NICE National Institute for Health and Care Excellence

NICE guidance

Tixagevimab plus cilgavimab for preventing COVID-19

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.

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1 Recommendations

1.1 Tixagevimab plus cilgavimab is not recommended, within its marketing authorisation, for the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to someone infected with SARS-CoV-2, and:

- who are unlikely to have an adequate immune response to COVID-19 vaccination, or
- for whom COVID-19 vaccination is not recommended.

Why the committee made this recommendation

The results of clinical studies of tixagevimab plus cilgavimab suggest it reduces infection with SARS-CoV-2 (the virus that causes COVID-19) compared with no preventative treatment. But these studies were done early in the pandemic when different variants of the virus were circulating. More recent studies done in laboratories report that tixagevimab plus cilgavimab is unlikely to prevent infection with most of the variants circulating when this guidance was produced.

Because of the lack of evidence of clinical effectiveness, the cost-effectiveness estimates for tixagevimab plus cilgavimab are highly uncertain. They are also likely to be much higher than what NICE considers an acceptable use of NHS resources. So, tixagevimab plus cilgavimab is not recommended. Further research is recommended to address some of the uncertainties in this rapidly changing disease area (see section 4).

2 Information about tixagevimab plus cilgavimab

Marketing authorisation indication

2.1 Tixagevimab plus cilgavimab (Evusheld, AstraZeneca) has a conditional marketing authorisation for 'the pre-exposure prophylaxis of COVID-19 in adults who are not currently infected with SARS-CoV-2 and who have not had a known recent exposure to an individual infected with SARS-CoV-2 and:

- who are unlikely to mount an adequate immune response to COVID-19 vaccination, or
- for whom COVID-19 vaccination is not recommended.'

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for tixagevimab plus cilgavimab.

Price

2.3 The list price of tixagevimab plus cilgavimab is £800 per 300 mg dose and £1,600 per 600 mg dose (excluding VAT; prices provided by company).

2.4 The company has a commercial arrangement, which would have applied if tixagevimab plus cilgavimab had been recommended.

3 Committee discussion

The evaluation committee considered evidence submitted by AstraZeneca, a review of this submission by the external assessment group (EAG), a report developed by an in vitro advisory group and responses from stakeholders. See the committee papers for full details of the evidence.

The condition

COVID-19

3.1 COVID-19 is an acute respiratory illness caused by the SARS-CoV-2 virus. Symptoms range from mild and self-limiting to severe with a risk of hospitalisation or death. After the initial SARS-CoV-2 infection, people may have ongoing symptoms (long COVID). Some people remain at high risk of serious illness from COVID-19, despite the availability of vaccines. These are generally people who would not benefit from vaccination or in whom there is not a good enough response to vaccination. This includes people:

- who have had a transplant
- with genetic disorders, some cancers, kidney or liver disease, or immune system disorders
- whose immune response is affected by the drug used to treat their condition.

Changing variants of concern

3.2 The virus that causes COVID-19 (SARS-CoV-2) has evolved over the course of the pandemic. Throughout most of 2021, Alpha and Delta were the main circulating variants. From late 2021 onwards, the Omicron variant began to dominate. Since then, the Omicron variant has continued to evolve into subvariants, each with different mutations on the spike protein. These changes can affect the continued efficacy of existing treatments, particularly neutralising monoclonal antibodies,

because the ability of the treatment to bind to the virus is reduced. The UK Health Security Agency (UKHSA) publishes a monthly technical briefing document, which reports variant prevalence. NICE used the data published in the UKHSA's March 2023 technical briefing 51 (based on all of the UK sequenced samples from 20 to 26 February 2023) to determine the variants circulating at the time of this evaluation. Most new cases were the Omicron subvariants BQ.1 and CH.1.1, or XBB lineage subvariants. The committee considered that SARS-CoV-2 is rapidly evolving and acknowledged that this makes assessing neutralising monoclonal antibodies difficult. It recalled from the in vitro advisory group report (see section 3.11) that the virus evolves in 2 different ways:

- Frequent small changes of the virus: new mutations on the spike protein may lead to incremental changes that incorporate many of the same mutations as before. This could be driven by selection pressure, so that viruses with mutations enabling them to evade neutralisation will proliferate.
- Infrequent larger shifts of the virus: older versions of the virus may be incubating (for example, in people who are immunocompromised, for whom viral clearance may be slower) and mutate to have an advantage over currently circulating variants (for example, the large change that occurred with the Omicron wave).

  The committee considered it most likely that new variants would be related to currently circulating variants unless there was a larger shift in the virus. It also considered the possibility that neutralising monoclonal antibodies which currently have low efficacy regain their efficacy against future variants. But it noted that the World Health Organization therapeutics and COVID-19 living guideline states that 'the likelihood of COVID-19 caused by former variants was extremely low'. So, it considered that the effectiveness of tixagevimab plus cilgavimab (from now, tix–cil) over the appropriate time period for this evaluation would be best indicated by neutralisation potential against currently dominant circulating variants and variants that are currently growing the fastest. The committee noted substantial uncertainty in estimating efficacy for future variants, given the current understanding of COVID-19 and the rapidly evolving virus. It understood from studies such as OpenSAFELY that, broadly, COVD-19 is waning in its severity. It understood that this was because immunity to SARS-CoV-2 has increased in the general population through vaccination and natural exposure, and because later variants of the virus have

reduced in pathogenicity. This means that the risks are now very low for the general population and substantially reduced for most people eligible for tix–cil compared with earlier in the COVID-19 pandemic. But the committee noted that the risks have not reduced for some groups such as people who have had transplants.

Patient perspectives

Ongoing impact of COVID-19

3.3 The patient experts described the ongoing impact of COVID-19 on their lives and the lives of others with a high risk of severe SARS-CoV-2 infection. One patient expert described how modifying their behaviour was mentally and physically exhausting, needing extensive planning for simple tasks like shopping. They described how nothing had changed for them since the start of the pandemic. In fact, they added, the situation had worsened for them because the rest of the country has returned to normal, meaning protective measures are no longer in place. They described how removing measures for limiting viral spread, such as mask wearing, working from home and social distancing, has placed all the responsibility for protection on individuals. They added that people who are immunocompromised need to navigate multiple environments that no longer have the COVID-19 mitigation measures that they value. Another patient expert described how they are only able to leave the house for routine medical appointments, and are on high alert to minimise the risk of infection whenever possible. Both patient experts also highlighted that the burden of responsibility extends to household family members, and affects work life and family relationships. People reported that their finances had been affected because of a lack of government support and increased costs of shielding. For people with children, there were concerns about the disruption of education on life chances and the long-lasting impact of this. They said that the availability of a preventative treatment that reduces infection risk could reduce the need for exhausting and isolating behavioural changes. The committee agreed that there is an urgent unmet need for a preventative therapy that would reduce the risk of SARS-CoV-2 infection for people at high risk of severe infection for whom vaccination is not suitable or does not provide

sufficient protection.

Benefits of tix–cil

3.4 The patient experts discussed their experiences of having tix–cil. One described their relief after having it. They explained that, even after treatment with tix–cil, they continued to be careful and still maintained social distancing. They acknowledged that tix–cil may not stop all SARS-CoV-2 infections, and that returning to normal would be a gradual process as their confidence in the treatment increased. Another patient expert agreed and added that, since having tix–cil, they have met people face to face, but continue to wear a mask and avoid crowded spaces. They added that, even with tix–cil, and with treatments for severe SARS-CoV-2 infection now available, this is not enough for them to abandon all caution.

Decision problem

Eligible population

3.5 The company explained in its original submission that it was positioning tix–cil in a narrower population than that of the marketing authorisation and the final NICE scope. That is, it positioned it in people who are at the 'highest risk of an adverse COVID-19 outcome'. In the original company submission, the company referred to the report produced by the independent advisory group set up by the Department of Health and Social Care (DHSC) to identify people at the very highest risk of an adverse COVID-19 outcome for treatment with antivirals and neutralising monoclonal antibodies. See the DHSC's independent report on the highest-risk subgroups with SARS-CoV-2 when considering neutralising monoclonal antibodies and antiviral drugs (from now, referred to as the McInnes report). The committee noted that a similar report, the independent advisory group report concerning the use of COVID-19 directed antibodies in the prophylaxis setting in the highest-risk clinical subgroups, had been produced by the same group. This stratified cohorts in order of risk. The committee recalled that the wording in the marketing authorisation for tix–cil included 'those unlikely to mount an

adequate immune response to COVID-19'. It considered that this would include people in groups A1, A2 and B of the independent advisory group's report. In response to consultation, the company considered that its target population should include people in groups A1 and A2, and people in group B without a serological response to vaccination. The clinical experts broadly agreed that the groups in the independent advisory group report aligned with the expected level of antibody response to vaccination. They also thought that people in groups A1 and A2 were likely to have the poorest response and so be at the greatest risk of severe SARS-CoV-2 infection. But they cautioned that the groups represent a spectrum of risk and that there was likely to be substantial heterogeneity within groups as well as across groups. The clinical experts added that some people may have poor outcomes despite having a response to vaccination. At the second meeting, the clinical experts and NHS England commissioning expert confirmed that serological testing to check response to vaccination is not done routinely in the NHS. So, they thought it was unclear how this would work in clinical practice for people in group B. The committee noted that, in people having a treatment that would place them in group B in the MELODY study, between 7.6% and 13.5% had no detectable antibodies after vaccination. So, the committee concluded that many people in group B would have to be tested to identify a single person eligible for treatment. It considered that the costs of this would be significant and had not been included in the company's model. The EAG noted that many of the inputs in the economic analysis were selected to reflect particular groups. So, it thought that they did not represent the eligible population as a whole and did not capture the heterogeneity within the eligible population. The committee agreed with the EAG that estimates of clinical and cost effectiveness would vary across different risk-based groups because of heterogeneity. At consultation, it was highlighted that certain groups may be at a higher risk of hospitalisation or death than the eligible population as a whole. For example, people with solid organ transplants may have more severe consequences of SARS-CoV-2 infection, such as transplant failure. The committee acknowledged the higher risk and costs in these groups. It considered that focusing on the most severe subgroups would reduce the decision risk. The committee added that, ideally, heterogeneity could be explored by considering separate subgroups in the economic model. But it noted that it had not

seen evidence of differential clinical or cost effectiveness to rule out other groups covered by the marketing authorisation. So, it maintained that the eligible population should be all groups covered by the marketing authorisation.

Treatment schedule

3.6 The summary of product characteristics for tix–cil recommends a dose of 300 mg. It states that a higher dose of 600 mg may be more appropriate for some SARS-CoV-2 variants (such as Omicron BA.1 and BA1.1) that show reduced susceptibility to tix–cil in vitro. So, the company used the cost of the higher 600 mg dose in its economic analysis. The summary of product characteristics also states that tix–cil may be effective for pre-exposure prophylaxis for 6 months after administration. In its original submission, the company assumed that the initial 600 mg dose was followed 6 months later by a second 600 mg dose. The EAG noted that this was not aligned with the summary of product characteristics. This says that tix–cil has only been studied in single-dose studies, and that no safety and efficacy data is available for repeat dosing. The committee was aware that the Medicines and Healthcare products Regulatory Agency (MHRA) had clarified to NICE that repeat dosing of tix–cil is outside the marketing authorisation and would be off-label use. Technology appraisal guidance recommendations must be within the marketing authorisation, so the committee concluded that the economic analysis should only include a single dose of tix–cil. In response to consultation, the company updated its model to only include a single dose of tix–cil. The committee was satisfied with the updated approach.

Clinical effectiveness

Outcomes

3.7 The company presented treatment outcomes in line with the NICE scope. These included reduction in risk and severity of SARS-CoV-2 infection, and improvements in anxiety, depression and health-related quality of life. The committee considered these appropriate outcomes for a preventative treatment. But the committee noted that there were

interactions between outcomes that had not been considered by the company, including:

- The interaction between the perceived efficacy of treatment and direct utility gain resulting from a reduction in shielding: the committee considered that, as perceived efficacy reduces, the reduction in shielding will also likely reduce, resulting in a reduced direct utility gain.
- The interaction between the extent of shielding and the risk of infection and severe outcomes: the committee considered that, as shielding reduces, the risk of infection and severe outcomes will increase.

  The patient experts at the first committee meeting explained that some shielding behaviours such as social distancing were likely to continue to some extent after having tix–cil (see section 3.4). They said that individual decisions about shielding behaviours can take into account many different factors. These factors include the risk from their underlying condition, the current risk posed by SARS-CoV-2 and other viruses, and the trust in the effectiveness of the treatment against current variants. People may also take into account the time of year, whether they have upcoming medical appointments and societal attitudes towards protective behaviour (such as mask wearing on public transport and using lateral flow tests). The committee considered that any change in shielding will depend on an individual's estimate of the risk reduction available from tix–cil and their degree of risk aversion. It noted that it is also important to understand how much shielding is because of COVID-19 risks and how much is related to other factors. The committee considered that, for people who are not shielding, having an effective preventative treatment would reduce the risk of severe illness and death but not result in any quality-of-life benefit from stopping shielding. Whereas, for people who are fully shielding, it thought that having an effective preventative treatment would allow them to stop shielding so their quality of life would be improved but their overall risk of infection would be the same. The committee considered that there would be many people who have a mixture of both direct utility gain and a reduced risk of infection. For example, this would be the case if they are partially shielding or cannot shield and this causes them anxiety. But the committee concluded that no one would have the full benefit of risk reduction and the full direct utility gain from stopping shielding, as was assumed by the company. The committee considered that the company's model may have double counted the benefit of treatment. This was because it incorporated a reduction in risk for

people who are fully and effectively shielding (and who are not at risk) as well as a direct utility benefit. It noted that the company had not provided any data on the relationship between efficacy, direct utility gain, shielding behaviours and increased infection risk. It also noted that the company had not modelled this relationship, so the impact on cost-effectiveness estimates could not be explored. The committee concluded that the company's model likely overestimated the benefit of treatment.

PROVENT trial

3.8 The company presented evidence from a phase 3, randomised, double-blind, placebo-controlled trial (PROVENT, Levin et al. 2022). PROVENT compared tix–cil (n=3,460) with placebo (n=1,737) for preventing SARS-CoV-2 infection in adults at increased risk of an inadequate response to vaccination or at an increased risk of SARS-CoV-2 infection. The results from PROVENT showed that tix–cil was associated with a statistically significant reduction in the incidence of COVID-19 (reverse transcription polymerase chain reaction-positive symptomatic illness) compared with placebo, with a relative risk reduction of 76.7% (equating to an absolute risk reduction of 0.8%). The company noted several limitations with the PROVENT trial:

- most participants were not at high risk of a severe COVID-19 outcome
- participants were unvaccinated
- it took place before there were significant levels of natural immunity in the population from prior infection
- it took place when earlier variants of COVID-19 were prevalent and before newer variants emerged.

Because of these limitations, the company did not include efficacy data from PROVENT in its economic model, despite using it as the randomised evidence for efficacy for its marketing authorisation application. The EAG also had other concerns, including:

- the overall small number of infection events
- the small proportion of participants on immunosuppressive treatments or with

immunosuppressive disease

- the need for all participants to have a negative point-of-care COVID-19 test, which is not expected in clinical practice.

The committee noted that the context of the disease was very different at the time of the PROVENT trial. It also noted that there was no information reported about how people in either arm modified their behaviour during the trial, which is particularly important for preventative treatments.

Observational evidence

3.9 The company presented data from 2 observational evidence studies, Young-Xu et al. (2022) and Kertes et al. (2022). Young-Xu et al. was a retrospective cohort study in US veterans who were immunocompromised (92%) or otherwise at high risk of COVID-19 (8%). People were recruited between January and April 2022, at the time when Omicron variants BA.1, BA.2 and BA.2.12.1 were circulating. A total of 1,733 people had tix–cil. One 600 mg dose of tix–cil was given to 83% of participants; the rest had a 300 mg dose. The outcomes of the study were SARS-CoV-2 infection, COVID-19-related hospitalisation and all-cause mortality. To generate estimates of comparative effectiveness, the study compared outcomes for people on tix–cil with propensity-matched controls (n=6,354). The resulting hazard ratios were 0.34 (95% confidence interval [CI] 0.13 to 0.87) for SARS-CoV-2 infection; 0.13 (95% CI 0.02 to 0.99) for COVID-19-related hospitalisation and 0.36 (95% CI 0.18 to 0.73) for all-cause mortality. Kertes et al. was a retrospective cohort study done in people who were immunocompromised and considered at high risk for SARS-CoV-2 infection and complications. People were recruited to the study between February and May 2022 at the time when Omicron variants BA.1 and BA.2 were circulating. A total of 825 people had one 300 mg dose of tix–cil. Compared with 4,299 people who did not have tix–cil, the odds ratio of SARS-CoV-2 infection was 0.51. The company considered that Young-Xu et al. provided the most robust evidence, and so used it for its base case for the economic model. The EAG had concerns about the methods and generalisability of both observational studies. It highlighted the wide confidence intervals and potential for residual confounding for Young-Xu

et al. It added that most of the US veterans were men and older, so the population may not be generalisable to that likely to be offered tix–cil in the UK. For Kertes et al., the EAG had concerns about the potential for selection bias, residual confounding and the shorter follow up in the treatment group than in the control group. The committee noted these limitations. It added that, for both studies, there would likely be systematic differences between people who sought tix–cil treatment and people in the control group who were eligible for tix–cil but did not have treatment.

Generalisability to the current circulating SARS-CoV-2 variants

3.10 In addition to the generalisability concerns discussed in section 3.8 and section 3.9, the committee had concerns about generalisability of the company's evidence to the current circulating SARS-CoV-2 variants. None of the clinical studies included evidence of efficacy against variants around at the time of this evaluation because of the rapidly evolving nature of the SARS-CoV-2 virus. The observational studies were done when the early Omicron variants BA.1, BA.2 and BA.2.12.1 were circulating, so their generalisability to the current UK context is unclear. The committee acknowledged the difficulties in doing trials in a rapidly evolving disease area, but it still considered that the evidence was too uncertain. It considered that in vitro data (from laboratory studies) may provide additional information as to whether there was a realistic clinical possibility of the technology retaining efficacy against currently circulating variants (see section 3.12).

In vitro advisory group

3.11 Neutralising monoclonal antibodies such as tixagevimab and cilgavimab target the spike protein of the SARS-CoV-2 virus. Mutations on the spike protein can quickly reduce the effectiveness of such treatments. This means that clinical trials done when older variants of SARS-CoV-2 were circulating may no longer apply in the current setting, so other types of evidence are needed. In vitro neutralisation assays can be used to assess whether treatments neutralise new variants, and so whether they retain clinical effectiveness over time as the virus evolves. An advantage of in vitro evidence is that it can be generated much faster than it takes

to do clinical trials. But NICE's technology appraisal committees are not used to interpreting and appraising in vitro data. Because of this, NICE commissioned an in vitro advisory group made up of experts in infectious disease, virology, vaccine epidemiology, immunology and pharmacology. They developed a decision framework to link the in vitro neutralisation data to clinical outcomes, and their report (the in vitro advisory group report in NICE's draft guidance consultation committee papers) provided guidance on interpreting in vitro evidence.

In vitro studies

3.12 Guided by the in vitro advisory group, the committee identified 5 studies that investigated tix–cil's ability in vitro to neutralise a range of SARS-CoV-2 variants and subvariants, including some of those circulating at the time of the evaluation. Because the landscape is rapidly evolving, a systematic review of the in vitro data was not possible. Studies by Cao et al. (2022) and Wang et al. (2022) reported no neutralisation activity for tix–cil against the Omicron subvariant BQ.1. Studies by Wang et al. (2023), Cao et al. (2023) and Imai et al. (2023) reported no neutralisation activity of tix–cil against XBB. During the first committee meeting, the committee recalled from the in vitro advisory group report that, if there was no neutralisation activity in vitro, this would suggest no clinical efficacy in people. The company and clinical experts considered that tix–cil may not be clinically effective against many new variants but considered that it could still be effective against some of them. One clinical expert also noted that it was possible that tix–cil may regain efficacy against future variants. The committee noted the company's and experts' views. But it considered that the prevalence of older variants against which tix–cil had shown in vitro efficacy (BA.5 and BA.2) was low and decreasing over time because of the relative speed of growth of other subvariants. The committee noted that subvariants that were not investigated in the in vitro studies, such as CH.1.1, had specific mutations that would likely be associated with reduced or no neutralisation activity of tix–cil. The committee acknowledged that there was the possibility for tix–cil to regain activity against future variants, but considered that the likelihood of this was low. In response to consultation, the company proposed that an appropriate threshold for neutralisation in vitro equating to clinical effectiveness in

vivo should be an IC50 of less than 10,000 nanograms per millilitre. The committee recalled the in vitro advisory group's conclusions in circumstances when there is a substantial change in neutralisation activity but some neutralisation is retained in vitro. In these circumstances, the advisory group concluded pharmacokinetic and pharmacodynamic (PK/PD) data is needed to try to link in vitro neutralisation data to clinical outcomes. Without PK/PD data, it is not possible to determine how a change in neutralisation activity may be associated with clinical outcomes. So, the committee did not consider the company's proposal to be appropriate for decision making. Full details are in the in vitro advisory group report in NICE's draft guidance consultation committee papers. The committee noted a recent update from the European Medicines Agency's emergency task force, which cautioned that neutralising monoclonal antibodies currently authorised for COVID-19 are unlikely to be effective against emerging strains of SARS-CoV-2. Shortly after the first committee meeting, the US Food and Drug Administration (FDA) also announced that tix–cil was no longer authorised for emergency use in the US. This was because it was unlikely to be effective against the variants responsible for more than 90% of infections. At the first meeting, the committee concluded that tix–cil was unlikely to retain sufficient neutralisation activity against most variants circulating at the time this guidance was produced. The committee noted there was uncertainty in relying solely on in vitro evidence. It would have preferred to triangulate the data with real-world evidence. But, in the context of changing variants, it considered the in vitro data for current variants more relevant to decision making than the older real-world studies in the company's submission. In response to consultation, the company acknowledged that it was reasonable to assume that total loss of neutralisation in vitro would mean no clinical effect. At the second meeting, the committee considered data from the UKHSA's March 2023 technical briefing 51. This briefing showed that there were only around 3% of circulating variants (BA.2 and BA.5) that tix–cil may be effective against. So, the committee concluded that there was no evidence that tix–cil would neutralise at least 97% of circulating variants as of March 2023.

Rapid evaluation process

3.13 During the first committee meeting, the patient experts expressed frustration that the COVID-19 virus is evolving rapidly. They said that there needs to be a faster mechanism to ensure effective preventative medicines are available when needed, particularly in winter when meeting people outside is more difficult. During consultation, the company and stakeholders agreed that a more flexible and responsive evaluation process is needed. They also thought that a system needs to be in place to monitor current variant mix because tix–cil may regain efficacy against future variants. The company suggested that an approach similar to that of the FDA should be adopted. The FDA has limited tix–cil's use to when the combined frequency of non-susceptible SARS-CoV-2 variants nationally is less than or equal to 90% (that is, when 10% or more variants are susceptible to neutralisation by tix–cil). The committee considered that, under the current single technology appraisal process, it could only make decisions based on the data available at the time of the committee meeting. But it noted that a more flexible evaluation process for COVID-19 technologies is currently being developed by NICE. Further details of the proposed process are provided in NICE's consultation document for the COVID-19 technology appraisal recommendations: surveillance and rapid update process statement.

Cost effectiveness

Economic model

3.14 The company's economic model consisted of a decision tree followed by a Markov model. The decision tree captured the impact of tix–cil on COVID-19 over the 6 months after preventative treatment and the 29-day (acute) period for anyone who was infected. The Markov model extrapolated survival and quality of life over the person's lifetime. The model assumed a direct utility benefit for everyone in the tix–cil arm, and an efficacy benefit from a reduced risk of SARS-CoV-2 infection and a reduced COVID-19 severity. The EAG considered the model structure to be appropriate, except for the company's handling of COVID-19 cases occurring after the initial treatment period. The model structure did not

allow for these people developing long COVID. The EAG thought that it would have been better if the company had attempted to model COVID-19 cases occurring after the initial treatment period using a model structure that tracked the number of people remaining at risk of long COVID over time. It thought that the company's model structure may have overestimated the benefit of tix–cil. This was because the model assumed that people who avoid COVID-19 during the initial treatment period by having tix–cil are then subsequently protected from long COVID. The committee noted the uncertainties in the model structure, particularly the challenge of considering a lifetime time horizon despite the uncertain natural history of COVID-19 and future variants. It acknowledged that it would be difficult to model the impact of COVID-19 accurately after the initial treatment period because SARS-CoV-2 is constantly evolving. The committee considered the model structure to be broadly appropriate. But it considered that key model inputs were highly uncertain, and that this resulted in highly uncertain cost-effectiveness estimates (see sections 3.16 to 3.20). The committee also noted that the interaction between many parameters had not been accounted for in the company's model (see section 3.7 and section 3.16).

Efficacy

3.15 In its original submission, the company used efficacy data from the observational evidence study by Young-Xu et al. (2022; see section 3.9). This study showed that tix–cil reduced the risk of symptomatic SARS-CoV-2 infection and hospitalisation related to COVID-19. In response to consultation, the company acknowledged the in vitro data discussed in section 3.12. It agreed that it had to be reasonable to assume that total loss of neutralisation in vitro would mean no clinical effect. But the company suggested that a more flexible approach was needed and that tix–cil should be recommended if it shows activity against a specific threshold of circulating SARS-CoV-2 variants. This approach is discussed further in section 3.13. The company suggested a hypothetical threshold for neutralisation against circulating variants of 10% in line with the FDA's approach. To implement this in the model, the company assumed that the relative risk reduction for SARS-CoV-2 infection based on Young-Xu et al. was reduced to 10% of its original value, resulting in a relative risk reduction for infection of 6.6%. The EAG

preferred to apply the 10% multiplier to the relative risk reduction for both infection and hospitalisation. This was because the company's base case still assumed a treatment effect based on Young-Xu et al. for the relative risk reduction of hospitalisation. The committee preferred the EAG's approach. But it noted that the 10% multiplier applied by both the company and EAG was still only hypothetical and much higher than the efficacy at the time of the second committee meeting (around 3%; see section 3.12).

Evidence for a direct utility gain

3.16 The company did a utility study to investigate the impact of the pandemic on people who are immunocompromised (Gallop et al. 2022). Subgroups in the study included people who were fully shielding, partially shielding and no longer shielding. The study collected quality-of-life data using the EQ-5D-5L questionnaire from people who were immunocompromised and had not had a preventative treatment (untreated group). The EQ-5D-5L rating for each state was scored for UK preference weights, using a mapping function to map from EQ-5D-5L to EQ-5D-3L. The study compared results with a hypothetical treated group using a vignette (a set of short statements describing the experience of a typical person having treatment). The vignette asked people to imagine a medicine that gives them 'a level of protection from COVID-19 which is similar to that given by vaccination in individuals who have a healthy immune system'. The utility gain for each subgroup was calculated as the difference between utility scores for the untreated and treated groups. The resulting utility gains were weighted according to the proportions shielding and partially shielding based on a survey by the Office for National Statistics. This gave a final utility gain of 0.098. In its updated model, the company applied the direct utility gain to everyone having tix–cil for 6 months after treatment (3 months for people who were infected with SARS-CoV-2, to account for their loss of confidence in protective treatment). The EAG highlighted several limitations with the company's vignette study. It considered that the vignette used in the study did not align with the effectiveness evidence for tix–cil. This was because there was no evidence that tix–cil provides comparable efficacy to vaccination in people with a healthy immune system. In response to consultation, the company provided supportive evidence for the direct

utility gain from an academic-in-confidence study. The EAG noted multiple issues with the company's supportive evidence. The committee agreed with the EAG's concerns about the company's evidence for direct utility gain. The committee recalled the patient experts' comments that some shielding behaviours were likely to continue to some extent after having tix–cil (see section 3.7). So, it concluded that the magnitude of the utility gain based on the company's evidence was not reflective of the anticipated utility gain for the group likely to have tix–cil in clinical practice.

Application of direct utility gain in the economic model

3.17 In its original submission, the company assumed that the direct utility gain should apply to everyone, regardless of whether they are shielding, partially shielding or not shielding. At consultation, the company updated its base case to apply the utility gain to the 82% of people shielding or partially shielding only, based on the survey by the Office for National Statistics. This was to align with the EAG's preference at the time of the first committee meeting. In its critique of the company's consultation response, the EAG noted that the company's vignette study reported that 50% of people would return to their pretreatment behaviour if there was a new variant against which tix–cil was not effective. The EAG noted that the in vitro data presented at the first committee meeting showed no neutralisation for tix–cil against most circulating variants. So, the EAG updated its base case to apply direct utility gain to only 50% of people. The EAG noted that the company's utility study did not specify a situation in which there could be no efficacy against 90% of circulating variants (as per the company's hypothetical base case). The EAG considered that, if tix–cil were to be offered when it was known to neutralise only 10% of circulating variants, this may not provide sufficient reassurance for most people to stop shielding. So, the EAG explored a scenario assuming that only 10% of people experience a direct utility gain. The patient experts at the second committee meeting considered that they would still have a utility benefit from treatment in situations in which tix–cil is only effective against 10% of circulating variants. At consultation, patient groups considered that even people who are not currently shielding because they are unable to could also benefit from prophylaxis because it could reduce anxiety. The committee considered

that there was a complex relationship between the perceived efficacy of tix–cil, the direct utility gain through reducing shielding and the increased risk of infection that would result from reducing shielding (see section 3.7). This relationship had not been modelled by the company. The committee considered that the extent of the direct utility gain would likely differ across patient groups. But it considered that most people would be reluctant to change their behaviour if they were told that treatment would only prevent 1 out of 10 infections, with the additional uncertainty that any remaining benefit of treatment could reduce as variants evolve. The committee concluded that the direct utility gain had been overestimated in both the company's and EAG's base cases. The committee considered the EAG's scenario in which direct utility gain was applied to only 10% of people to be more appropriate than both base cases. But the committee concluded that many people may not feel confident enough in treatment to change their behaviour in the company's hypothetical situation in which tix–cil is effective against 10% of variants. It thought that this could result in no direct utility gain. At the time of the second committee meeting, the committee considered that there was no evidence of effectiveness against 97% of circulating variants. This meant that the actual utility gain would have been much lower and the incremental cost-effectiveness ratio (ICER) would have been much higher than in the EAG's scenario.

Administration costs

3.18 In its original submission, the company said that tix–cil should be offered as part of routine outpatient appointments or through secondary care-led community services. It originally assumed a cost per administration of £41, based on 1 hour of band 5 hospital nurse time. It later updated its administration cost to £216 per administration based on the cost used by NHS England in the budget impact assessment for tix–cil. During the meeting, the company revised its suggested cost for administration to be half of this. The company explained that this was because the cost of £216 is for 2 doses of tix–cil, but tix–cil is given as a single dose. The EAG did not think that the cost of delivering tix–cil had been properly accounted for by the company. This was because it was not clear whether everyone who was eligible would be having routine appointments often enough to have tix–cil in such an appointment soon

after it became available. Also, it thought that the 1-hour observation period after administration required by the marketing authorisation may be impractical in a hospital setting. The EAG preferred to use a cost based on administration in COVID-19 Medicine Delivery Units (CMDUs). It considered the CMDU unit cost of £410 per administration of an oral antiviral to better reflect the cost for administering tix–cil. This was because it thought that a similar bespoke system would be needed to implement tix–cil in the NHS. At the first meeting, an integrated care system commissioning expert explained that their preference was for tix–cil to be delivered in primary care. This was because administration is relatively simple and there is additional complexity implementing the treatment in secondary care. At the second meeting, the NHS England expert explained that the setting in which tix–cil would be given is unclear. They advised that the committee should consider both the company's and EAG's estimates for the cost of administration. The committee concluded that the administration setting for tix–cil is uncertain. It considered both the company's and EAG's administration costs in its decision making.

Infection risk without tix–cil

3.19 To generate estimates of comparative effectiveness, the company estimated the risk of SARS-CoV-2 infection for people who did not have tix–cil. The relative risk reduction associated with treatment was applied to this risk to calculate the risk of infection for people having tix–cil. The company assumed the risk of symptomatic infection for people not having tix–cil was 22.58% annually. This was based on the average 7-day risk of reporting a positive test for SARS-CoV-2 in the general population of England between August 2021 and August 2022. The EAG highlighted that historical risks may not reflect current or future risks because this depends on circulating variants and protection offered by vaccines. It added that data for the general population may not be generalisable to people likely to have tix–cil. The committee initially considered it likely that the risk of infection in people eligible for tix–cil may be lower than the general population. This is because they modify their behaviour, which remains an effective way to reduce risk of infection, despite the substantial burden. It added that it was uncertain how risk may vary across different risk-based groups. The committee considered that

further research is needed to understand the background risk of infection in different populations. It considered that in the interim, a range of scenario analyses would help inform the sensitivity of the model to changes in the background risk of infection. In response to consultation, the company provided scenario analyses varying the risk of symptomatic infection in people not having tix–cil by 20% above and below the value used in its base case. The EAG did not consider this sufficient to cover the broad uncertainty about future risk of infection. The EAG added that the period used to estimate risk included the large peak of cases in late 2021 and early 2022. Restricting this period to estimate the risk in the last 3 months of data provided by the company (May to August 2022) provided an annualised risk of 8%. This was much lower than the lower bound estimate tested in the company's scenario analysis. The EAG explored the impact of scenarios halving and doubling the risk assumed in the company's base case. During the second meeting, the patient experts explained that a lack information to help them assess risk (outbreaks, case numbers) in local areas makes it more challenging for people who are immunocompromised to avoid infection. The committee acknowledged that testing for SARS-CoV-2 has now been significantly reduced. This means general population data may no longer be representative of actual case numbers. It also heard that patterns of infection in the general population are different now that COVID-19 is endemic. This is because rate of infection is driven by population-level resistance to mutations rather than the population transmission seen earlier in the pandemic that led to distinct waves of infection. The committee noted that the company had not provided any new data for the target population for the risk of infection in people not having tix–cil, so the risk was still uncertain. It concluded that, given the high uncertainty, both of the EAG's scenarios (halving and doubling the risk) should be considered in decision making.

Hospitalisation risk without tix–cil

3.20 The company estimated the risk of hospitalisation caused by COVID-19 for people who have not had tix–cil. The company's preferred source of data to estimate this risk was a study by Shields et al. (2022). This study assessed how vaccination affected hospitalisation and mortality for people with primary and secondary immunodeficiency in the UK. Based

on Shields et al., the hospitalisation rate for SARS-CoV-2 infection in the Omicron wave for people who did not have treatment was 15.9%. At the first meeting, the committee noted that the Shields et al. estimate was much higher than an estimate from Patel et al. (2022), which was considered in NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19. Patel et al. was a retrospective cohort study of people who had early treatment for, or who were diagnosed with, COVID-19 between 1 December 2021 and 31 May 2022. The study reported that 2.8% of people who had not had treatment were hospitalised with COVID-19 as the primary diagnosis. The committee concluded that Patel et al. included people eligible for COVID-19 treatment under the criteria defined by the McInnes report (see section 3.5). These criteria better aligned with the full marketing authorisation for tix–cil, but not with the subgroup used in the economic modelling. In response to consultation, the company stated that Patel et al. considered a broader population than the company are targeting. In addition, the company and other stakeholders highlighted that certain groups such as people with solid organ transplants or people with lymphoma or leukaemia may be at a much higher risk of hospitalisation or death due to COVID-19 than the eligible population as a whole. Stakeholders emphasised the need for separate analyses in these subgroups. In its critique of the company's response to consultation, the EAG acknowledged that specific patient groups are likely to have a higher hospitalisation risk. It noted that the company's model did not consider specific subgroups. So, it considered that the best approach was to use the average risk reported across the population in the marketing authorisation as provided by Patel et al. The EAG assumed a hospitalisation risk of 2.8% based on Patel et al. in its base case. But it explored higher rates of hospitalisation in its scenario analysis to reflect the potential higher risk in some specific groups. The committee had seen evidence from the OpenSAFELY study that validated the Patel et al study. OpenSAFELY calculated the hospitalisation rate for people at highest risk of hospitalisation (as outlined in the McInnes report) to be about 2.4%. It also calculated the hospitalisation rate for a subgroup of this group with renal impairment to be about 4.0%. During the second committee meeting, the clinical experts explained that SARS-CoV-2 has become less pathogenic and has caused less severe COVID-19 as it has

mutated. They noted that people with COVID-19 are now more likely to present with upper rather than lower respiratory tract infections, and that these are less severe. The committee considered that this meant that changes in the pathogenicity of the virus will result in changes to the hospitalisation rate. It concluded that the rate of hospitalisation is uncertain, but the estimate based on Shields et al. was high. The committee added that the estimate in Shields et al. was unlikely to represent the current risk of hospitalisation for most people eligible for treatment according to the marketing authorisation. The committee preferred to assume a hospitalisation rate closer to Patel et al., but noted that the rate would be dependent on the risk group under consideration (see section 3.5).

Long COVID

3.21 There were several differences between the company's and EAG's base case for long-COVID parameters. The cumulative impact of these assumptions on the ICER was substantial. Compared with the company's submission, the EAG preferred to assume a:

- lower risk of long COVID for people not hospitalised
- shorter duration of long COVID
- lower cost of managing long COVID
- smaller impact of long COVID on long-term utility.

In response to consultation, the company updated its base case to align with the EAG's preference for the cost and utility impact of long COVID. But the risk of long COVID for people not hospitalised and the duration of long COVID remained the same as for the first committee meeting. The committee considered that there was substantial uncertainty about the effects of long COVID. It also thought that it was unclear how long-COVID assumptions interact with the other modelled elements, for example, the risk of infection. It preferred the EAG's estimates because these were more closely aligned with the estimates used in NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19.

Invasive mechanical ventilation

3.22 To determine hospitalisation costs for acute COVID-19, estimates of the distribution across levels of hospitalisation care are needed. The company's model assumed that this distribution is the same for anyone hospitalised, regardless of whether they had prophylaxis with tix–cil. Levels of hospitalisation care included in the model were 'no oxygen', 'low-flow oxygen', 'non-invasive ventilation or high-flow oxygen' and 'invasive mechanical ventilation (IMV) or extra corporeal membrane oxygenation (ECMO)'. The company used a study by Cusinato et al. (2022), which considered data from a single UK hospital averaged across the first and second waves of COVID-19. Based on Cusinato et al., the proportion needing IMV was 15.40%. The EAG noted that Cusinato et al. provided data estimated separately for the first and second waves of COVID-19 and that the proportion needing IMV during the second (Omicron) wave was much lower than during the first wave. In its base case, the EAG preferred to use an estimate for the proportion needing IMV based on data for the general population. Based on this data, the proportion needing IMV was 4.92% for the year up to October 2022 and 2.51% for the most recent 3 months (August to October 2022). The EAG preferred to use the upper estimate of 4.92% because it acknowledged that the proportion of people on IMV may be higher in the population likely to be eligible for tix–cil. The committee agreed with the EAG that the risk of needing IMV had reduced since the start of the pandemic, and that data from the Omicron wave was more generalisable to the current situation. The clinical experts explained that the risk of needing IMV may be lower in people who are immunocompromised than in the general population. This is because of a reduced risk of hyperinflammatory reactions. The committee noted that, in NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19, the proportion needing IMV was 4.12%, which is closer to the EAG's preferred base case. It concluded that the EAG's estimate for the proportion needing IMV was preferred.

Cost-effectiveness estimates

Committee's preferred estimates

3.23 With the patient access scheme discount for tix–cil applied, the company's base case deterministic ICER was £15,201 per quality-adjusted life year (QALY) gained. This was on the hypothetical condition that tix–cil has neutralisation activity against 10% of circulating variants. The committee considered the company's hypothetical scenario to be outside of the single technology appraisal process. The committee can only consider efficacy estimates based on the available evidence at the point of decision making. The committee noted that, at the time of evaluation, tix–cil only likely retained neutralisation activity against around 3% of circulating variants. But it also noted that the company's scenario was relevant for future NICE processes (see section 3.13). It also noted that most of the QALY gain in the company's model came from the direct utility gain that was applied independently of efficacy. The EAG's base case of £54,668 per QALY gained included an assumption that the direct utility gain only applied to 50% of people. The EAG also provided a scenario in which the direct utility gain applied to only 10% of people, resulting in an ICER of £242,097 per QALY gained. But the committee considered the EAG's scenario with the direct utility benefit applied to 10% of people to be the most appropriate of the scenarios it had seen. This resulted in an ICER that would not be in a range that would usually be considered a cost-effective use of NHS resources. It was also conditional on tix–cil having evidence of effectiveness against 10% of circulating variants, which was not the case at the time of the evaluation. The committee thought that there was substantial uncertainty around important elements of the model. So, it was unable to conclude what the preferred ICER range was for tix–cil compared with no preventative treatment. Additionally, the committee was concerned that the uncertainty around the administration setting for tix–cil would mean that the benefit of the confidential patient access scheme may not be realised by all parts of the NHS.

Other factors

Equality issues

3.24 The committee discussed the potential equality issues raised during the evaluation. It noted comments from stakeholders that:

- People eligible for tix–cil are likely to be covered under the Equality Act 2010 because of long-term health problems and disabilities. It may also be harder for people with learning disabilities to implement and maintain protective measures against SARS-CoV-2 infection.
- Some minority ethnic groups are less likely to opt in for vaccination or post-exposure treatments, and are more likely to have health conditions that put them at greater risk of severe COVID-19.
- A disproportionate number of people unable to shield are from minority ethnic groups because of the higher likelihood that they are in employment without remote working options.
- People eligible for tix–cil are also more likely to experience mobility difficulties or be resident in health and social care settings. Travel to treatment centres may be an additional barrier.

  The committee considered that these were important issues. But its decision was based on a lack of expected clinical effectiveness and so very high ICERs. The committee did not expect its conclusions to differ across these groups. At consultation, patient groups emphasised that people who are immunocompromised should be able to have the same level of protection from COVID-19 as the general population has through vaccines. They added that immunocompromised people still cannot return to a more normal life, and that addressing the risk of COVID-19 in people who are immunocompromised must be prioritised. The committee acknowledged there was an unmet need for an effective prophylactic treatment in high-risk groups. But it considered that tix–cil could not meet this need because there was no evidence that it worked against 97% of circulating variants when guidance was produced.

Severity

3.25 The company did not make the case for the severity modifier, and the committee agreed that NICE's advice about conditions with a high degree of severity did not apply.

Uncaptured benefits

3.26 The committee considered whether there were any benefits not captured by the QALY calculations. The clinical experts noted that, if tix–cil were effective, it may reduce the number of people who are immunocompromised and have COVID-19. This could ultimately reduce the rate of variant change and mean fewer people being infected. The committee agreed that this was a theoretical benefit of treatment. But it concluded that clinical efficacy with tix–cil had to have been shown to justify this benefit. So, it did not consider that this benefit was relevant for decision making.

Conclusion

Recommendation

3.27 The committee agreed that there is an urgent unmet need for an effective prophylactic treatment for people who do not have an adequate response to vaccination. But the committee concluded that tix–cil should not be recommended because it is unlikely to be effective against most of the relevant variants at the time this guidance was produced. For this reason, the committee also considered that managed access was not appropriate. Instead, it concluded that further data collection would be a more appropriate way to resolve the key uncertainties (see section 4).

4 Recommendations for research

4.1 The committee acknowledged the need for tix–cil to be evaluated quickly against all new variants. It also suggested that the company enter tix–cil into ongoing platform trials. This would create a real-time link between in vitro and in vivo data.

4.2 The committee noted the lack of evidence on how the availability of a preventative treatment would affect shielding behaviours, and subsequently affect treatment efficacy. It also noted a lack of data on the relationship between perceived efficacy and direct utility gain. It considered that further research into these areas would be useful.

5 Implementation

Collaboration with Scottish Medicines Consortium

5.1 In Scotland, the advice will have the same status for health board consideration as other Scottish Medicines Consortium advice on new medicines.

6 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 members from across the 4 committees.

Committee members are asked to declare any interests in the technology 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

Richard Nicholas
Vice chair, technology appraisal committee C

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.

Anna Willis
Technical lead

Adam Brooke
Technical adviser

Louise Jafferally
Project manager

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