

**NATIONAL INSTITUTE FOR HEALTH AND CARE
EXCELLENCE**

Draft guidance consultation

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

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

This document has been prepared for consultation with the stakeholders. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the stakeholders for this evaluation and the public. This document should be read along with the evidence (see the [committee papers](#)).

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Note that this document is not NICE's final guidance on these technologies. The recommendations in section 1 may change after consultation.

After consultation:

- The evaluation committee will meet again to consider the evidence, this evaluation consultation document and comments from the stakeholders.
- At that meeting, the committee will also consider comments made by people who are not stakeholders.
- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using ivacaftor–tezacaftor–elexacaftor, tezacaftor–ivacaftor and lumacaftor–ivacaftor in the NHS in England.
- The Scottish Medicines Consortium (SMC) will use the final recommendations to produce separate advice for the NHS health boards in Scotland.

For further details, see [NICE's manual on health technology evaluation](#).

The key dates for this evaluation are:

- Closing date for comments: 24 November 2023
- Second evaluation committee meeting: 14 December 2023
- Details of the evaluation committee are given in section 4

1 Recommendations

- 1.1 Ivacaftor–tezacaftor–elexacaftor (IVA–TEZ–ELX) plus ivacaftor (IVA) alone is not recommended within its marketing authorisation, as an option for treating cystic fibrosis (CF) in people 6 years and over who have at least 1 F508del mutation in the CF transmembrane conductance regulator (CFTR) gene.
- 1.2 Tezacaftor–ivacaftor (TEZ–IVA) plus IVA alone is not recommended, within its marketing authorisation, for treating CF 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 not recommended, within its marketing authorisation, for treating CF in people 1 year and over who have 2 copies of the CFTR gene with F508del mutations.
- 1.4 These recommendations are not intended to affect treatment with IVA–TEZ–ELX, TEZ–IVA or LUM–IVA that was started in the NHS before this guidance was published. People having treatment outside these recommendations may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For children or young people, this decision should be made jointly by the clinician, the child or young person, and their parents or carers.

Why the committee made these recommendations

CF causes a range of challenging symptoms that affect the lungs, digestive system and liver. People with CF 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 CF 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 on 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.

Even 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 above the range that NICE considers an acceptable use of NHS resources. So, they are not 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 6 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 The dosage schedule for IVA–TEZ–ELX is available in the [summary of product characteristics for IVA–TEZ–ELX](#).
- 2.5 The dosage schedule for TEZ–IVA is available in the [summary of product characteristics for TEZ–IVA](#).
- 2.6 The dosage schedule for LUM–IVA is available in the [summary of product characteristics for LUM–IVA](#).

Price

- 2.7 The list price for IVA–TEZ–ELX is £8,346.30 (excluding VAT; BNF online, accessed October 2023) 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 TEZ–IVA is £6,293.91 (excluding VAT; BNF online, accessed October 2023) per 28-tablet pack of:
- TEZ 50 mg and IVA 75 mg or
 - TEZ 100 mg and IVA 150 mg.
- 2.9 The list price for LUM–IVA is £8,000 (excluding VAT; BNF online, accessed October 2023) per 112-tablet pack of:
- LUM 100 mg and IVA 125 mg or
 - LUM 200 mg and IVA 125 mg.

- 2.10 LUM–IVA is also available in 56-sachet packs. The list price is £8,000 (excluding VAT; BNFc online, accessed October 2023) 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.
- 2.11 The list price for a 28-tablet pack of ivacaftor (IVA) 75 mg or IVA 150 mg is £7,000 (excluding VAT; BNF online accessed October 2023). IVA is also available in 28-sachet packs of 25 mg, 50 mg or 75 mg, but the price is commercial in confidence and cannot be reported here.
- 2.12 The company has a commercial arrangement, which would have applied if IVA–TEZ–ELX, TEZ–IVA or LUM–IVA had been recommended.

3 Committee discussion

The [evaluation committee](#) considered from a number of sources. See the [committee papers](#) for full details of the evidence.

The condition

Cystic fibrosis

- 3.1 Cystic fibrosis (CF) is a genetic condition. It is usually caused by a mutation in the CF 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 CF 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 CF 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 CF 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 CF-related diabetes. CF significantly shortens people's lives, with a median age of death in 2021 of 38 years. CF substantially impacts people's mental and emotional wellbeing and can have a large financial burden. Patient submissions also described the substantial impact on carers, due to the chronic and severe nature of CF. Caring for someone with CF is physically demanding and involves daily activities such as manual physiotherapy, administration of medicines, sterilising medical equipment and facilitating hospital visits. Parents have also described the difficulty of ensuring their children are a healthy weight and managing the high-calorie diet required. As well as being physically demanding, caring for someone with CF 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 CF is a lifelong condition, carers can experience these effects over a long period of time. As well as impact on the primary caregiver, there is an impact on the whole family including siblings and grandparents. Patient experts at the 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 CF was severely curtailed and the considerable mental toll of living with the condition. The committee acknowledged the substantial difficulties faced

by people with CF. It recognised that CF is a chronic and severe condition that affects the body across multiple organ systems, can impact the mental wellbeing of people with the condition and their carers. It also acknowledged that CF 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 committee meeting explained that CF 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 CF-related diabetes are common, and additional medicine is needed to manage these. Patient experts 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 CF are regularly admitted to hospital for intravenous antibiotics. The committee agreed that CF has a substantial treatment burden and there is an unmet need for targeted and effective treatments.

CFTR modulators

3.3 In 2019, an agreement was reached between NHS England and Vertex to make LUM–IVA and TEZ–IVA available on the NHS while more evidence was collected. In 2020, the agreement was updated to include IVA–TEZ–ELX. Based on 2021 data from the UK Cystic Fibrosis Registry, 72.6% of people with CF were taking a CFTR modulator and, of those, 72.1% were taking IVA–TEZ–ELX. The proportion taking IVA–TEZ–ELX increased in 2022, but the exact numbers are considered confidential by the company

and so cannot be reported here. Patient submissions explained how the availability of CFTR modulators had changed the nature of CF 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 CF. 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 A systematic review was conducted by the external assessment group (EAG) to identify clinical evidence for CFTR modulators. The EAG identified 21 trials across a range of age groups and the following CF 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.

Where 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 aims to collect longer-term data for CFTR modulators to help resolve key uncertainties in the evidence base. A key source of data was the UK Cystic Fibrosis Registry (UKCFR). It included data from all care centres and clinics in the UK, covering 99% of the UK CF 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 (measured in ppFEV1) decline for people with CF on standard care, the EAG used data from Szczesniak (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 CF 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 CF 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 (2022). This was a retrospective study of lung function decline across different age groups in people with CFTR modulator-untreated CF. 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 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 committee meeting explained that the rate of decline in CF 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 receive 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. 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 (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 CF. That is, the long-term changes in ppFEV1 reflect only those related to age, sex and height, with no adjustment for CF 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 (Griese 2022) and another study comparing this data with a control group who had not had treatment (Lee 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 the open-label extension study of IVA–TEZ–ELX 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 shielding and other pandemic precautions 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 (2022), which was conducted 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 (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 described how the benefits of IVA–TEZ–ELX treatment had been maintained over time. Clinical experts at the committee meeting had similar experiences with IVA–TEZ–ELX. 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 CF, there may still be a decline in lung function over time because of existing lung damage. Regarding the effects of the COVID-19 pandemic on longer-term data, patient experts explained that many people with CF 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. The committee considered that COVID-19 infection itself 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 CF in

the UK, and so was generalisable to people having CFTR modulators in the NHS. 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. The committee considered that additional analyses investigating the effect of COVID-19 confounding would be helpful in exploring this uncertainty. It concluded that it preferred to use data on the long-term relative reduction in ppFEV1 decline for IVA–TEZ–ELX based on analysis of the UKCFR data provided by the company. This produced an estimate of long-term relative reduction in ppFEV1 decline between the company base case assumption of 100% and EAG base case assumption of 61% (the exact relative reduction in ppFEV1 decline from the UKCFR is considered confidential by the company and cannot be reported here).

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 (2021) and Konstan (2017) respectively. It then performed propensity score matching to compare 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, 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. But, the committee recalled the EAG’s concern that the data only excluded the first 21 to 25 days and so considered that this may be an optimistic assumption. The committee added that it would like to see a scenario analysis that extended the acute treatment effect window up to week 24. This would have ensured that acute effects were fully excluded when assessing the impact on long-term efficacy estimates.

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 (Griese 2022) showed a 78% and 71% reduction in annualised PEx requiring antibiotics or leading to hospitalisation, respectively. Patient experts 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 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 that they had seen a large reduction in the need for intravenous antibiotics and hospitalisation in children treated with 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 CF 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 following the acute period based on data collected for IVA–TEZ–ELX from the UKCFR. The exact rate is considered confidential by the company and cannot be reported here. A patient expert at the 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. Therefore, the committee concluded that the rate of adherence from the UKCFR was the most appropriate source of data to estimate adherence for the 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 to 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 committee meeting also commented that they had been able to stop some existing treatments that had troublesome side effects. The committee concluded that the effects of reduced use of non-CFTR modulator treatments on long-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 performed a critique of 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 and the model used in the previous technology appraisal of LUM-IVA ([NICE technology appraisal guidance 398](#), from here TA398) and other published models in CF.

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 (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 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 (2001). The patient expert also noted that there may be benefit in reducing bacterial colonisation. 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. The committee concluded that the EAG's model structure was largely appropriate, but there were likely to be some uncaptured benefits.

Implementation of the EAG's model

3.14 At consultation, 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. After consultation, the EAG 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. 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. The company argued that differential discount rates of 1.5% for QALYs and 3.5% for costs should be used. 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. The committee agreed that people with CF 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 CF to full health, but rather prevents decline. Patient experts explained that IVA–TEZ–ELX may prevent decline if started early enough in young children before lung damage occurs. The committee acknowledged the potential additional benefits of IVA–TEZ–ELX in young children, but it had not seen any evidence to support this. It also noted the method 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 concluded that, based on the evidence provided for decision making, an annual discount rate of 3.5% should be used for costs and QALYs.

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 CF. It explained this was because people who have had CF 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 recalled 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 recalled 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. 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. The committee considered that they do not usually include treatment-specific benefits. So, the company would need to re-run the regression model to provide additional health-state utility values based on the CFQ-R. The committee recalled the economic

model is an individual patient simulation model. This model structure, combined with using health-state utility values from Acaster et al. (2015), meant the effect of treatment with CFTR modulators on quality of life should already be captured. So the committee concluded it was not appropriate to include a separate treatment-specific utility benefit.

Caregiver utility benefit

3.18 The company included a caregiver utility benefit based on data collected in the UK-based, longitudinal MAGNIFY study. MAGNIFY collected data from 25 carers of children aged 6 to 11 years of age having IVA–TEZ–ELX. Data was collected using the Care-related Quality of Life instrument (CarerQoL). 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 of age having IVA–TEZ–ELX. The EAG did not include a caregiver utility benefit in the model because it considered that the evidence supporting this was uncertain. The committee recalled the substantial impact CF 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 CF, 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 CF, leading to vast improvements in carer quality of life. The committee agreed that the impact of CF on carers is large. It noted that

the beneficial effects of treatment with IVA–TEZ–ELX may extend to multiple carers and to the families of people with CF. The committee considered the age groups of people with CF at which a caregiver utility benefit should apply. It noted that in the company’s original model, caregiver utility was only applied for younger children in line with the available data. The committee noted that this was a conservative assumption because it heard from patient experts that the caregiver impact was likely to continue well beyond the period of observed data, and may impact more than 1 carer. But it concluded that, based on the evidence, a caregiver utility benefit of 0.03 should be applied in the model for carers of children from the start of IVA–TEZ–ELX treatment to 11 years of age, as proposed by the company. It considered that the actual benefit was likely to be greater than this and considered any impact past the age of 11 to currently be an uncaptured benefit in the model. The committee added that it would like to see a scenario analysis with carer utility benefit applied from treatment initiation to 18 years of age.

Costs

Disease-management costs

3.19 As discussed in [section 3.1](#) and [section 3.2](#), managing CF is intensive. It involves physical therapy and a broad range of prescribed oral and inhaled treatments. Because CF 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 CF medicines, split by ppFEV1 status (Granger et al. 2022). For healthcare costs, the EAG used a resource-use questionnaire, which was part of a trial to assess adherence to inhaled medicines (Tappenden et al. 2023). The company preferred to use a retrospective chart review of people with CF aged 6 years and over across 8 specialist CF centres in the UK (Ramagopalan et al. 2014). This provided aggregated medicines and

health care 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 and company 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. 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 were 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. The committee noted that more research was needed into whether CFTR modulators reduced the need for standard care and if reduced standard care affects the long-term efficacy of CFTR modulators. But, the committee concluded that cost savings from a reduced need for standard care associated with CFTR modulators was a potential uncaptured benefit in the model.

Severity

3.20 The committee considered the severity of CF (the future health lost by people living with CF 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. The EAG's model provided absolute and proportional QALY shortfall estimates in line with the [NICE health technology evaluations manual 2022](#). Based on the EAG's calculation, absolute shortfall and proportional shortfall did not meet the threshold for any additional QALY weighting for

any genotype. So, the EAG concluded that a severity modifier of 1 was appropriate. The company noted that CF is a severe condition, and based on the company's model, a severity modifier of 1.7 should apply. The committee acknowledged the substantial impact of CF. Neither the EAG's nor the company's analyses incorporated all of the assumptions identified as the most plausible. So the committee considered that the resulting absolute and proportional shortfalls generated could not be used to inform its decision making on severity. It was therefore unable to conclude if a severity modifier should be applied.

Cost-effectiveness estimates

Committee preferred assumptions

3.21 The committee recalled many of the preferred modelling assumptions differed between the EAG and company. It agreed it would prefer the cost-effectiveness analysis to be generated using the EAG's model and that it should include the following assumptions:

- Long-term relative reduction in ppFEV1 decline with standard care using a non-linear decline based on Szczesniak (2023).
- Long-term relative reduction in ppFEV1 decline with IVA–TEZ–ELX using the company analysis of UKCFR data, which provided an estimate of the rate of decline in between the company's and EAG's estimates.
- Long-term relative reduction in ppFEV1 decline with TEZ–IVA of 61.5% based on the Flume (2021) open-label extension study.
- Long-term relative reduction in ppFEV1 decline with LUM–IVA of 42% based on Konstan (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 UKCFR data.
- Health-state utility values based on EQ-5D from Acaster et al. (2015).
- No treatment-specific utility benefit applied.

- Carer utility benefit applied for carers of children on IVA–TEZ–ELX from treatment initiation to 11 years of age.
- Disease-management costs based on Granger (2022) and Tappenden (2023) should be used.

Cost-effectiveness results

3.22 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 company base case ICER for IVA–TEZ–ELX was above the range that NICE considers an acceptable use of NHS resources. The EAG’s base case and scenario analysis ICERs for IVA–TEZ–ELX, LUM–IVA and TEZ–IVA grossly exceeded the range for all genotypes. The committee was not presented with analyses that incorporated all of its preferred assumptions. But, the committee understood that its preferred ICER would fall between the company and EAG base cases. So it would be substantially above the range that NICE considers an acceptable use of NHS resources for IVA–TEZ–ELX, LUM–IVA and TEZ–IVA in all genotypes.

Uncaptured benefits

3.23 The committee considered that there were several important uncaptured benefits of treatment with CFTR modulators. These included potential additional benefits of treatment that were not captured by the modelling, such as:

- the impact on pancreatic recovery in children
- improved glycaemic control and reductions in CF-related diabetes
- reduced bacterial colonisation and its impact on survival and quality of life (see [section 3.13](#)).

In addition, the committee considered that the impact on carers may be larger than what was included in the company’s model. This is because the duration of caregiving is likely to be longer than that observed during

clinical trial follow up and could increase over time because of disease progression. It could also affect multiple members of the family. The committee also noted the impact CFTR modulators have on the wider NHS. 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 receiving care in the NHS.

Acceptable ICER

3.24 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 there were several uncaptured benefits of treatment with CFTR modulators (see [section 3.23](#)). The committee was willing to be flexible, taking into consideration the significant unmet need for effective treatments in routine commissioning. But it noted that departing from NICE's usual range needs to be done with caution. This is because it displaces funding from what may be more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain (see [the principles that guide the development of NICE guidance and standards](#)). For this reason, the committee considered an acceptable ICER to be around £30,000 per QALY gained.

Equality

3.25 The committee considered the potential equality issues raised by stakeholders. It noted that around 10% of people with CF do not have an F508del mutation and therefore cannot have IVA–TEZ–ELX, TEZ–IVA or LUM–IVA. The committee noted that people with CF who cannot have IVA–TEZ–ELX, TEZ–IVA or LUM–IVA are more likely to be from Black, Asian and minority ethnic 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

3.26 The committee recognised that CF can substantially affect the lives of people with the condition, their families and carers. It understood the only alternatives 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 CF with at least 1 F508del mutation.

Recommendation

3.27 Following the committee meeting ICERs were generated using the committee's preferred assumptions (see [section 3.21](#)) and included all commercial arrangements for IVA–TEZ–ELX, TEZ–IVA and LUM–IVA. The treatments were compared with each other and standard care in all genotypes. The resulting ICERs were all substantially above £30,000 per QALY gained (the exact ICERs are confidential and cannot be reported here). The committee considered that CFTR modulators are clinically effective treatments and it is likely there are benefits not captured in the economic modelling. But despite this, the cost-effectiveness estimates were substantially above the range NICE considers an acceptable use of NHS resources. So IVA–TEZ–ELX, TEZ–IVA and LUM–IVA could not be recommended for routine use.

4 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

Stephen Smith

Vice 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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ISBN: [to be added at publication]