NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19

In exceptional circumstances, the government, the NHS or the UK Health Security Agency may choose to use these treatments in a different way to that set out in section 1 of the guidance in situations such as:

- the widespread incidence of variants of COVID 19 to which the general population has no natural or vaccine immunity, or
- local or national circumstances of high rates of hospitalisation for 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 remdesivir and 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?

Issue date: January 2024

Note that this document is not NICE's final guidance on remdesivir and tixagevimab plus cilgavimab. 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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using remdesivir and tixagevimab plus cilgavimab in the NHS in England.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: 8 February 2024
- Second evaluation committee meeting: TBC
- Details of the evaluation committee are given in section 5

1 Recommendations

1.1 Remdesivir is recommended as an option for treating COVID-19 in:

- adults, only if they:
  - are in hospital with pneumonia, and
  - need low-flow supplemental oxygen, and
  - have a high risk of serious illness (risk factors as defined in section 5 of NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19).
- babies, children and young people, only if they:
  - are aged 4 weeks to 17 years and weigh at least 3 kg, and
  - are in hospital with pneumonia, and
  - need supplemental oxygen.

  Remdesivir is only recommended if the company provides it according to the commercial arrangement (see section 2).

1.2 Tixagevimab plus cilgavimab is not recommended, within its marketing authorisation, for treating COVID-19 in adults who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19.

Why the committee made these recommendations

Most of the clinical evidence for remdesivir and tixagevimab plus cilgavimab is highly uncertain because it comes from studies done before the dominant Omicron variants of SARS-CoV-2 (the virus that causes COVID-19). Also, some evidence does not reflect clinical practice at the time of this evaluation.

The cost-effectiveness estimates are highly dependent on how well each treatment works compared with standard care, and hospitalisation and mortality rates. Hospitalisation and mortality rates are lower with Omicron variants than earlier

variants in the pandemic. These lower rates increase the cost-effectiveness estimates.

Remdesivir in adults

Clinical evidence suggests remdesivir is effective for treating mild COVID-19 in adults. Clinical evidence on remdesivir for treating COVID-19 in adults in hospital with pneumonia is highly uncertain. But, it suggests that remdesivir can improve survival for adults needing low-flow supplemental oxygen compared with standard care.

The cost-effectiveness estimates for remdesivir are only likely to be within what NICE considers a cost-effective use of NHS resources for adults in hospital with pneumonia who need low-flow supplemental oxygen and who have a high risk of serious illness. So, remdesivir is recommended for treating COVID-19 in this group.

Remdesivir in babies, children and young people

The committee considered remdesivir for babies, children and young people (aged 4 weeks to 17 years and weighing at least 3 kg) in hospital with pneumonia who need supplemental oxygen.

There is limited clinical evidence comparing remdesivir with standard care for treating severe COVID-19 in babies, children and young people in hospital with pneumonia who need supplemental oxygen. So the cost-effectiveness estimates are highly uncertain. But there are limited treatment options licensed for this group and the number who would have remdesivir is very small. So, remdesivir is recommended for treating COVID-19 in this group.

Tixagevimab plus cilgavimab in adults

Evidence suggests that it is highly uncertain that tixagevimab plus cilgavimab is effective against Omicron variants of COVID-19. Because of this, it is not possible to reliably estimate its cost effectiveness, so it is not recommended.

2 Information about the treatments

Marketing authorisation indications

2.1 Remdesivir (Veklury, Gilead Sciences) is 'indicated for the treatment of coronavirus disease 2019 (COVID-19) in:

- adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment)'
- adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19'.

2.2 Tixagevimab plus cilgavimab (Evusheld, AstraZeneca) is indicated 'for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19'.

Dosage in the marketing authorisation

2.3 The dosage schedule for remdesivir is available in the summary of product characteristics for remdesivir.

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

Price

2.5 The list price for remdesivir is £340 per 100-mg vial (excluding VAT; BNF online, accessed October 2022). Costs may vary in different settings because of negotiated procurement discounts.

2.6 The company has a commercial arrangement (simple discount patient access scheme). This makes remdesivir available to the NHS with a discount. The size of the discount is commercial in confidence. It is the company's responsibility to let relevant NHS organisations know details of the discount.

2.7 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). 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 from several sources. See the committee papers for this evaluation and the committee papers for NICE's technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19 (TA878) for full details of the evidence.

Background

Impact of COVID-19

3.1 COVID-19 is the acute respiratory illness caused by the SARS-CoV-2 virus. It can range from mild to severe. In severe disease, excessive immune response to the virus may cause severe complications associated with hospitalisation and death. The need for organ system support, particularly respiratory support, is also a key feature of severe disease and can lead to substantial longer-term morbidity. COVID-19 may cause long-term symptoms that continue or develop after acute infection called 'long COVID'. These are health problems that fluctuate and can last several months or years which severely impact a person's physical and mental health, and potentially affect their ability to work, attend school or do their usual activities. During the first draft guidance consultation, consultees highlighted the treatment gap for children. At the second evaluation committee meeting (referred to as second meeting from now on) one clinical expert explained that COVID-19 rarely makes children unwell. But there is a small proportion of children with underlying conditions who have an increased risk of severe COVID-19 comparable with adults with underlying conditions. Many people are at increased risk of hospitalisation or death from COVID-19, including people who are

immunosuppressed (who have, for example, primary immunodeficiency, chemotherapy, or a transplant) or who have comorbidities (such as heart disease, respiratory disease, diabetes, neurological conditions). Some immunocompromised people are at risk of persistent viral infection if their immune system cannot control the virus. Patient experts explained that the increased risk of hospitalisation and death has led to some people changing their treatment, lifestyle and behaviour during the COVID-19 pandemic because of the need to shield. Patient organisations emphasised the need for treatments to prevent progression to severe COVID-19. They considered that routine availability of these treatments would support a return to normality for many people who already have disease burden from other comorbidities. The committee agreed that the risk of hospitalisation and death, and other longer-term impacts of COVID-19, can result in severe physical and mental burden and that there is an unmet need in this population.

The rapidly evolving SARS-CoV-2 virus

3.2 The global COVID-19 pandemic has caused unprecedented challenges to the healthcare system and this is reflected in the evidence collected on COVID-19 and treatments for it. The SARS-CoV-2 virus has evolved throughout the pandemic, as has the healthcare system's ability to respond to the virus. New variants of the virus and subvariants, referred to as variants of concern, have emerged throughout the pandemic. The properties of each variant can differ, such as levels of transmissibility and disease severity. The clinical experts explained that understanding of the disease has changed throughout the pandemic, with increasingly effective supportive care, vaccination and greater natural immunity. The committee understood that overall hospitalisation and mortality from COVID-19 has reduced, and the incidence of COVID-19 pneumonitis in hospital has lowered, as has the need for supplemental oxygen or mechanical ventilation.

3.3 At the time of the first evaluation committee meeting (referred to as first meeting from here on), the dominant variant of concern in the UK was the Omicron (B.1.1.529) sublineage BA.5. B.1.1.529 has multiple subvariants based on mutations in specific spike proteins. The clinical experts explained that changes in the epidemiology and context of COVID-19 have led to different characteristics of people with COVID-19 than seen earlier in the pandemic. At further committee meetings, the committee understood that circulating variants had continued to change and used the UK Health Security Agency's (UKHSA) technical briefings to monitor these variants. The clinical experts reported that 'viral persistence' from chronic infection is a concern in immunocompromised people because new variants or subvariants can develop if the viral infection persists. They also noted that offering a clinically ineffective treatment unable to clear the infection may increase the risk of future variants developing. At the third evaluation committee meeting (referred to as third meeting from here on), the clinical experts explained that there are better treatments available for COVID-19 and better knowledge of when to use them than earlier in the pandemic. Even so, they noted that hospital admissions for COVID-19 are still seen in people who are unvaccinated, no longer up to date with vaccination or who did not develop enough protection against COVID-19 after vaccination. The NHS England representative considered the current COVID-19 setting in clinical practice to be different to that of 12 months before the third meeting. They noted that COVID-19 policy was becoming 'business as usual' and transitioning into routine commissioning. The committee noted the changing nature of SARS-CoV-2, and context of the pandemic, affect the generalisability of the evidence for the treatments being evaluated. It agreed that the most appropriate approach would be to consider how relevant the clinical data are to the current endemic context of the disease at the time of this evaluation.

Remdesivir treatment positioning

3.4 For the third meeting, Gilead positioned remdesivir only for adults with pneumonia needing low-flow oxygen, for adults with pneumonia needing

low-flow oxygen who are immunocompromised and for children. It noted that:

- adults having low-flow oxygen:
  - this subgroup is distinct and readily defined and
  - the European Society of Clinical Microbiology and Infectious Diseases Guidelines (Bartoletti et al. 2022a and Bartoletti et al. 2022b) conditionally recommend remdesivir for COVID-19 in hospitalised adults needing no or low-flow oxygen.
- people who are immunocompromised have worse clinical outcomes with COVID-19 than the general population yet limited treatment options are available for this subgroup
- remdesivir is the only licensed treatment option for COVID-19 for children aged under 12 years and that very small numbers of children are hospitalised or die from COVID-19.

Clinical experts at the third meeting explained that it is incorrect to assume that a requirement for low-flow oxygen means less-severe disease because people having low-flow oxygen are considered to be critically unwell. They agreed that the number of children hospitalised because of COVID-19 is small. They also noted that many of the people admitted to hospital with severe COVID-19 have multimorbidity or are immunocompromised, because vaccinations are less effective for them. The committee concluded that there is an unmet need for more effective treatment options for people who need low-flow oxygen, people who are immunocompromised and children.

Defining target populations

Key definitions

3.5 The committee noted that the marketing authorisations for remdesivir and tixagevimab plus cilgavimab, which lower the risk of progression to severe COVID-19, were based on evidence from populations with slightly different definitions of high risk. For example, some trials included people

with at least 1 risk factor for severe COVID-19 whereas some had specific age requirements. Understanding of the prognostic effects of risk factors has developed throughout the pandemic, and therefore the available evidence may represent a heterogeneous population. The committee acknowledged the potential limitations of the available evidence but considered it important to clearly define high risk and therefore treatment eligibility. PANORAMIC was a large UK platform trial that included people with many different potential risk factors, including chronic conditions and immunosuppression, and allowed enrolment of people aged over 50 years. It also allowed for clinical judgement of clinical vulnerability. The independent advisory group report commissioned by the Department of Health and Social Care (the McInnes report from here on) defined groups of people with the highest risk for adverse COVID-19 outcomes, including hospitalisation and death (see section 5 of TA878). The NHS interim commissioning policy on treatments for non-hospitalised patients with COVID-19 (now superseded, see section 3.11) used the McInnes report to define high risk. The clinical experts noted that some treatments were available through the interim commissioning policy at the time of PANORAMIC enrolment. The interim commissioning policy's and McInnes report's high-risk definition would have influenced the risk level of people who enrolled in PANORAMIC. At the first meeting, the committee considered this in its evaluation of the clinical evidence. The committee considered the different definitions of risk and concluded that PANORAMIC included people who had a lower risk of severe COVID-19 compared with the McInnes high-risk definition.

Other key risk groups

3.6 The clinical experts gave examples of additional considerations around how high-risk groups are affected differently:

- They highlighted different observed responses to vaccination. The OCTAVE study assessed vaccine response in immunocompromised people, including people with inflammatory arthritis, liver disease and

kidney disease. OCTAVE showed differential antibody reactivity depending on disease group. The committee considered how this may affect who is at high risk. This is because people with a lower vaccine response have increased risk of adverse outcomes from COVID-19 infection compared with the general population, particularly if they are having rituximab.

- They cited an OpenSAFELY cohort analysis study that assessed the risk of severe COVID-19 in people with immune-mediated inflammatory diseases. This showed that people with inflammatory diseases who are having systemic therapies had similar rates of hospitalisation and death as people having targeted therapies, except for rituximab. The committee considered the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are taken, but the relationship may be complex and differ in other disease areas.

The clinical experts explained that there is a small group of children who are also at high risk of severe COVID-19 and may not be able to access treatment. The committee noted that the McInnes report has made additional consideration for people 12 years and over in its definition of high risk. The committee concluded that it would expect clinicians to offer treatments using the McInnes high-risk criteria when applicable across all age groups, in line with product marketing authorisations.

Age as an independent risk factor

3.7 PANORAMIC allowed enrolment of people aged over 50 years who did not have any comorbidities. The committee questioned the inclusion of age over 50 years as an independent risk factor for progression to severe COVID-19. The clinical experts considered that age was an important risk factor. They cited the International Severe Acute Respiratory and emerging Infections Consortium (ISARIC) study of mortality in the earlier stages of the pandemic that defined age over 50 years as a risk factor

(Knight et al. 2020). They noted that age over 70 years may be an important determinant of mortality but also considered that the relationship between age and comorbidities is complex, particularly for immunocompromised people. One of the companies considered that age was an important risk factor but noted ongoing debate about what age is appropriate for inclusion in the high-risk group. The clinical experts agreed it was challenging to define an exact age that defines high risk. The committee was concerned that making a recommendation based on age might cause inequality, given that age is a protected characteristic. For this reason, NICE technology appraisal guidance on medicines for cardiovascular disease do not include criteria based on age, despite it being a well-recognised risk factor. The committee noted that age is a protected characteristic and any recommendation including age would need to be assessed for impact on equity of treatment. At the first meeting the committee concluded that more evidence was needed on the impact of age to justify including it as an independent factor that increases risk at similar levels to other risk factors defined in the McInnes report. This should include evidence, adjusted for these risk factors, from a vaccinated population who are infected with the Omicron variant. At the second meeting, the committee noted the additional evidence provided by consultees which showed a statistical relationship between age and comorbidities. The committee acknowledged that age is a risk factor for progression to severe COVID-19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee concluded that age over 70 years is likely to be confounded by underlying conditions which could also contribute to increased risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. It said the evidence should include age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects. The committee concluded that the McInnes report's definition of high risk included the

most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor.

High risk of progression to severe COVID-19 definition

3.8 The assessment group (AG) explained the approach used to model high-risk groups in its economic model (see section 3.27). At the first meeting, it assumed that people had general population survival, with a starting age of 56.6 years and the same hospitalisation rate as PANORAMIC. Therefore, no individual high-risk subgroups were modelled based on specific baseline characteristics, and these characteristics were explored in sensitivity analyses that represented the entire group eligible for treatment. The clinical experts acknowledged the difficulties of defining high risk by separate subgroups. The committee recognised that the decision problem for this evaluation required a definition of who has a high risk for progressing to severe COVID-19. It recognised the limitations of the model in characterising a group at high risk but considered the hospitalisation rate to be the most important variable for sensitivity to the clinical inputs (see sections 3.26 to 3.27). At the second meeting, the committee repeated these limitations of modelling separate high-risk groups and concluded that a single definition of high risk should be used. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. For example, additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. The committee did not see additional evidence to justify splitting the high-risk group. The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19, and this did not include age as an independent risk factor. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people

who were infected with Omicron variants. The committee considered the use of the Q-COVID risk calculator in clinical practice but concluded it had limited applicability because of the limitations of the model. The committee noted a wider definition of risk, from PANORAMIC, was included in the marketing authorisations for each of the treatments (see section 3.5). However, it concluded that the definition of risk in the McInnes report is the most robust definition. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected.

Immunocompromised definition

3.9 For remdesivir in the severe COVID-19 setting, Gilead positioned people who are immunocompromised as a separate subgroup (see section 3.4). Limited evidence was provided to define the subgroup of people who could be considered to have an immunocompromising condition. The NHS England commissioning policy for remdesivir defines people who are significantly immunocompromised as having "significant impairment of humoral immune response (antibody production) and/or cellular immune competence". The committee agreed it was appropriate to consider people who are immunocompromised as a separate subgroup. This is because the evidence suggests that survival and the clinical course of the disease in this group is different than in the general population. This is partly because vaccinations are less effective for people who are immunocompromised. The committee noted that the McInnes report defines conditions that impact immune function and could be used to identify people who are immunocompromised and may benefit from treatment with remdesivir in clinical practice. It considered that the McInnes report, despite being developed for people with high risk of progression to severe COVID-19, provides a comprehensive definition for people who are immunocompromised in the severe COVID-19 setting.

Children

3.10 Gilead considered a separate analysis should be done for remdesivir in children with pneumonia requiring supplemental oxygen. This is because it is the only licensed treatment option for COVID-19 in children aged under 12 years. A separate analysis was not considered for children with mild COVID-19. The committee noted that very small numbers of children are hospitalised or die from COVID-19. The clinical experts explained that, unlike in adults, severe COVID-19 in children is generally driven by viral reproduction rather than hyperinflammatory response. Therefore, there is clinical rationale for why remdesivir, an antiviral, would be effective in children and resolve unmet need for this population. The committee considered this subgroup appropriate but noted limited clinical evidence in this population.

Current clinical management of COVID-19

Treatments for mild COVID-19

3.11 Current clinical management of mild COVID-19 (includes hospital-onset COVID-19) in people who have a high risk for progression to severe COVID-19 includes treatments commissioned through an NHS interim commissioning policy. In December 2023, the policy was:

- first-line treatment: nirmatrelvir plus ritonavir (antiviral), as per TA878
- second-line treatment: sotrovimab (neutralising monoclonal antibody) as per TA878
- third-line treatment: remdesivir (antiviral), where supply is available
- fourth-line treatment: molnupiravir (antiviral).

People who have symptoms and are not showing signs of a clinical recovery must start treatment as soon as possible after testing positive for COVID-19. The professional organisations explained there are different aims of treatments at this stage of COVID-19. Antivirals aim to reduce viral load and viral replication, which may reduce risk of severe disease. They are administered orally or intravenously. Neutralising monoclonal

antibodies also aim to do this by binding to specific viral proteins to block viral infection. They are administered as injections or infusions (intravenously, intramuscularly or subcutaneously, depending on the treatment).

Treatments for severe COVID-19

3.12 For people hospitalised with severe COVID-19, the suitability of certain interventions can vary based on respiratory support requirements, minimum COVID-19 symptom duration or renal impairment status:

- People admitted to hospital with COVID-19 who do not need oxygen: remdesivir is an option through the NHS interim clinical commissioning policy on remdesivir for people who are significantly immunocompromised.
- People admitted to hospital with COVID-19 who need low-flow oxygen or non-invasive mechanical ventilation:
  - dexamethasone is standard care
  - remdesivir is an option subject to eligibility criteria, through the NHS interim clinical commissioning policy on remdesivir
  - tocilizumab is an option as per TA878.

Clinical effectiveness

Assessment group's indirect comparison approach

3.13 In line with best practice guidance for assessing COVID-19 treatments (Elvidge et al. 2021), the AG used systematic reviews and network meta-analyses (NMAs) from publicly available sources. These reviews (COVID-NMA and metaEvidence) are updated regularly as 'living' systematic reviews.

The mild COVID-19 setting included these clinical endpoints:

- relative risk of hospitalisation or death
- relative risk of all-cause mortality at 28 days.

The severe COVID-19 setting included these clinical endpoints:

- hazard ratio of time to death
- hazard ratio of time to discharge
- relative risk of clinical improvement at 28 days.

The AG highlighted some significant limitations of their approach, because of the changing nature of COVID-19 (see section 3.2). Each trial included in the analysis was done at a different time in the pandemic. Most trials compared an individual treatment against the standard care at the time. Standard care has evolved in response to better understanding of the disease course, changes to respiratory support and use of dexamethasone. The context of the disease also changed with different circulating variants of concern, and changes in protection through vaccinations and natural immunity over time. Each of these limitations were compounded by significant differences in trial design, baseline characteristics and geographical locations. The AG explained that the analysis assumed any relative effect of treatment is transferable to current clinical management. The clinical experts commented that meta-analysing the trial results may not be appropriate. This is because the weighting of each trial in a meta-analysis may not consider the relevance of the context of each trial within the analysis, for example, with different variants. The committee recognised the high levels of uncertainty with each treatment effect and the context-specific nature of the evidence. To characterise the uncertainty, rather than use probabilistic sensitivity analysis, the AG ran scenarios using the mean and the upper and lower confidence limits of each efficacy estimate. This provided scenarios showing 'mean efficacy', 'lower efficacy' and 'higher efficacy' estimates. At the third meeting, this was replaced by 'mean efficacy', 'low efficacy' and 'mean–low efficacy' (the midpoint between the mean and low efficacy scenarios). The AG cautioned the committee that the lower and higher efficacy scenarios had limitations because they represented a different uncertainty to that in the evidence base; they represented uncertainty on the estimates in the trial

and were therefore sensitive to the number of events in each trial, rather than the context in which the trial happened. Therefore, they would not be sensitive to changes in efficacy against new circulating variants of concern. The committee understood the limitations of the scenario analysis. The committee considered it represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty. At the first draft guidance consultation, consultees highlighted the lower efficacy scenarios were arbitrary and a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The NICE health technology evaluations manual states that the committee's preferred cost-effectiveness estimate and scenario analyses should be probabilistic unless deterministic model results can be justified. Probabilistic sensitivity analysis explores the uncertainty around the mean health and cost input parameters in the model, within distributions chosen to characterise the uncertainty associated with the precision of mean parameter values. The committee noted that the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. The uncertainty from whether the efficacy data reflected NHS clinical practice was greater than uncertainty from the efficacy estimates and would not have been captured in the probabilistic sensitivity analysis. A probabilistic sensitivity analysis was therefore considered inappropriate for capturing the high uncertainty in the models and uninformative for decision making. Consultees also noted that the mortality assumptions meant that treatment in hospital had a higher mortality risk compared with standard care. In response, the AG updated this assumption and capped the mortality rate to equal 1 for the low-efficacy scenario. At the third meeting, the hazard ratios used for the risk of mortality for remdesivir were all below 1. So, the AG did not apply capping to these scenarios because it considered it plausible that other aspects such as time to discharge and clinical improvement could be worse as a result of preventing death. Consultees noted the systematic reviews which informed the NMAs did not adhere to established reviewing

methods and missed 2 key clinical trials (SOLIDARITY and ACTT-1). The AG addressed this concern and provided scenarios for the committee which included evidence from SOLIDARITY and a scenario in which time to discharge for remdesivir was informed by ACTT-1.

Generalisability of trial evidence to current endemic context

3.14 The committee acknowledged that most trials informing the clinical efficacy data pre-dated the Omicron variant, which was the dominant circulating variant of concern at the time of this evaluation. Clinical experts said extrapolating data from past trials was misleading because epidemiology and virus characteristics have changed (see section 3.2). The clinical experts and the committee considered it appropriate to consider how the clinical evidence would generalise to the endemic setting. It considered the main generalisability concerns to be:

- changes in population immunity through natural immunity and vaccination
- changes in the pathogenicity of the virus
- increased effectiveness of supportive care as knowledge of the virus evolved
- other differences specific to the context of a pandemic setting, including staff shortages, access to personal protective equipment, greater urgency for data collection, fear, and social distancing that reduced the opportunity for transmission.

The absolute changes in these settings were considered in the economic modelling when possible. However, the committee considered the relative risks from these trials would also lack generalisability because there would be interaction between some of these concerns and treatment effect in the trial. This would likely favour the treatments compared with standard care, because the trials were done when key outcomes of hospitalisation and mortality were significantly higher. Therefore, the committee considered that mean-

efficacy scenarios from these trials likely reflect the highest clinical effectiveness or 'ceiling efficacy' of the treatment. The committee concluded that changes in best supportive care and higher vaccination rates mean that any limited relative treatment effects seen during the pandemic setting would have less effect in an endemic setting. This is because any limited benefit in the pandemic setting would likely be further limited or potentially have no difference in treatment effect compared with standard care (hazard ratios would tend towards 1) in an endemic setting.

3.15 The committee recognised that the treatment effects need to be considered separately as follows:

- **Remdesivir in the mild COVID-19 setting**: Evidence on remdesivir was collected before the Delta wave and before the widely vaccinated and naturally immune population.
- **Remdesivir in the severe COVID-19 setting**: The committee considered the additional evidence on remdesivir from SOLIDARITY provided by Gilead during the first draft guidance consultation. It understood that inclusion of SOLIDARITY in the NMA resulted in a statistically significant but smaller mortality benefit for remdesivir compared with standard care. The committee noted that SOLIDARITY was done before the Delta and Omicron waves, and widespread vaccination. It also noted key study limitations highlighted in the trial publication, including that standard care differed within and across countries. The committee understood that standard care including dexamethasone use, and the hospital practices of escalation to mechanical ventilation as part of standard care, varied in hospitals when SOLIDARITY was done. The committee also noted that the standard care arm in the economic model is modelled on the dexamethasone arm of the RECOVERY trial which enrolled people hospitalised with COVID-19 in the UK. The committee considered the inclusion of SOLIDARITY in the NMA important and appropriate for

remdesivir. Because of the generalisability issues arising from trial limitations, the applicability of the mean-efficacy estimate from SOLIDARITY to the current NHS setting is highly uncertain and likely to be the ceiling efficacy estimate (see section 3.14). The committee remained cautious about the treatment effect of remdesivir shown in observational evidence submitted by Gilead during the first draft guidance consultation when the original SOLIDARITY evidence already showed limited mortality benefit. The committee concluded that SOLIDARITY was an early study in the pandemic and there was no clinical evidence available for remdesivir in the context of the current endemic setting with a widely vaccinated and naturally immune population and the Omicron variant. The committee concluded that significant uncertainty remained in terms of generalisability of the trial evidence for remdesivir.

- **Tixagevimab plus cilgavimab (mild COVID-19 setting)**: The collected evidence on tixagevimab plus cilgavimab partly covered the timeline of the Delta wave but was before the Omicron wave. The committee noted that considerable uncertainty remained about the relative treatment effects on hospitalisation and mortality rates. This is because of generalisability of trial evidence to the endemic setting with a widely vaccinated population with additional and natural immunity, as well as the particular sensitivity of these antibodies to changes in variants.

In vitro evidence

3.16 In vitro (laboratory) evidence may provide additional information on whether there is a realistic clinical possibility that a treatment retains efficacy against currently circulating variants. In vitro neutralisation assays can be used to assess if treatments can neutralise new variants, which can then be used to infer 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 clinical trial evidence. A large body of in vitro evidence suggests that specific COVID-19 treatments may no longer

show neutralisation activity against some circulating Omicron variants. In the first meeting, the committee could not comment on the validity of in vitro data and welcomed comments in response to consultation. Because of this, NICE commissioned an 'in vitro expert advisory group' made up of experts in infectious disease, virology, vaccine epidemiology, immunology and pharmacology (see the in vitro expert advisory group report in the final draft guidance committee papers for TA878). The group developed a decision framework to link in vitro neutralisation data to clinical outcomes and helped the committee use the framework to interpret the in vitro evidence. The committee understood this framework and also noted the latest in vitro evidence.

3.17 The in vitro evidence considered by the committee was against newly circulating variants and was available shortly before the second meeting. Because the COVID-19 landscape is rapidly evolving, a systematic review of the in vitro data was not possible. Guided by the in vitro expert advisory group, the committee identified 5 in vitro studies that investigated the effectiveness of the neutralising monoclonal antibodies on circulating variants at the time of the analysis (BQ.1.1 and XBB). One in vitro study (Imai et al. 2023) also investigated the effectiveness of the antivirals against BQ.1.1 and XBB. The in vitro studies showed that some antiviral treatments retain the ability to neutralise a range of SARS-CoV-2 variants and subvariants, including those circulating at the time of this evaluation and that are rapidly increasing. The committee also considered the in vitro evidence that was systematically collected and summarised by multiple organisations including the 'Stanford Coronavirus Resistance Database'. For further details on the in vitro evidence, see the in vitro slides in the final draft guidance committee papers for TA878.

Generalisability of clinical effectiveness

3.18 By using the framework and the evidence the committee concluded that there was no in vitro evidence showing reduced clinical efficacy of remdesivir across the variants tested. However, as discussed in the first

meeting and based on the in vitro expert advisory group framework, the committee confirmed that the neutralising monoclonal antibodies such as tixagevimab plus cilgavimab bind to spike proteins which are changing with each new variant and subvariant. The committee concluded that neutralising monoclonal antibodies may lose the ability to neutralise the virus over time, potentially as a result of the virus evolving to evade the treatments in use.

3.19 At the second meeting, the committee noted that BQ.1 and BQ.1.1 were the currently circulating Omicron subvariants (see section 3.2) in the UK. These are different to BA.5 which was prevalent at the time of the first meeting. As noted in section 3.18, the clinical effectiveness of neutralising monoclonal antibodies is likely to vary by variant. At the second meeting, the committee carefully considered in vitro evidence for these treatments against the dominant variants. The committee understood that in vitro studies differ by how they are done and their quality. The clinical experts agreed with the in vitro expert advisory group's framework and explained that evidence showing no or limited neutralisation activity against a specific variant means there is unlikely to be any plausible clinical activity against that variant. The committee acknowledged that there was the possibility for tixagevimab plus cilgavimab 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. Taking account of study differences, clinical expert conclusions and the framework (see sections 3.16 to 3.18) the committee concluded that tixagevimab plus cilgavimab was unlikely to retain sufficient neutralisation activity against most variants circulating at the time of this evaluation. Also, this was the most useful estimate of effect against future variants. The committee concluded the clinical effectiveness of tixagevimab plus cilgavimab is highly uncertain in terms of reducing hospitalisation or mortality rates.

Relative treatment effects for mild COVID-19

3.20 For the mild COVID-19 setting, the clinical experts considered the relative treatment effects of each treatment to be uncertain without considering the wider context of the trials (see section 3.2). The committee noted the potential for bias in all the comparisons because the indirect comparison used pairwise analysis rather than a network to produce its comparisons. They also noted that multiple interventions could be required and cautioned against the side-by-side comparison of treatment effects (as a fully incremental analysis). The committee considered that the heterogeneity of trial outputs and generalisability contributed greater uncertainty to the decision problem.

- **Discussion on remdesivir**: The committee noted the statistically significant reduced risk of hospitalisation from the evidence synthesis based on the PINETREE trial (a double-blind, randomised controlled trial of remdesivir in the mild COVID-19 [non-hospital] setting, Gottlieb et al. 2022).The committee also acknowledged the lack of evidence of any survival benefit for remdesivir with no events in either arm. It considered all efficacy estimates for remdesivir in the mild COVID-19 setting because of the uncertainty.
- **Discussion on tixagevimab plus cilgavimab:** The committee did not consider the relative efficacy of tixagevimab plus cilgavimab to be generalisable to currently circulating variants because of concerns over its ability to neutralise these variants. So, it did not consider relative treatment effects for tixagevimab plus cilgavimab.

Relative treatment effects for severe COVID-19

3.21 For people presenting to hospital with COVID-19, the clinical experts noted that standard care had significantly changed over time (see section 3.2). They also cautioned against directly comparing treatments because there is a distinct pathway of care for severe COVID-19. This includes when to use respiratory support, anticoagulation treatments and corticosteroids. The clinical experts considered that remdesivir is currently

used for some people with lower oxygen needs but its use is not clearly defined. The committee noted that remdesivir, a broad-spectrum antiviral, was one of the first available treatments and has historic use as a standard care early in the pandemic. The committee considered the individual evidence from SOLIDARITY as well as the updated NMA with the SOLIDARITY results. In SOLIDARITY the mortality rate ratio was 0.91 (95% CI 0.82 to 1.02) in the overall group, 1.13 (95% CI 0.89 to 1.42) in people having ventilation and 0.87 (95% CI 0.76 to 0.99) in people not having ventilation and having oxygen. The updated NMA for remdesivir shows a hazard ratio of 0.85 (95% CI 0.76 to 0.95) for mortality versus standard care. The committee noted that it was not possible to make a decision based on the confidence intervals of data from SOLIDARITY and the pooled NMA analysis. This is because the precision around the confidential interval is reflective of population characteristics and standard care practices earlier on in the pandemic. The committee said these were important considerations for severe COVID-19, for which standard care has considerably changed since the start of the pandemic when SOLIDARITY was done. It said this would have a considerable impact on the limited relative mortality benefit seen for remdesivir (see section 3.14). The committee therefore interpreted the available evidence with caution and considered a threshold analysis using the mortality rate ratios of 0.85 to 1.00. The committee was more certain that the relative mortality rate ratio would tend towards 1.00 because of generalisability concerns (see section 3.14). The committee noted that any mortality benefit is likely to be minimal when the HRs are close to 1, and stronger clinical evidence is needed to justify a difference in relative clinical effects. The committee concluded that it could not be certain of remdesivir's clinical efficacy in terms of mortality benefit when the potential benefit is minimal. The committee concluded there was insufficient evidence to show meaningful difference in mortality benefit versus standard care.

Subgroup analyses for remdesivir

3.22 For the third meeting, Gilead provided a targeted evidence submission for the populations with severe COVID-19 in which it considered remdesivir to be most effective. This included the subgroups of adults needing low-flow oxygen, people who are immunocompromised, and children (see section 3.4).

Low-flow oxygen at baseline subgroup

3.23 The committee considered the antiviral mechanism of remdesivir in the context of COVID-19. It considered there may be plausible differences in effectiveness explained by oxygen requirements at the start of treatment. This is because the need for low-flow oxygen can suggest an earlier phase of severe COVID-19 that may respond to an antiviral better than disease with higher-flow oxygen requirements. The committee also noted significant differences between low-flow and high-flow oxygen requirements in some of the evidence. For the third meeting, Gilead submitted 3 systematic literature reviews and meta-analyses of randomised controlled trials reported by Beckerman et al. (2022), Amstutz et al. (2023) and Huang et al. (2023). These reviews showed a significant 28-day mortality benefit for remdesivir compared with standard care in adults who need low-flow oxygen. This benefit was further validated by several real-world evidence studies. Gilead preferred to use Huang et al. to inform 28-day mortality in the model. This was because the data searches by Huang et al. were done up to the most recent time period (February 2023). Also because the risk ratio outcome aligns with the input parameter used in the AG model and was a more conservative estimate of 28-day mortality compared with Beckerman et al. The AG preferred to use the individual patient data meta-analysis results from Amstutz et al. to inform 28-day mortality in the model. Gilead was concerned that Amstutz et al. reported results for people with both no oxygen and low-flow oxygen requirements and did not focus on the low-flow oxygen subgroup that was being considered in the third meeting. The AG noted that a sensitivity analysis by Amstutz et al. did not show a significant difference in relative benefit between the no oxygen and the low-flow oxygen groups. It also

noted that the panel for NICE's rapid guideline on managing COVID-19 agreed to include people having supplemental oxygen in the SOLIDARITY meta-analyses for people having low-flow or no oxygen at baseline. The AG combined the evidence for the no oxygen and the low-flow oxygen groups to reduce the uncertainty in the efficacy estimate for remdesivir. But, it also did analyses excluding data from SOLIDARITY and including data only for the low-flow oxygen group. At the third meeting, the clinical experts noted that people who do not need supplementary oxygen are clinically distinct to people who need low-flow oxygen and that they have different clinical outcomes. The committee agreed that differences in absolute effects may vary but that the relative effect was expected to remain the same between people who do not need supplementary oxygen and people who need low-flow oxygen. The AG scenarios also applied 3 assumed efficacy levels (mean, low and mean–low; see Section 3.13) for each of the combinations of mortality estimates for remdesivir (Amstutz et al. with SOLIDARITY, Amstutz et al. without SOLIDARITY and Huang et al.). The committee recalled the consideration from earlier meetings that including SOLIDARITY in the NMA was important and appropriate for remdesivir (see section 3.15). It considered the mean efficacy scenarios were likely to overestimate the benefit of remdesivir compared with standard care in the current endemic setting (see section 3.14). So, it preferred the low and the mean–low efficacy scenarios.

People who are immunocompromised

3.24 The committee noted that there was no randomised clinical evidence provided for people who are immunocompromised in the current endemic setting. Gilead referenced a large real-world evidence database study (Mozaffari et al. 2023) that suggested a benefit for remdesivir compared with standard care. The AG considered the relative efficacy from this study was less robust than transporting the relative clinical effect from the meta-analysis of randomised trials from Amstutz et al. The committee agreed with the AG and noted that using non-randomised evidence has

substantial potential for risk of bias, but noted substantial uncertainty with the AG's approach.

Children with severe COVID-19

3.25 The committee noted that there was no comparative clinical evidence provided for children with severe COVID-19. However, limited evidence showed that remdesivir is safe and well tolerated. The AG considered the relative effect from Amstutz et al. (2023) should also be used for this population in the absence of any comparative efficacy evidence. The committee considered that using Amstutz et al. was appropriate for this population.

Economic model

Model structure and key drivers of cost effectiveness

3.26 The economic model for this appraisal was developed by the AG and informed by Rafia et al. 2022 that evaluated COVID-19 treatment in a pre-hospital setting. The AG used a decision tree model structure for treatments in the mild COVID-19 (non-hospital) setting that joined with a partitioned survival model in the severe COVID-19 (hospital) setting. The decision tree had either an active treatment or standard care arm offered to people with COVID-19. People were hospitalised at a baseline standard care rate, or not hospitalised. Those that were hospitalised entered the partitioned survival model. This section of the model had 3 mutually exclusive health states: discharged from hospital and alive, hospitalised with or without COVID-19, and death (from COVID-19 or any other cause). For people in hospital, level of respiratory support was assumed based on COVID-19 severity, with associated costs and disutilities by health state. The clinical inputs for each of the clinical efficacy scenarios were from the indirect treatment comparison (see section 3.13). The AG fitted parametric distributions to long COVID data from the Office for National Statistics. Consultees highlighted that the long COVID duration was underestimated and should be higher than the 108.6 weeks used by

the AG. In response the AG updated the model which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. The AG assumed that 100% of people in the severe COVID-19 setting and 10% in the mild COVID-19 setting would have long COVID. Consultees noted that the proportion should be reduced for the severe COVID-19 setting and increased for the mild COVID-19 setting. The AG considered its original assumption to be conservative and therefore appropriate because alternative evidence had not been explored. The committee noted that the treatment efficacy was highly uncertain and the most important driver of cost effectiveness, but also noted the following other key drivers of model outputs:

- The key driver of the outputs in the mild COVID-19 setting was the baseline rate of hospitalisation. This is because it determined how many people were included in the high-cost and low-utility hospital setting.
- The key drivers of the outputs in the severe COVID-19 setting were the baseline standard care assumptions for overall survival and time to discharge. The model was adjusted so the baseline standard care assumptions were reflective of current UK clinical practice. NICE's rapid guidelines on COVID-19 were used to make this adjustment. The clinical experts commented that, because of changes to the disease, the outcomes for these treatments are now more nuanced than hospitalisation and mortality. The committee considered that relative treatment effect, and reduced hospitalisation and mortality rates, are key drivers of benefit, but acknowledged that the model was not sensitive to other benefits of treatment like faster resolution of symptoms. For the third meeting, Gilead submitted its own cost-effectiveness model for remdesivir in the low-flow oxygen subgroup. Gilead explained it had constructed its own model as a validation exercise for the EAG's model. The AG did not critique Gilead's model because of time constraints, but it noted that the incremental cost-effectiveness ratios (ICERs) were moderately lower in the AG model

when using comparable input parameters. At the third meeting, Gilead acknowledged that the AG's model had been scrutinised by several companies and considered appropriate by the committee in TA878. Gilead agreed to the continued use of the AG's model as the basis for decision making for remdesivir. The AG amended its model for the third meeting to place the full population at ordinal scale 5 to reflect Gilead's positioning of remdesivir only for people having low-flow oxygen. The EAG was concerned that the company had not submitted any data for children or people who are immunocompromised to inform the cost-effectiveness model. The clinical experts acknowledged that the availability of data was limited because of the small number of children with severe COVID-19 who need hospitalisation. They noted that the aim of treatment with remdesivir in both adults needing low flow oxygen and children is to prevent progression to more serious illness. The committee noted that the only parameter changed for each of the subgroups in the analysis was the mortality rate, and there was no further exploration of changes to costs, utility values or other outcomes such as time to recovery. The committee recognised this as a limitation in the analysis but were not presented with subgroup specific estimates for each of the model inputs. The committee considered the AG's model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19.

Hospitalisation rates

3.27 The rate of hospitalisation is a key driver of model outputs (see section 3.26) with multiple potential evidence sources. Hospitalisation rate is one of the key model input variables that define the group at high risk. To closely align with the marketing authorisations, for the first meeting the AG used a hospitalisation rate of 0.77% from PANORAMIC in its base case to generate the decision-making ICERs. PANORAMIC was reflective of the current COVID-19 landscape, including the Omicron variant. However comments at the first draft guidance consultation further

highlighted that PANORAMIC would have excluded people at higher risk who were eligible for treatment through NHS interim clinical commissioning policies (see section 3.11). Consultees provided a range of hospitalisation rates identified through targeted reviews. The committee saw overall hospitalisation rates defined by the McInnes high-risk definition including: OpenSAFELY 2.41% (untreated but eligible using McInnes definition), 1.37% (untreated but eligible group without contraindications to nirmatrelvir plus ritonavir) and 2.82% (DISCOVER-NOW database, UK observational study of people covered in the McInnes report). Hospitalisation rates also varied across different conditions, including between 4.15% and 4.4% for advanced renal kidney diseases and 15.9% (study of people with primary and secondary immunodeficiency [Shields et al. 2022]). In the first meeting the clinical experts agreed, given the committee's preferred definition of high risk (see section 3.8), that 0.77% could be an underestimation because the highest risk group may have been underrepresented in PANORAMIC (see section 3.5). They acknowledged the difficulty of determining hospitalisation rate without analysing the baseline population and all appropriate groups at risk. The rate is likely to vary substantially based on types of underlying conditions in the high-risk group, with potentially higher rates for severely immunocompromised people, such as people who have had a transplant and people having chemotherapy. The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have high risk of progression to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.82% from the DISCOVER-NOW database. The committee concluded that the hospitalisation rate for the McInnes high-risk group is between 2.41% and 2.82% based on OpenSAFELY and DISCOVER-NOW. For people contraindicated to nirmatrelvir plus ritonavir the hospitalisation rate is assumed to be about 4% as an upper limit using advanced renal disease as proxy from OpenSAFELY.

Time to discharge

3.28 The amount of time spent in hospital is a key driver of cost effectiveness because of hospitalisation costs. Evidence on each treatment showed a relative reduction in time spent in hospital. One consultee highlighted during the first draft guidance consultation that the time to discharge data from ACTT-1 should have been included for remdesivir. In response the AG included the time to discharge data for remdesivir which resulted in a large reduction in the cost-effectiveness estimates. In its submission for the third meeting, Gilead acknowledged that neither ACTT-1 nor the discharge results reported by Spinner et al. (2020) were analysed for a population having low-flow oxygen. Spinner et al. was the only other randomised controlled trial that reported data on time to discharge for remdesivir. Gilead preferred to continue using the time to discharge data from ACTT-1 to inform the model because it had a larger sample size than Spinner et al. The AG had previously noted the time to discharge evidence was collected during the early stages of the pandemic, which could lead to substantial generalisability concerns because the context of care has changed in the endemic setting. The committee noted that in clinical practice, time to discharge can sometimes overestimate time in high-cost health states because it can depend on multiple factors (for example, waiting for a negative COVID-19 test). Time to discharge was also considered more important for people who are being discharged to a care home. The committee also noted that clinical experts in the committee meetings explained that people hospitalised with COVID-19 have very different symptoms at present (the time of this evaluation) compared with early stages of the pandemic. Also that the population is heterogeneous (see sections 3.2 and 3.3). The AG included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try and account for these potential uncertainties. At the first meeting the committee considered these scenarios to be plausible but conservative if treatments had effects outside of hospitalisation and mortality. The committee was cautious

about applying differences in time to discharge or clinical improvement between remdesivir and standard care in the model and was uncertain about the treatment benefit in the endemic setting. The committee noted that time to discharge may also be dependent on individual subgroups. For example, people who are immunocompromised may have longer hospital stays because they are unable to clear the virus for longer time periods. The committee concluded it was reasonable to remove any treatment effects on time to discharge for remdesivir in the absence of stronger evidence of reducing time in hospital.

Mortality

3.29 For the third meeting, the mortality rate used in the model for remdesivir was amended to account for the reduced severity of disease in people needing low-flow oxygen than in people needing high-flow oxygen or mechanical invasive ventilation. The company suggested a mortality rate of 10% at 15 days for people needing low-flow oxygen. The AG preferred to use a mortality rate of 14% at 28 days based on Amstutz et al. (2023). The committee noted that most estimates of in-hospital mortality were generated from evidence collected earlier in the pandemic, and noted sources suggesting total mortality has significantly decreased. At the third meeting, a clinical expert estimated that the mortality rate for people needing oxygen and care from a respiratory consultant was around 12%. Another clinical expert calculated a mortality rate of around 6% in people with COVID-19 in critical care and 2% in the overall population hospitalised with COVID-19, from an analysis between November 2022 and May 2023. The committee understood that the differences in mortality rates in clinical practice may be because of diversity in the patient populations or different severities of COVID-19 included in the rates being described by the experts. The committee concluded that the company's and AG's mortality rates were likely to overestimate current in-hospital mortality in the subgroup of people needing low-flow oxygen, but the appropriate estimate was highly uncertain. It considered further investigation was needed to give a more accurate estimate of mortality in

this population, because of the sensitivity of the cost-effectiveness estimates to this parameter. For children, the AG modelled two alternate values for the probability of death at 28 days: 0.45% based on Ward et al. (2023) and 0.19% based on Wilde et al. (2023). The clinical experts agreed that the mortality rate in children is lower than in adults but that it was difficult to give an exact value because of very small patient numbers. The AG assumed the probability of death for people who are immunocompromised to be 24.98% based on a study by Evans et al. (2023). The committee considered the probability of death for people who are immunocompromised would be less than 24.98% and more likely to be closer to 14%, as used in the AG's base case analysis. The committee concluded that the mortality rates for children and people who are immunocompromised were highly uncertain.

Utility values

Utility value assumptions

3.30 The AG used UK age- and sex-adjusted utility values (EQ-5D-3L) for the baseline utility estimates in the model. The AG did not apply additional utility decrements in the mild COVID-19 setting for people who did not have long COVID. The age- and sex-adjusted UK general population utility estimates were used for this population instead. During consultation on the AG's draft report, stakeholders critiqued this assumption. They said this may not capture the full benefit of the treatments compared with standard care and disadvantaged community-based treatments. The AG agreed this was a simplified assumption, but scenario analysis showed it had limited impact on the final ICERs. The committee agreed with the AG's assumption and acknowledged the minor impact on the ICERs. For the severe COVID-19 setting, the AG used utility decrements from a recent publication of a cost-effectiveness analysis of remdesivir (Rafia et al. 2022). The utility decrements were originally from a population with recurrent *Clostridioides difficile* infection and influenza. The same in-hospital utility decrements were also applied across ordinal scales 3 to 5.

The ordinal scale was an 8-point scale (1 to 8) used to define progression of COVID-19 severity in the model. During consultation, stakeholders critiqued the use of utility decrements from a non-COVID-19 population. An alternative approach for a utility study was proposed. The approach was to use COVID-19 severity-specific vignettes with EQ-5D-3L questionnaires completed by the UK general population. Some stakeholders also highlighted recent COVID-19 utility-specific systematic reviews that could be used. The AG said a vignette study would not be possible because of the restricted timelines. Across both settings, the AG did not find alternative COVID-19 utility decrements from the stakeholder-suggested systematic reviews. The AG used post-discharge long COVID utility decrements from Evans et al. (2022). The same utility decrement was assumed regardless of ordinal scale status at hospital admission. At AG report consultation, stakeholders suggested an alternative source of post-discharge utility decrements split by history of ordinal scale status. The AG explained that the model structure was unable to allocate post-discharge utility based on historical ordinal scale admission status. It also said that these utility decrements are only applied for the duration of long COVID and are not a key driver of ICERs. The committee agreed with the AG's rationale and the long COVID utility decrement assumptions.

Costs

Long COVID costs

3.31 In the first meeting the AG assumed the annual per person management costs of long COVID to be comparable with chronic fatigue syndrome (£1,013). The clinical experts explained there were differences between people with long COVID who were in hospital versus not in hospital. People in hospital would be more likely to have severe complications that incur greater costs from multisystem complications. The AG considered the costs had minimal impact on the cost-effectiveness estimates because they were only applied for the duration of long COVID. But, it also provided scenario analyses with increased average yearly costs (£2,500).

The committee agreed these scenarios had minimal effect on the cost-effectiveness estimates but considered that any new UK-specific evidence on long COVID costs should be included if available. During the first draft guidance consultation a consultee said the AG's base-case long COVID cost underestimates the true burden of long COVID and provided an alternative higher cost from Vos-Vromans et al. (2017). The AG accepted this new evidence and inflated the cost to £2,267 per year (to reflect 2021/2022). The committee agreed with the updated base-case value.

Administration costs

3.32 The AG did not originally include administration costs for oral or subcutaneous treatments. For intravenous treatments a cost of £221 was assumed based on NHS reference code SB12Z. After the first draft guidance consultation, the AG updated the assumptions in the model with costs provided by NHS England. NHS England provided COVID Medicines Delivery Unit (CMDU) deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care. However, future delivery may be in primary care, which would likely reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs. They also noted that these costs were calculated before implementation of nirmatrelvir plus ritonavir (an oral antiviral) which may increase resource use because of expected requirements to assess contraindications. The AG explained that changes in administration costs can be evaluated by looking at differences in net monetary benefit. The committee considered the differences in administration costs in relation to the net monetary benefit outcomes, noting the uncertainty about future delivery models.

Hospitalisation costs

3.33 The AG used unit costs per hospital bed-day from the NHS National Schedule of NHS costs. During AG report consultation, the AG updated the costs for ordinal scales 3, 4 and 5 based on stakeholder suggestions. During the first draft guidance consultation, consultees said the approach to costing ordinal scales 4 and 5 underestimated the true cost. The AG agreed with the changes suggested and updated the costs. The final codes were as follows:

- ordinal scale 3: weighted average of DZ11R to DZ11V (Lobar, Atypical or Viral Pneumonia, without Interventions) for a regular day or night admission
- ordinal scale 4: weighted average cost of DZ19R to DZ19V (lobar, atypical or viral pneumonia, without interventions) for non-elective long stay (see the AG report in the committee papers for TA878 for further adjustments that were applied)
- ordinal scale 5: weighted average cost of DZ19N to DZ19Q (lobar, atypical or viral pneumonia, with single intervention) for non-elective long stay (see the AG report in the committee papers for further adjustments that were applied)
- ordinal scale 6: using XC07Z (Adult Critical Care, 0 Organs Supported)
- ordinal scale 7: weighted average cost for adult critical care, 1 or more organs supported (XC01Z to XC06Z).

The committee acknowledged the changes implemented by the AG and agreed with the AG's final approach. The committee noted some uncertainty about hospitalisation costs for the remdesivir subgroups of people who are immunocompromised and children, who may have longer hospital stays or higher costs, but did not explore this further.

Cost-effectiveness estimates

Treatments for mild COVID-19

3.34 For the mild COVID-19 setting, ICERs and net monetary benefits were calculated for remdesivir and tixagevimab plus cilgavimab. The committee looked at the pairwise ICERs compared with standard care presented by the AG:

The committee reviewed results for the low-, mean- and high-efficacy scenarios (see section 3.13). The committee noted its preferred assumptions to include combinations of the following:

- hospitalisation rates between 2.41% and 2.82%, and 4.00% for people contraindicated to nirmatrelvir plus ritonavir
- mean and low efficacy relative treatment effects (noting the limitations of the scenarios in section 3.13).

The committee noted substantial uncertainty with the relative treatment effects of tixagevimab plus cilgavimab. The committee concluded tixagevimab plus cilgavimab has limited and uncertain clinical effectiveness in terms of reducing hospitalisation or mortality rates and therefore the ICERs were considered very uncertain (see section 3.19). The ICERs for tixagevimab plus cilgavimab compared with standard care are not reported here because they are considered uninformative based on the level of uncertainty.

The ICERs for remdesivir compared with standard care were substantially higher than £20,000 per QALY gained. The committee concluded that remdesivir is not a cost-effective use of NHS resources for treating mild COVID-19.

Remdesivir for severe COVID-19

3.35 For the third meeting, Gilead positioned remdesivir only for the subgroup of people having low-flow oxygen at baseline, for people who are immunocompromised and for children. The AG presented ICERs and the incremental net monetary benefit compared with standard care for 27 efficacy scenarios, all of which assumed a positive impact of

remdesivir on mortality. The ICERs cannot be reported here because of confidential prices. The committee reviewed results for the low, mean and mean–low efficacy scenarios across the 3 sources of mortality estimates for remdesivir (see section 3.23). Scenarios also differed in whether they showed a mortality benefit only, or if they also included differences in clinical improvement or time to discharge. The committee noted its preferred assumptions included combinations of the following:

- not applying differences in clinical improvement or time to discharge (see section 3.28)
- mortality hazard ratios for remdesivir from Amstutz et al. (2023) with SOLIDARITY (see section 3.29)
- mean–low and low efficacy relative treatment effects (see section 3.23).

The ICERs for remdesivir in adults with COVID-19 who have pneumonia needing low-flow supplemental oxygen (as defined in section 5 of TA878) were all below £30,000 per QALY gained when a 14% mortality rate was used. The committee considered that for immunocompromised people, the mortality rate was likely to be higher than 14%, so remdesivir is a cost-effective use of NHS resources in this group. However, the ICERs were above £20,000 per QALY gained for mortality rates lower than 14%. The committee considered that the mortality rate would be lower than 14% for all people requiring low-flow oxygen, so remdesivir would not be a cost-effective use of NHS resources. The committee considered further investigation was needed to give a more accurate estimate of mortality in this population, because of the sensitivity of the cost-effectiveness estimates to this parameter.

For children with severe COVID-19, the ICERs were high and substantially above what NICE considers a cost-effective use of NHS resources. The committee understood that the population of children who would have remdesivir is very small. Because of this, the committee understood that the evidence was limited and the ICERs were considered very uncertain.

Other factors

Uncaptured benefits

3.36 Clinical experts said hospitalisation and mortality rates are becoming less-relevant clinical efficacy measures for COVID-19 treatments. They explained this was because of the changing COVID-19 landscape (see section 3.2). In future COVID-19 evaluations, higher QALY gains or cost savings could be captured if the model includes the impact of treatments on the following outcomes:

- impact on incidence and duration of long COVID
- virological outcomes
- ability to alter selective pressure on the virus and generation of future variants
- transmission to healthcare professionals
- enabling other NHS healthcare services to proceed (for example, routine operations and reducing impact on waiting lists)
- access to treatment within the window of clinical effectiveness
- value of treatment options available as insurance for people who are shielding.

The committee considered that some of these benefits fall outside of the NICE reference case or there is limited evidence to support them. The committee noted community treatments may not limit transmission of the virus, because it mostly spreads when people are asymptomatic. The committee considered the advice in section 6.2.36 of NICE's manual on health technology evaluations. The committee concluded that it had not been presented with strong evidence that the health benefits of the technologies have been inadequately captured and may therefore misrepresent the health utility gained.

Equality issues

3.37 In TA878, the committee recommended sotrovimab in the mild COVID-19 setting for people for whom nirmatrelvir plus ritonavir is unsuitable. Sotrovimab's marketing authorisation includes adolescents (aged 12 years and over), so this is an option for them, if they have a high risk of progression to severe COVID-19 as defined by the McInnes report. For younger children in the mild COVID-19 setting, the only option in this setting is remdesivir. But, the ICERs for remdesivir in this setting (for adults) are very high and substantially above what NICE considers a cost-effective use of NHS resources (see section 3.34). No ICERs were presented for children in this setting.

3.38 In TA878, the committee recommended tocilizumab in the severe COVID-19 setting. But tocilizumab's marketing authorisation does not include people aged under 18 years. So, there is a risk of indirectly discriminating against children and young people. The committee recognised the unmet need in this population. It understood the difficulties in generating evidence for children in the severe COVID-19 setting because of the very small numbers of children who are hospitalised or die from COVID-19 (see section 3.25 and 3.29). However, the ICERs for children were high and substantially above what NICE considers a cost-effective use of NHS resources. The committee also considered that the decision problem for remdesivir for children in the severe COVID-19 setting was different than that for adults in the severe COVID-19 setting. This is because severe COVID-19 is virologically driven in children and so there is clinical rationale for why remdesivir, an antiviral, would be effective in this population (see section 3.10).

Addressing health inequalities

3.39 The committee noted the equalities issues outlined in section 3.37, and considered flexibility as part of the principles that guide the development of NICE guidance and standards. This emphasises the importance of considering the distribution of health resources fairly within society as a whole, and factors other than relative costs and benefits alone. It noted

that the issues raised could affect some people with protected characteristics disproportionately which would contribute to health inequality. The committee said that in theory it would be willing to accept an ICER slightly more than what is usually acceptable if it addressed such health inequalities. However, it noted that departing from NICE's usual range needs to be done with caution, because it risks displacing funding from more cost-effective treatments elsewhere in the NHS, with an overall net loss of health gain.

Conclusion

Recommendations

3.40 Tixagevimab plus cilgavimab is not recommended for treating COVID-19 because it is unclear if it is effective at treating later variants of COVID-19 and the cost-effectiveness estimates are very uncertain.

3.41 Remdesivir is only likely to be cost effective for treating COVID-19 in groups with higher rates of baseline in-hospital mortality, such as people who are immunocompromised. The committee considered remdesivir likely to be a cost-effective use of NHS resources for treating COVID-19 in adults in hospital with pneumonia who need low-flow supplemental oxygen and who have a high risk of serious illness (criteria as defined in section 5 of TA878). So, remdesivir is recommended in this population.

3.42 The committee acknowledged that the cost-effectiveness estimates for remdesivir in children were above the range NICE normally considers an acceptable use of NHS resources. However, it considered other important factors in its decision making. The committee acknowledged the difficulty in collecting clinical evidence because of the very small numbers of children who are hospitalised or die from COVID-19. This made the ICERs for remdesivir in children very uncertain. The committee recalled that there were benefits associated with remdesivir that may not have been captured in the economic analyses for children. It recognised the unmet need and the equality issues for this population. It considered

these factors and therefore considered it appropriate to recommend remdesivir for treating COVID-19 in children in hospital with pneumonia who need supplemental oxygen to mitigate against the potential for indirect discrimination as there are no licensed treatments available for children.

4 Implementation

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

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

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if someone has COVID-19, and the doctor responsible for their care thinks that remdesivir is the right treatment, it should be available for use, in line with NICE's recommendations.

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

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal evaluation committees are standing advisory committees of NICE. This topic was considered at the first and second meetings by members from across the 4 committees. At the third meeting, this topic was considered by committee C.

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

Stephen O'Brien

Chair, Technology appraisal evaluation 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.

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Technical leads

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