulator inhaled treatments. The EAG noted that the long-term rate of ppFEV1 decline and other clinical outcomes for people taking CFTR modulators may therefore be influenced by adherence to these other treatments. If adherence to non-CFTR modulators declines after treatment with CFTR modulators starts, it may lower the real-world effectiveness of the CFTR modulators compared with the effectiveness shown in clinical trials. Feedback received from patient groups acknowledged that, since CFTR modulators became available, the use of nebulised therapies, pancreatic enzymes and insulin had reduced in clinical practice. A patient expert at the first committee meeting also commented that they had been able to stop some existing treatments that had troublesome side effects. In response to consultation, a professional organisation presented data from the National Efficacy-Effectiveness CFTR Modulator Optimisation (NEEMO)

study. The data showed that ppFEV1 was reduced in people with low adherence to inhaled treatments after 2 years on IVA–TEZ–ELX. During the second committee meeting, the company noted that the NEEMO study was done in adults and did not include people under 18 years without established lung disease. One clinical expert added that it was not known whether people in the NEEMO study with low adherence to inhaled treatments also had low adherence to CFTR modulators. This may have biased the results. The clinical expert added that there is evidence from the 6-week SIMPLIFY study to suggest that lung function is maintained when stopping either hypertonic saline or dornase alfa, while continuing with airway clearance and IVA–TEZ–ELX as prescribed. The committee concluded that the effects of reduced use of non-CFTR modulator treatments on the longer-term efficacy of CFTR modulators is uncertain and more research into this is needed.

Economic model

EAG's critique of company's model

3.12 The EAG critiqued the company's submitted models. The EAG noted that the company had submitted 3 separate models, 1 for each CFTR modulator. So an incremental analysis was not possible. The EAG also noted that some aspects of the model were not aligned with NICE's reference case and some of the company's assumptions were inappropriate or lacked face validity. The company's models also did not include all the age groups covered by licence extensions. So, the EAG developed its own model that could address these issues. Its model largely followed the structure of the company's models, the model used in the previous technology appraisal of LUM–IVA (NICE technology appraisal guidance on lumacaftor–ivacaftor for treating cystic fibrosis homozygous for the F508del mutation [from here, TA398]) and other published models in cystic fibrosis.

EAG's model structure

3.13 The EAG model was an individual patient simulation model. It predicted survival

using a Cox proportional hazards model developed by Liou et al. (2001), which was based on 9 individual characteristics. They were:

- age
- sex
- weight-for-age z score
- ppFEV1
- PEx
- Staphylococcus aureus infection
- Burkholderia cepacia infection
- pancreatic sufficiency status, and
- cystic fibrosis-related diabetes status.

Age, ppFEV1, PEx, weight-for-age z score and cystic fibrosis-related diabetes status were updated in each model cycle. The remaining characteristics (sex, pancreatic sufficiency status and baseline infections) were assumed to remain the same. The treatment effect of CFTR modulators was captured in the model through changes in people's weight-for-age z score, ppFEV1 and PEx. Clinical and patient experts at the first committee meeting commented on the clinical validity of the model. A patient expert added that pseudomonas infection is also an important predictor of mortality, and considered it unclear why this was not included in the published model by Liou et al. The patient expert also noted that there may be additional benefits of treatment in reducing bacterial colonisation, which had not been captured. Clinical experts explained that, as well as CFTR modulator treatment having an impact on lung function, there has been some pancreatic recovery in children. They added that CFTR modulators may also improve glycaemic control and cystic fibrosis-related diabetes. The committee concluded that the EAG's model structure was largely appropriate, but there were likely to be some uncaptured benefits (see section 3.24).

Implementation of the EAG's model

3.14 Before the first committee meeting, the company identified some technical errors in the EAG's model. In addition, the company highlighted the overall complexity of the equations and programming. The company preferred its original submission model to be used because it had been quality-control checked, peer-reviewed and published. The EAG subsequently corrected the technical errors identified. The EAG noted that the incorporation of model fixes did not have a substantial impact on any of the incremental cost-effectiveness ratios (ICERs). The EAG also explained that it had completed an additional quality assurance step. It implemented the company's preferred assumptions for IVA–TEZ–ELX in the EAG's model and compared results with the company's original submitted model in ages 6 years and over, using list prices. The resulting ICERs were broadly comparable, providing evidence of reliability of the EAG model. In response to the draft guidance consultation, the company adopted an updated version of the EAG's model. The committee concluded that the EAG's updated model was suitable for decision making.

Annual discount rates

3.15 The EAG's model used annual discount rates of 3.5% for costs and quality-adjusted life years (QALYs) in line with the NICE reference case. Initially, the company argued that differential discount rates of 1.5% for QALYs and 3.5% for costs should be used. At the first meeting the committee agreed that the EAG had followed the NICE health technology evaluations manual (2022), which states costs and health effects should be discounted at the same rate of 3.5% per year for the reference case. But it noted that the NICE manual states that the committee may consider analyses using a non-reference case annual discount rate of 1.5% for both costs and QALYs if all the following criteria are met:

- the technology is for people who would otherwise die or have a very severely impaired life
- it is likely to restore them to full or near-full health
- the benefits are likely to be sustained over a very long period.

The committee discussed whether IVA–TEZ–ELX would fulfil these criteria. It was aware that, when considering analyses using a 1.5% discount rate, it must be confident that there is a highly plausible case for the maintenance of benefits. It also noted the health technology evaluation manual's requirement that the committee must be satisfied that any irrecoverable costs associated with the technology have been appropriately captured in the economic model or mitigated through commercial arrangements. The committee agreed that people with cystic fibrosis have a severely impaired quality of life and the benefits of treatment are likely to be sustained over a long period. But the committee noted that treatment with IVA–TEZ–ELX does not restore people with cystic fibrosis to full health, but rather prevents decline. Patient experts at the first committee meeting explained that IVA–TEZ–ELX may prevent decline beyond that associated with age, if started early enough in young children before lung damage occurs.

In response to the draft guidance consultation, the company revised its base case to apply the same 1.5% discount rate to costs and QALYs. It provided data from the US CFFPR and UKCFR showing that median predicted survival had increased since IVA–TEZ–ELX became available. The company also provided evidence from a study that used the company's original submission model to predict survival for people starting treatment with IVA–TEZ–ELX at 12 to 17 years and 18 to 24 years (Lopez et al. 2023). Predicted survival was 82.5 years and 77.9 years, respectively. The company argued that starting treatment before lung damage occurs preserves lung function, leading to prolonged clinical benefits and a near-normal life expectancy. The EAG maintained its base-case discount rate of 3.5% for costs and QALYs. After the second committee meeting, it was noted that the discount rate had only a small impact on cost-effectiveness results when the committee's preferred assumptions were implemented in the model (see section 3.22 and section 3.23).

Utility values

Health-state utility values

3.16 The EAG's preferred health-state utility values were based on EQ-5D-3L data from the LUM–IVA trials (TRAFFIC and TRANSPORT), as presented in TA398. The company argued that EQ-5D is not sensitive to meaningful differences in lung function in people with cystic fibrosis. It explained this was because people who have had cystic fibrosis since birth score highly, leading to ceiling effects when there are improvements in health. The company preferred to use health-state utility values based on the disease-specific Cystic Fibrosis Questionnaire-Revised (CFQ-R) utility measure. CFQ-R data was collected as part of the data collection agreement from the TRAJECTORY study and scored using the CFQ-R-8D algorithm. Both the company and EAG presented a scenario using EQ-5D data based on Acaster et al. (2015), which was presented as an alternative source in TA398. Patient experts at the committee meeting described the huge beneficial impact that treatment with IVA–TEZ–ELX has had on physical and mental health and wellbeing. A patient expert explained how the benefits of treatment did not solely affect lung function, and the ability to sleep better and do more exercise impacts the whole body. The patient expert was asked which utility values were most appropriate. They explained that the Acaster et al. (2015) values were most appropriate, because it was the only source that reflected the large difference in utility between the best and worst health states. The committee noted that the data collection agreement specified that NICE should use EQ-5D and the CFQ-R with appropriate mapping to generate utility as inputs for the cost-effectiveness model. The committee would have liked to have seen utilities mapped from CFQ-R to EQ-5D but this had not been provided by the company. In the absence of mapped utilities, the committee considered the 3 available sources. The committee noted that the EAG's base-case utility values from the LUM–IVA clinical trials had smaller differences in utility between ppFEV1 health states than Acaster et al. (2015). They therefore did not align with patient expert testimony. The committee also disagreed with the company that EQ-5D was not sensitive to changes in health-related quality of life, because the Acaster et al. (2015) values (based on EQ-5D) showed the largest differences between best and worst health states. The committee noted that the NICE health technology evaluations manual (2022) states EQ-5D is the preferred method to measure health-related quality of life. Other methods should only be used if EQ-5D is inappropriate. The committee

concluded that, of the values presented, the Acaster et al. (2015) utilities based on EQ-5D best reflected patient experience and should be used for decision making.

Treatment-specific utility benefit

3.17 The EAG's health-state utility values were based on ppFEV1 status with additional decrements applied for PEx. A treatment-specific utility increment was not applied. The EAG considered that the impact of treatment was already captured in the model through changes in ppFEV1 status and PEx. The company argued that applying utilities based only on ppFEV1 and PEx fails to capture additional non-respiratory benefits of treatments. The company's analysis of TRAJECTORY data resulted in a treatment-specific utility benefit for IVA–TEZ–ELX for all genotypes, and for TEZ–IVA for the F/RF genotype only (treatment-specific utility values are considered confidential by the company and cannot be reported here). The company jointly estimated health-state and treatment-specific utility values in a single regression model. They argued that because the treatment variable was statistically significant, it captures health-related quality-of-life benefits above that attributable to lung function alone.

In response to the draft guidance consultation, the company agreed with the committee's preference to use health-state utility values based on Acaster et al. (2015). But the company argued that a treatment-specific utility benefit should still apply. The company presented data from TRAJECTORY that compared CFQ-R-8D utility values at baseline and after starting treatment with IVA–TEZ–ELX. Results of the company's analysis showed increases in CFQ-R-8D utility scores when remaining within the same ppFEV1 grouping (the exact utility values are considered confidential by the company and cannot be reported here). The company also provided results of a mixed model repeated measures (MMRM) analysis, to predict the impact of starting IVA–TEZ–ELX on CFQ-R-8D utility scores, adjusted for ppFEV1 category. During the second committee meeting, clinical experts emphasised the multi-system nature of cystic fibrosis. They added that improving lung function is not the only important goal of treatment. Quality of life can be improved through reducing tiredness and fatigue and avoiding supplemental nutrition. The patient expert agreed that the benefits of treatment go far beyond changes in lung function alone. Improvements in chronic

pancreatitis, a reduced need for nutritional support, increased energy, being able to participate in normal activities, reduced liver disease and reduced cystic fibrosis-related diabetes all have a huge impact on quality of life for people with cystic fibrosis. The patient expert explained that even people who have started treatment and not experienced an improvement in lung function report substantial improvements in their quality of life. Clinical experts agreed it was plausible that someone on treatment with IVA–TEZ–ELX may have a better quality of life than someone on standard care, even if their lung function was worse. The committee considered that the company's approach was inconsistent because it applied a treatment-specific utility benefit based on CFQ-R data from TRAJECTORY to health-state utility values based on EQ-5D from Acaster et al. (2015). It noted that the company's MMRM analysis was not based on data from a randomised controlled trial but instead compared utilities for people having IVA–TEZ–ELX to baseline values, so there was a high risk of bias. It recalled that its preferred health-state utility values based on Acaster et al. (2015) were the most favourable because they showed the largest differences between best and worst health states. It also recalled that the Acaster et al. (2015) utility values were preferred by the patient expert attending the first committee meeting (see section 3.16). The committee considered that the Acaster et al. (2015) utility values should already capture the impact of treatment on ppFEV1 and any other aspects of cystic fibrosis that are correlated with ppFEV1. So, including a treatment-specific benefit in addition to using Acaster et al. (2015) utilities may be double counting. The committee concluded that the company's approach to estimating and applying a treatment-specific utility value was not appropriate. But the committee acknowledged the responses to the draft guidance consultation from people with cystic fibrosis, carers and healthcare professionals, and the testimonies of the patient and clinical experts at the second committee meeting. It agreed with concerns that the economic model did not capture all of benefits of treatment with IVA–TEZ–ELX (see section 3.13 and section 3.24). The committee considered that the uncaptured benefits were likely to have a substantial impact on the quality of life of people with cystic fibrosis. In the absence of a model that captures these benefits, the committee concluded that the company's treatment-specific utility benefit should apply despite the limitations.

Carer utility benefit

3.18 At the first committee meeting, the company preferred to include a carer utility benefit based on the MAGNIFY study. MAGNIFY collected data from 25 carers of children aged 6 to 11 years having IVA–TEZ–ELX in the UK. Data was collected using the Care-related Quality of Life instrument. Utility at baseline was 0.85 compared with 0.88 at interim analysis. So the company applied a utility increment of 0.03 for carers of children aged 6 to 11 years to the IVA–TEZ–ELX arm. The EAG did not include a carer utility benefit in the model because it considered that the evidence supporting this was uncertain. Patient experts at the first committee meeting described the substantial impact cystic fibrosis had on carers before CFTR modulators were available (see section 3.1 and section 3.2). Patient submissions described the huge daily burden of providing physiotherapy and help with medicine administration, as well as the impact on mental health and wellbeing. Patient submissions also noted the financial impact of caring for someone with cystic fibrosis, with many carers having to leave their jobs. Patient submissions highlighted the impact of CFTR modulators on carer quality of life, citing improvements in mental and physical health and the ability to return to work. Patient experts at the committee meeting described the high levels of anxiety, depression and fear about the future experienced by carers. They explained that the care burden does not stop after childhood because the condition worsens over time. A patient expert added that people who have had a transplant also need substantial social support. Patient experts described how IVA–TEZ–ELX has stabilised the health of people with cystic fibrosis, leading to vast improvements in carer quality of life.

In response to the draft guidance consultation, the company revised its base case for the ages at which the carer utility increment of 0.03 from MAGNIFY applies. Instead of applying the utility increment to carers of children aged 6 to 11 years having IVA–TEZ–ELX, in line with the data, the company applied the utility increment for a lifetime; that is, without an upper age limit. Consultation responses from people with cystic fibrosis, their carers and clinical experts described the large impact of caring for someone with cystic fibrosis, which continues into adolescence and adulthood. The committee considered that as people with cystic fibrosis get older, they may be able to take on more responsibility for managing their own condition. But the committee acknowledged that cystic fibrosis progresses over time, complications increase with age and

people over 11 are still likely to need considerable support. The committee disagreed with the methods used to incorporate carer utility impact in the model. This was because the company preferred to apply a utility increment to the IVA–TEZ–ELX arm rather than applying a utility decrement to the standard care arm. So, the carer utility benefit continued over the patient's entire lifetime, beyond the carer's life expectancy and the life expectancy of someone with cystic fibrosis on standard care. The committee agreed that it would have been more appropriate to apply a utility decrement to the standard care arm, to better reflect the carer burden. The committee noted evidence for a carer utility benefit was only presented for carers of children aged 6 to 11 years. But it noted responses to the draft guidance consultation supporting a carer benefit beyond the age of 11. The committee concluded that the company's preferred approach of applying a carer benefit for carers of people on IVA–TEZ–ELX for a lifetime in the model likely overestimated the utility benefit. But it agreed that the carer benefit would likely continue beyond age 11. The committee concluded it would be more appropriate to apply a carer utility decrement to the standard care arm in the model. In the absence of this functionality in the model, the committee accepted applying a carer utility benefit for carers of people with cystic fibrosis from the start of IVA–TEZ–ELX treatment to age 18. The committee considered any impact past the age of 18 years to currently be an uncaptured benefit in the model (see section 3.24).

Costs

Disease-management costs

3.19 As discussed in section 3.1 and section 3.2, managing cystic fibrosis is intensive. It involves physical therapy and a broad range of prescribed oral and inhaled treatments. Because cystic fibrosis affects the whole body, a multidisciplinary team is involved. The EAG included non-CFTR modulator medicine costs and healthcare costs as separate disease-management cost categories in the model. For medicine costs, the EAG used UKCFR data to inform the proportion of people taking the most common cystic fibrosis medicines, split by ppFEV1 status (Granger et al. 2022). For healthcare costs, the EAG used a resource-use questionnaire that was part of a trial to assess adherence to inhaled medicines

(Tappenden et al. 2023). Initially, the company preferred to use a retrospective chart review of people with cystic fibrosis aged 6 years and over across 8 specialist cystic fibrosis centres in the UK (Ramagopalan et al. 2014). This provided aggregated medicines and healthcare costs. Reductions in medicine costs for people prescribed CFTR modulators was based on Simmonds et al. (2022). Costs for PEx were included separately in both the EAG's and company's base cases. The EAG commented that although clarification on the company's methods to derive disease-management costs had been sought, some aspects of the company's approach still lacked clarity. In addition, the Ramagopalan et al. (2014) cost estimates were only available in poster and abstract form, with limited detail available. At the first meeting, the committee considered that the EAG's disease-management costs were more transparent and because they were from a more recent source, they better reflected current clinical practice. The committee was cautious to accept a poster as evidence, without additional information, because there is no peer review or detailed scrutiny. The committee concluded that the EAG's disease-management costs, based on Granger et al. (2022) and Tappenden et al. (2023), should be used. The committee further noted that CFTR modulators may allow people to reduce other prescribed medicines that form part of standard care, leading to cost savings to the NHS. In response to the draft guidance consultation, the company argued that the EAG's approach for including disease-management costs lacked face validity. This was because it assumed that the drug costs, health-state costs and costs for managing a PEx episode for people in the CFTR modulator arm were the same as for people in the standard care arm. The company also argued that the modelled health-state costs should better reflect the different severities of disease according to ppFEV1.

In response to the draft guidance consultation, people with cystic fibrosis, carers and healthcare professionals explained that CFTR modulators generate substantial cost savings for the NHS. They explained that this is because of a reduced need for prescribed medicines such as pancreatic enzyme replacement therapy, oral nutritional supplements and insulin. They added that healthcare costs are also reduced because of reduced hospitalisations for treatment of PEx, fewer central lines and fewer lung transplants. In response to the draft guidance consultation, the company accepted the committee's preference at the first committee meeting to use the EAG's preferred costs but made several amendments. They included:

- assuming a 70% reduction in prescribed medicines and health-state costs for CFTR modulators compared with standard care, based on studies of IVA
- applying a 50% reduction in the cost for treating a PEx episode for CFTR modulators compared with standard care, based on UKCFR and Simmonds et al. (2022)
- stratifying health-state costs from Tappenden et al. (2023) based on disease severity
- assuming a reduction of 81% for drug costs between the most and least severe health states, based on Ramagopalan et al. (2014).

The EAG considered that the changes made by the company overestimate the reduction in costs based on the evidence available. The EAG noted that the company's estimated reduction in prescribed medicines and health-state costs of 70% for CFTR modulators may be an overestimate. This is because it includes the impact of reduced hospitalisations and IV antibiotics, through reduced PEx, which are already captured by the model. But the EAG acknowledged that CFTR modulator treatment would likely lead to cost savings. So, the EAG provided alternative scenarios in which prescribed medicine and health-state costs were reduced by 23% and 40% based on Granger et al. (2022). The EAG also noted that UKCFR data may be confounded because of the COVID-19 pandemic. But it acknowledged that people having CFTR modulators may have less need for IV antibiotics to treat a PEx event and provided a scenario applying a 50% reduction in the cost of treating a PEx. The EAG highlighted that the company's approach of stratifying costs by disease severity and reducing prescribed medicine costs for the least severe health state may not have fully removed PEx costs and so may be double counting. The EAG also noted that healthcare professional visits in Ramagopalan et al. (2014) were similar across severity groups, in line with Tappenden et al. (2023). At the second committee meeting, the committee agreed that there were likely to be reductions in prescribed medicines and healthcare resource use for people on CFTR modulators. The committee noted comments from healthcare professionals who cautioned that the reduced adherence to inhaled therapies after starting treatment with IVA–TEZ–ELX may reduce long-term efficacy. But the committee noted that even if inhaled therapies were continued, there would likely be substantial

cost savings elsewhere, such as through reduced nutritional support. So, the committee agreed that cost savings through reduced use of prescribed medicines and healthcare resources should be included in the model. The committee considered the different approaches available for modelling the reduction in costs and acknowledged the limited data available at the time of this appraisal. It concluded that the EAG's scenario assuming a 40% reduction in prescribed medicines and healthcare costs for people on CFTR modulators was most appropriate and best aligned with the available evidence and testimony. The committee also acknowledged feedback from people with cystic fibrosis and clinical experts, who agreed that, since starting IVA–TEZ–ELX, PEx have become easier to treat with oral antibiotics and are now resolved more quickly. So, the committee concluded it was appropriate to assume a 50% reduction in PEx costs for people on CFTR modulators.

Severity

3.20 The committee considered the severity of cystic fibrosis (the future health lost by people living with cystic fibrosis who are having standard care in the NHS). The committee can apply a greater weight to QALYs (a severity modifier) if technologies are indicated for conditions with a high degree of severity. Absolute and proportional QALY shortfall estimates were calculated in line with the NICE health technology evaluations manual (2022). The calculation for both the company's preferred assumptions and the committee's preferred assumptions after the first meeting resulted in a 1.2 severity weighting for the F/F, F/MF and F/Gating genotypes and a 1.0 severity weighting for the F/RF genotype. The company argued that despite the calculated severity weightings, cystic fibrosis should qualify for the highest weighting of 1.7. In its critique of the company's draft guidance response, the EAG noted that the severity modifier is based on a pre-determined calculation estimated from the inputs of the economic model and not on a subjective judgement of disease severity. Patient experts at the second meeting described how cystic fibrosis is a debilitating and chronic condition affecting people from birth. So, for people with cystic fibrosis, severity starts from the very beginning of life, unlike for other conditions that have a later onset. The committee acknowledged the chronic and severe nature of cystic fibrosis

and the considerable impact on morbidity and mortality for people on standard care. It agreed that appropriate inputs had been used in the QALY shortfall calculation, and that the severity of cystic fibrosis was reflected by the calculated modifier of 1.2. It concluded that the severity modifier should be applied to the population covered by the marketing authorisations, and the 1.2 severity modifier should apply to all genotypes.

Ivacaftor as a comparator

3.21 In response to the draft guidance consultation, the company explained that IVA should be included as a comparator in the F/Gating population, despite it not being included in the final NICE scope. The company explained that people with an F508del mutation may be eligible for IVA if they also have a gating or R117H mutation. During the second committee meeting, clinical experts explained that ivacaftor may be used in specific groups of people, although many have now switched to IVA–TEZ–ELX. The NHS commissioning expert added that ivacaftor is routinely commissioned. The committee concluded that ivacaftor should be included as a comparator in the economic model in line with its marketing authorisation.

Cost-effectiveness estimates

Committee's preferred assumptions

3.22 The committee's preferred assumptions include:

- long-term relative reduction in ppFEV1 decline with standard care using a non-linear decline based on Szczesniak et al. (2023)
- long-term relative reduction in ppFEV1 decline with IVA–TEZ–ELX greater than the estimate from the UKCFR but less than 100%
- long-term relative reduction in ppFEV1 decline with TEZ–IVA of 61.5% based on the Flume et al. (2021) open-label extension study

- long-term relative reduction in ppFEV1 decline with LUM–IVA of 42% based on the Konstan et al. (2017) open-label extension study
- applying the treatment effect of CFTR modulators on PEx for a person's lifetime
- applying a rate of adherence based on pharmacy home-delivery data from the data collection agreement for CFTR modulators
- health-state utility values based on EQ-5D from Acaster et al. (2015)
- a treatment-specific utility benefit applied for IVA–TEZ–ELX in all genotypes, and for TEZ–IVA in the F/RF genotype only
- a carer utility benefit applied for carers of children on IVA–TEZ–ELX from treatment initiation to 18 years of age
- reduced disease-management costs for people on CFTR modulators, including a 40% reduction in standard care medicines and healthcare costs based on Granger et al. (2022) and a 50% reduction in PEx costs based on the UKCFR and Simmonds et al. (2022).

Cost-effectiveness results

3.23 After the committee meeting, ICERs were generated using the committee's preferred assumptions (see section 3.22) and including all commercial arrangements for IVA–TEZ–ELX, TEZ–IVA and LUM–IVA. Because of confidential discounts for CFTR modulators included in the model, the exact cost-effectiveness results are commercial in confidence and cannot be reported here. The committee's preferred base-case deterministic ICERs for IVA–TEZ–ELX, LUM–IVA and TEZ–IVA were all within the range that NICE considers an acceptable use of NHS resources, when accounting for uncaptured benefits (see section 3.24 and section 3.25).

Uncaptured benefits

3.24 In response to the draft guidance consultation, stakeholders considered that there were many important benefits and cost savings resulting from the use of CFTR modulators that had not been captured in the cost-effectiveness analysis, such as:

- pancreatic recovery and the ability to stop or reduce pancreatic enzyme replacement therapy
- improved glycaemic control and reductions in cystic fibrosis-related diabetes
- reduced liver disease, liver failure and liver transplants
- improved abdominal symptoms, and bowel and bladder control
- reduced sinus inflammation
- reduced bacterial colonisation of the lungs
- reduced hospitalisations and requirement for IV antibiotics
- respiratory infections are now easier to treat
- improved sleep, energy levels, motivation and health stability
- improved mental health, positivity, hope and confidence for people with cystic fibrosis, and their carers and wider families
- reduced need for prescribed medications
- use of primary care rather than higher-tier services.

The committee agreed that it was important to capture these benefits and cost savings, to ensure that the results of the analysis reflected the true value of treatment. The committee noted that many of the uncaptured benefits raised during consultation had now been captured as part of the committee's preferred assumptions for the long-term rate of ppFEV1 decline (see section 3.7), treatment-specific utility benefit (see section 3.17) and disease-management costs (see section 3.19). The committee considered that there may be additional benefits when treatment is started early. The

committee also considered that by reducing standard care costs, hospital admissions, the requirement for lung transplants, and transplant organs themselves, CFTR modulators would free up valuable resources for other people having care in the NHS. The inclusion of a carer utility (see section 3.18) captures the benefits of treatment to carers of people with cystic fibrosis up to 18 years old. The committee noted that carer responsibility likely continues beyond age 18. These additional considerations are reflected in the committee's preferred cost-effectiveness threshold (see section 3.25). The committee acknowledged the benefits of CFTR modulators on the wider economy, such as enabling people with cystic fibrosis and their carers to return to work. The committee agreed that these were important considerations but noted that the perspective adopted on costs should be that of the NHS and personal and social services.

Maximum acceptable ICER

3.25 The committee considered that the evidence base for CFTR modulators was large and robust. Long-term data collection has also further reduced uncertainty around the ongoing effects of CFTR modulators. But the committee noted that some uncertainty remained, particularly around the long-term rate of relative ppFEV1 decline for CFTR modulators. The committee noted that its preferred assumptions, in particular including a treatment-specific utility benefit, captured most of the additional benefits of treatment with CFTR modulators raised at consultation. But it noted there are still several uncaptured benefits (see section 3.24). Had these benefits been modelled, cost effectiveness would likely improve. So, the committee concluded that the maximum acceptable ICER could be slightly higher than the range normally considered to be a cost-effective use of NHS resources.

Equality

3.26 The committee considered the potential equality issues raised by stakeholders. It noted that about 10% of people with cystic fibrosis do not have an F508del mutation and therefore cannot have IVA–TEZ–ELX, TEZ–IVA or LUM–IVA. The

committee noted that people with cystic fibrosis who cannot have IVA–TEZ–ELX, TEZ–IVA or LUM–IVA are more likely to be from ethnic minority backgrounds. The committee considered that eligibility for treatment according to genotype is a feature of the marketing authorisations, and not an issue that can be addressed by the committee's recommendations.

Conclusion and recommendation

3.27 The committee recognised that cystic fibrosis can substantially affect the lives of people with the condition, and their families and carers. It understood that the only alternative to CFTR modulators is standard care, which is burdensome and treats symptoms rather than the underlying cause. After considering all available evidence, and the opinions of the clinical and patient experts, the committee agreed that CFTR modulators are clinically effective treatments with important benefits for people with cystic fibrosis with at least 1 F508del mutation. After the committee meeting, ICERs were generated using the committee's preferred assumptions (see section 3.22) and included all commercial arrangements for IVA–TEZ–ELX, TEZ–IVA and LUM–IVA. The relevant treatments were compared with standard care in the F/F, F/MF and F/RF genotypes, and with IVA in the F/Gating genotype. The resulting deterministic ICERs for IVA–TEZ–ELX, LUM–IVA and TEZ–IVA were all within the range that NICE considers an acceptable use of NHS resources, when accounting for uncaptured benefits (see section 3.25). The exact ICERs are confidential and cannot be reported here. So, IVA–TEZ–ELX, TEZ–IVA and LUM–IVA are recommended for routine use.

4 Implementation

4.1 Section 7 of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final draft guidance.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has cystic fibrosis and the health professional responsible for their care thinks that IVA–TEZ–ELX, TEZ–IVA or LUM–IVA is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Scottish Medicines Consortium collaborated with NICE on this guidance. In Scotland, the advice will have the same status for health board consideration as other Scottish Medicines Consortium advice on new medicines.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee D.

Committee members are asked to declare any interests in the technologies being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Megan John
Chair, technology appraisal committee D

NICE project team

Each evaluation is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the evaluation), a technical adviser and a project manager.

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