

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Tixagevimab plus cilgavimab for preventing COVID-19

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using tixagevimab plus cilgavimab 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 this technology. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using tixagevimab plus cilgavimab in the NHS in England.

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

The key dates for this evaluation are:

- Closing date for comments: 9 March 2023
- Second evaluation committee meeting: anticipated 4 April 2023
- Details of membership of the evaluation committee are given in section 5

1 Recommendations

1.1 Tixagevimab plus cilgavimab is not recommended, within its marketing authorisation, for preventing 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 these recommendations

Although clinical studies of tixagevimab plus cilgavimab suggest a reduction in COVID-19 infection compared with no preventative treatment, these studies were done early in the pandemic when different variants of the COVID-19 virus were circulating. More recent studies done in laboratories report that tixagevimab plus cilgavimab is unlikely to prevent infection with most of the relevant variants in the appropriate time period for this evaluation (January 2023 and the 6 months after).

The limitations in the clinical evidence mean it is not possible to make a reliable cost-effectiveness estimate. Tixagevimab plus cilgavimab is unlikely to be an acceptable use of NHS resources, so it 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, from now on referred to as tix–cil) 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 data expert 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 COVID-19 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 do not have a good enough response to vaccination. This includes people with genetic disorders, cancer, kidney or liver disease, transplant recipients, those with immune system disorders and those 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 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 [January 2023 technical briefing document 49](#) (based on all of the UK sequenced samples from 26 December 2022 to 1 January 2023) to determine the variants circulating at the time of this evaluation. Most new cases were Omicron subvariants BQ.1 and CH.1.1, but there were also concerns about fast-growing XBB lineage subvariants. The committee considered that SARS-CoV-2 is rapidly evolving and acknowledged that this makes assessing neutralising monoclonal antibodies difficult. The committee 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, whereby viruses with mutations that enable them to evade neutralisation will proliferate.
- Infrequent larger shifts of the virus – older versions of the virus may be incubating (for example in immunocompromised people, 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. The committee considered the possibility that neutralising monoclonal antibodies which currently have low efficacy regain their efficacy against future variants. The committee 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’. It therefore considered that the effectiveness of tixagevimab plus cilgavimab (tix–cil) over the appropriate time period of the future 6 months would be best indicated by neutralisation potential against currently dominant circulating variants and those that are currently growing the fastest. But the committee noted substantial uncertainty in estimating efficacy for future variants given the current understanding of the disease, and the rapidly evolving virus.

Patient perspectives

Ongoing impact of COVID-19

- 3.3 Patient experts described the ongoing impact of COVID-19 on their lives and the lives of others with a high risk of severe 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, and that people who are immunocompromised need to navigate multiple environments which no longer have the COVID-19 mitigation measures that they value. Another patient expert described how they were only able to leave the house for routine medical appointments and were 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. Patients 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 if a preventative treatment that reduces infection risk was available it 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 COVID-19 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 taking 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 COVID-19 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 continued to wear a mask and avoid crowded spaces. They added that even with tix–cil, and with treatments for severe COVID-19 infection available on the NHS, it was not enough for them to abandon all caution. Both patient experts expressed frustration that COVID-19 was developing rapidly and said that there needs to be a faster mechanism to ensure effective preventative medicines are available when needed, particularly over winter when meeting people outside is more difficult.

Decision problem

Eligible population

3.5 The company said in its submission that it was positioning tix–cil in a narrower population than that of the marketing authorisation and the final NICE scope, in those who are at the ‘highest risk of an adverse COVID-19

outcome'. In the 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 patients 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](#)). The committee noted that a similar report had been produced by the same group, which stratified cohorts in order of risk for preventative treatment (see the independent advisory group report concerning the use of COVID-19 directed antibodies in the prophylaxis setting in the highest risk clinical subgroups – [document 8 of the committee papers for the draft guidance](#)).

The committee recalled the marketing authorisation wording for tix-cil included 'those unlikely to mount an adequate immune response to COVID-19' and considered that this would include people in groups A1, A2 and B of the independent advisory group's report. The EAG noted that it was not clear from the company submission how the population that is eligible for tix-cil should be defined. It added that many of the inputs in the economic analysis were selected to reflect particular groups, and do not represent the eligible population as a whole, nor do they capture the heterogeneity within the eligible population. During the committee meeting, the company explained that it considered tix-cil should be made available to people with the highest risk only: those in groups A1 and A2. The clinical experts broadly agreed that the groups in the independent advisory group report aligned with the expected level of antibody response to vaccination, and that people in groups A1 and A2 were likely to have the poorest response and so be at the greatest risk of severe COVID-19 infection. But they cautioned that the groups represent a spectrum of risk, and added that some people have poor outcomes despite responding to vaccination. The clinical experts added that there was heterogeneity within the groups as well as across groups. The committee considered that the independent advisory group report was

appropriate for stratifying the need for preventative treatment. It agreed with the EAG that estimates of clinical effectiveness and cost effectiveness would vary across different risk-based groups because of heterogeneity. The committee would have preferred to see an analysis that included the whole population covered by the marketing authorisation (A1, A2 and B), in addition to a subgroup analysis in those with the highest risk (A1 and A2). The committee considered that focusing on the most severe subgroups would reduce the decision risk, but it had seen no evidence of different clinical or cost effectiveness to rule out group B, when the marketing authorisation includes this group. So, it concluded the eligible population should be groups A1, A2 and B.

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, which 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 company also 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, which 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 include a single dose of tix-cil only.

Clinical effectiveness

Outcomes

3.7 The company presented treatment outcomes in line with the NICE scope, including reduction in risk and severity of infection and improvements in anxiety, depression and health-related quality of life. The committee considered these appropriate outcomes for a preventative treatment but noted the EAG's comment that none of the clinical effectiveness studies provided by the company reported changes in health-related quality of life, anxiety or depression in those receiving tix-cil. The committee noted that there were additional complexities that needed further attention in addition to the original scope, such as the relationship between risk of infection, shielding behaviours and improvements in health-related quality of life. The patient experts explained that some shielding behaviours such as social distancing were likely to continue to some extent while taking tix-cil (see [section 3.4](#)). They said that decisions about distancing behaviours can take into account lots of different factors. For example, the risk from their existing condition, the current risk posed by COVID-19 and other viruses and the trust in the effectiveness of the treatment against current variants. People 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 the relationship between any reduction in infection risk from tix-cil and the potential benefit of a reduced need for shielding behaviours was complex. The committee considered that people may have different attitudes to risk of infection after treatment with tix-cil. There was the potential for some people to resume normal activities and possibly increase their risk of infection; or if they had limited trust in the treatment's effectiveness, they may not realise any quality-of-life benefit from the ability to reduce shielding behaviour. The committee acknowledged the challenges in relating efficacy of a preventative treatment to reduction in risk of infection, given the importance of behavioural changes leading to increased quality of life. This was made harder by a lack of health-related quality-of-life data from the trials. It added that the relationship between these factors was not reflected in the company's analysis, and that no

data had been presented on behavioural change. The committee noted the considerable uncertainty and considered this when interpreting the clinical evidence.

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 inadequate response to vaccination or at 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 (RT-PCR-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 was done before there were significant levels of natural immunity in the population from prior infection
- it was done when earlier variants of COVID-19 were prevalent and before newer variants emerged
- it used a single 300 mg dose of tix-cil.

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 patients on immunosuppressive treatments or with immunosuppressive disease
- the requirement 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, BA.2 were circulating. A total of 825 people received one 300 mg dose of tix-cil. Compared with 4,299 controls 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 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. and added that the population of US veterans was mostly male and older and may not be generalisable to the population 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 and added that with both studies, that there would likely be systematic differences between people who sought tix–cil treatment and those 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 [sections 3.8 and 3.9](#), the committee had concerns about generalisability 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 data expert 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 if treatments neutralise new variants, and therefore if 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 would take 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 data expert 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 ([document 9 of the committee papers for the draft guidance](#)) 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 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. 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 argued 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 and experts' views but 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. 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 committee meeting, the US Food and Drug Administration also announced that tix–cil is no longer authorised for emergency use in the US as it is unlikely to be effective against the variants responsible for more than 90% of infections. The committee concluded that tix–cil was unlikely to retain sufficient neutralisation activity against most variants circulating at the time, and this was the most useful estimate of effect against future variants (see [section 3.2](#)). 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.

Cost effectiveness

Economic model

3.13 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 year 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 patient’s lifetime. The model assumed a direct utility benefit for all patients in the tix–cil arm, as well as an efficacy benefit from a reduced risk of infection and a reduced severity of illness. The EAG considered the model structure to be appropriate except for the company’s handling of COVID-19 cases occurring after the first year. The model structure does not allow these patients to develop long COVID. The EAG believed that it would be better if the company attempted to model post year 1 cases of COVID-19 using

a model structure that tracks the number of patients who remain at risk of long COVID over time. It felt that the structure may have overestimated the benefit of tix-cil because it assumed that people who avoid a year 1 case of COVID-19 by having tix-cil are then protected from long COVID during all subsequent years. 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. The committee considered the model structure to be broadly appropriate, and felt that it would be difficult to model the impact of COVID-19 accurately after the first year because the virus is constantly evolving. The committee considered that modelling the benefit of tix-cil both from the utility gain from a reduction in shielding behaviours, and from reducing infection is uncertain when the interaction between these is complex (see [section 3.7](#)).

Direct utility gain

3.14 The company did a utility study to investigate the impact of the pandemic on people who are immunocompromised. Subgroups in the study included those who were fully shielding, partially shielding, and no longer shielding. The study collected quality-of-life data using the EQ-5D questionnaire from people who were immunocompromised and had not had a preventative treatment (untreated group). The study compared results to 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 which 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 according to a survey by the Office for National Statistics, to give a final utility gain. The company applied this to all patients taking tix-cil for a year after treatment (6 months for those experiencing infection, to account for the loss of

confidence in treatment in these people). The results of the study are considered confidential by the company so cannot be reported here. The EAG highlighted several limitations with the company's study. Most notably, the company assumed that the utility gain should apply to all patients. The EAG preferred to apply the utility gain only to people fully or partially shielding (82%). This was because it considered that those people not shielding, yet who are still eligible for tix-cil according to the marketing authorisation, would not benefit from a direct utility gain on having treatment. The EAG noted that this aspect of the economic analysis was subject to considerable uncertainty, because it was unclear how people's behaviour would change after having tix-cil, taking into account the relationship between changes in behaviour and the perceived efficacy of tix-cil (see [section 3.7](#)). The committee considered that the vignette describing someone having tix-cil did not align with the evidence for effectiveness or patient expert testimony, and is likely to overestimate the direct utility gain associated with tix-cil. The committee considered that there is a trade-off between the extent of shielding and the utility gain from stopping or reducing this, and the level of risk reduction that tix-cil will deliver before and after a decision to stop or reduce shielding. For example, if people's risk of infection reduces such that they interact more with others, the risk of infection would then increase. This complexity was not captured in the model. The committee agreed with the EAG that the change in shielding that will actually happen depends on someone's individual 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 (see [section 3.7](#)). The committee questioned whether this was adequately reflected in the vignettes presented to patients in the study. It concluded that the interaction between utility and tix-cil's effectiveness is likely to be complex and is not captured in the model or the vignette.

Administration costs

3.15 The company said that tix–cil should be offered as part of routine outpatient appointments or through secondary care-led community services. The company assumed a cost per administration of £41, based on 1 hour of band 5 hospital nurse time. 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 if everyone who was eligible would be having routine appointments often enough to have tix–cil in a routine appointment soon after it became available. Also, it felt that the 1-hour observation period after administration required by the marketing authorisation may be impractical in a hospital. 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 because it believed a similar bespoke system would be needed to implement tix–cil in the NHS. The committee heard from an integrated care system commissioning expert who explained that their preference was for tix–cil to be delivered in primary care, given that administration is relatively simple and given the additional complexity of implementation in secondary care. The committee considered that there was a substantial gap between company and CMDU estimates of administration cost, but concluded that the more conservative estimate using the CMDU costs was more appropriate, given the uncertainty about how tix–cil would be delivered.

Infection risk (without tix–cil)

3.16 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 those 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 those likely to have tix–cil. The committee considered it likely that the risk of infection in those eligible for tix–cil would be lower than the general population. This is because those eligible for tix–cil 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.

Hospitalisation risk (without tix–cil)

3.17 The company estimated the risk of hospitalisation caused by COVID-19 for people who did not have tix–cil. The company's and the EAG's preferred source of data to estimate this risk was a study by Shields et al. (2022), which 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 in the Omicron wave for people not treated in CMDUs was 15.9%. This was considered to best represent the risk of hospitalisation in the group likely to have tix–cil while not including the impact of treatments for COVID-19 infection that were not in routine commissioning. The committee noted that the Shields et al. estimate was much higher than an estimate considered from Patel et al. (2022) in [NICE's ongoing technology appraisal guidance on COVID-19 treatments](#). Patel et al. was a retrospective cohort study of non-hospitalised patients who received 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 untreated patients 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 DHSC's independent report on the highest-risk subgroups

with SARS-CoV-2 (see [section 3.5](#)), which better aligned with the full marketing authorisation for tix–cil, but not with the subgroup used in the economic modelling. It considered that the estimate in Shields et al. (2022) was unlikely to represent the current context of the disease for most people eligible for treatment according to the marketing authorisation. The committee concluded that the rate of hospitalisation is uncertain, but the estimate based on Shields et al. was high. The committee preferred to assume a rate of hospitalisation closer to Patel et al. but noted that hospitalisation rate would be dependent on the risk group under consideration (see [section 3.5](#)).

Long COVID

3.18 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 incremental cost-effectiveness ratio (ICER) was significant. 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.

The committee considered that there was substantial uncertainty about the effects of long COVID and about how these parameters interact with the other modelled elements, for example the risk of infection. It preferred to align with the EAG’s estimates as these are more closely aligned with the estimates used in [NICE's ongoing technology appraisal guidance on COVID-19 treatments](#).

Cost-effectiveness estimates

Company and EAG estimates

3.19 With the patient access scheme discount for tix–cil applied, the company’s base case deterministic ICER was £5,004 per quality-adjusted life year

(QALY) gained, and the EAG's was £18,646 per QALY gained. Probabilistic ICERs were broadly aligned with deterministic ICERs. The committee noted that, although both ICER estimates were below the threshold generally considered a cost-effective use of NHS resources, neither fully reflected the committee's concerns. The committee's key concern related to efficacy. Both base cases used real-world evidence from early in the pandemic, which is no longer generalisable to the current UK context (see [section 3.10](#)). The committee was concerned that tix-cil was unlikely to have significant efficacy against most variants circulating at the time of the evaluation. Secondary concerns included:

- Direct utility gain: both base cases assumed a relatively large direct utility gain for people treated with tix-cil, owing to their ability to reduce shielding behaviour, despite the patient experts saying that changes to their behaviour would be more limited than suggested by the vignette.
- Risk of SARS-CoV-2 infection without tix-cil: both base cases applied an annual risk of SARS-CoV-2 infection without tix-cil of 22.58%, which is highly uncertain and likely too high.
- Repeated dosing: both base cases assumed 2 doses of tix-cil would be given, which is outside tix-cil's marketing authorisation.
- Risk of hospitalisation for COVID-19 without tix-cil: both base cases assumed a hospitalisation rate of 15.9% which was felt to be unfeasibly high and much higher than the value preferred in [NICE's ongoing technology appraisal guidance on COVID-19 treatments](#).

Additionally, the committee was concerned that the commissioning expert's preference for administering tix-cil in primary care would mean that the benefit of the confidential patient access scheme would not be realised by all parts of the NHS.

Given the substantial uncertainty around important elements of the model, the committee was unable to conclude on an appropriate ICER for tix-cil compared with no preventative treatment. It considered that

tix–cil is not likely to be effective against most of the variants circulating in the near future, which would result in very high ICERs. The committee noted a scenario analysis which was mentioned by the company during the meeting. The company stated that when efficacy was reduced by 90% and utility gain reduced by 50% the ICER was still below the threshold for cost effectiveness. But the committee considered that if efficacy was reduced by 90%, the utility benefit would be minimal, as most people would not feel protected. So, it did not consider this scenario appropriate for decision making.

Other factors

Equality issues

3.20 The committee discussed the potential equality issues raised during the appraisal. 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 COVID-19 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.
- Those 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 not based on cost effectiveness, but rather a lack of clinical effectiveness, which it did not expect to be different in these groups.

Severity

- 3.21 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

- 3.22 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 immunocompromised patients with COVID-19, which 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 concluded that tix-cil had to have demonstrated clinical efficacy to justify this benefit and so did not consider that this benefit was relevant for decision making.

Conclusion

Recommendation

- 3.23 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 in the appropriate time period for this evaluation (January 2023 and the 6 months after). For this reason, the committee also considered that managed access was not appropriate. The committee instead concluded that further data collection as part of a clinical trial 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 an ongoing platform trial for preventative therapy (PROTECT-V) or other studies such as RAPID-PROTECTION. This would create a real-time link between in vitro and in vivo data.

- 4.2 The committee recommended that the healthcare system develop a rapid appraisal process for neutralising monoclonal antibodies such as tix-cil so that effective products can be fast-tracked to eligible patients.
- 4.3 The committee noted the lack of evidence on how the availability of a preventative treatment would impact on shielding behaviours, to determine the impact on both health-related quality of life and efficacy of treatment. It noted that conducting a survey; similar to that done by the Office for National Statistics, which investigated the proportion of high-risk patients shielding; would be useful.

5 Evaluation committee members and NICE project team

Evaluation committee members

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

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Technical adviser

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