NICE National Institute for Health and Care Excellence

NICE guidance

Remdesivir and tixagevimab plus cilgavimab for treating COVID-19

Technology appraisal guidance
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1 Recommendations

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

- adults, only if they have a high risk of serious illness (risk factors as defined in section 5 of NICE's technology appraisal guidance on 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:
    - have pneumonia, and
    - need supplemental oxygen, or
  - weigh at least 40 kg, and have a high risk of serious illness (risk factors as defined in section 5 of NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19).

    Remdesivir is only recommended if the company provides it according to the commercial arrangement.

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.

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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 is highly uncertain. But it suggests that remdesivir can increase how long adults needing low-flow supplemental oxygen live compared with standard care.

The cost-effectiveness estimates for remdesivir are only likely to be within what NICE considers an acceptable use of NHS resources for adults in hospital 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 who:

- are aged 4 weeks to 17 years, weigh at least 3 kg, and are in hospital with pneumonia and need supplemental oxygen, or
- who weigh at least 40 kg, are in hospital and have a high risk of serious illness.

There is limited clinical evidence comparing remdesivir with standard care for treating severe COVID-19 in these groups. So, the cost-effectiveness estimates are highly uncertain. But there are limited treatment options licensed for these groups and the number who would have remdesivir is very small. So, remdesivir is recommended for treating COVID-19 in these groups.

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.

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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.

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2.6 The company has a commercial arrangement. 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.

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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 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. They can severely affect a person's physical and mental health, and potentially 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), 1 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. This includes people who are immunosuppressed (who, for example, have primary immunodeficiency, are having chemotherapy or have had a transplant) or who have comorbidities (such as heart disease, respiratory disease, diabetes or neurological conditions). Some people who are immunocompromised are at risk of persistent viral infection if their immune system cannot control the virus. The 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

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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. It also understood that the incidence of COVID-19 pneumonitis in hospital has lowered, as has the need for supplemental oxygen or mechanical ventilation.

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 sublineage BA.5. The Omicron variant (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 people who are immunocompromised 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

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developing. At the third evaluation committee meeting (referred to as third meeting from now 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
- are no longer up to date with vaccination
- 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 is to the current endemic context of the disease at the time of this evaluation.

Remdesivir treatment positioning

3.3 For the third and fourth meetings, Gilead positioned remdesivir only for adults with pneumonia needing low-flow oxygen, for people who are immunocompromised, and for babies, children and young people as described in the marketing authorisation (from now, children). It noted that:

- for 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 adults who are hospitalised, and needing no or low-flow oxygen

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- 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 very small numbers of children are hospitalised or die from COVID-19.

  The clinical experts at the third meeting explained that it is incorrect to assume that a requirement for low-flow oxygen means less-severe disease. This is 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 adults who need low-flow oxygen, people who are immunocompromised and children.

Defining target populations

Key definitions

3.4 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, so 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 so treatment eligibility. PANORAMIC was a large UK platform trial that included people with many different potential risk factors, including chronic conditions and immunosuppression. It allowed enrolment of people aged over 50 years. It also

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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 England interim commissioning policy on treatments for people who are not hospitalised with COVID-19 (now superseded, see section 3.10) 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

3.5 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 people who are immunocompromised, 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 that the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are taken, but the relationship may be

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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 who may not be able to access treatment. The committee noted that the McInnes report has made additional consideration for people aged 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

3.6 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 they also considered that the relationship between age and comorbidities is complex, particularly for people who are immunocompromised. 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.

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At the second meeting, the committee noted the additional evidence provided by consultees that 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 for people with a high risk of 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

3.7 The assessment group (AG) explained the approach used to model high-risk groups in its economic model (see section 3.22). 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. So, 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 of 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 3.22 and 3.23). 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 needed to make differential subgroup recommendations. But this would

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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 of progressing to severe COVID-19. It added that 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. Also, it has provided some evidence from people who had been vaccinated and who were infected with Omicron variants. The committee considered the use of the Q-COVID risk calculator in clinical practice but concluded that 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 3.4). But 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

3.8 For remdesivir in the severe COVID-19 setting, Gilead positioned people who are immunocompromised as a separate subgroup (see section 3.3). 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'. In response to the second draft guidance consultation, Gilead explained that its positioning included people who are immunocompromised in hospital without needing supplementary oxygen. Gilead was concerned that a requirement for people who are immunocompromised to already be having low-flow oxygen would severely restrict access earlier in the disease course for people who are most likely to benefit from remdesivir. The committee agreed it was appropriate to consider people who are immunocompromised as a subgroup. This is because the evidence suggests that survival and the clinical course of the disease in this group is different from the general population. The different disease course is partly because vaccinations

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are less effective for people who are immunocompromised. The committee also considered that, in practice, clinical judgement would be used to identify people who are immunocompromised and in hospital who could benefit most from remdesivir. This would be based on risk of progressing to more serious disease. It would also be regardless of whether they needed oxygen at baseline because this is less clinically significant for people who are immunocompromised. The company noted that the immunocompromised subgroup could include people waiting for a stem cell transplant or CAR-T therapy. The committee agreed that this would be representative of when remdesivir could have the most benefit. It noted that the McInnes report defines conditions that affect immune function. It added that the report could be used to identify people who are immunocompromised and may benefit from treatment with remdesivir in clinical practice. The committee considered that, despite the McInnes report being developed for people with high risk of progressing to severe COVID-19, it provides a comprehensive definition for people who are immunocompromised in the severe COVID-19 setting.

Children

3.9 Gilead considered a separate analysis should be done for remdesivir in children in hospital with pneumonia and needing supplemental oxygen, and in children in hospital at high risk of serious illness. 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. So, 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.

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Current clinical management of COVID-19

Treatments for mild COVID-19

3.10 Current clinical management of mild COVID-19 (includes hospital-onset COVID-19) in people who have a high risk of progressing to severe COVID-19 includes treatments commissioned through an NHS England 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

3.11 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 England interim clinical commissioning policy on remdesivir (now superseded) for people who are

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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

3.12 In line with best practice guidance for assessing COVID-19 treatments (Elvidge and Dawoud 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 its 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

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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 a 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 so were sensitive to the number of events in each trial, rather than the context in which the trial happened. So, 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. In response to 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

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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. So, a probabilistic sensitivity analysis was 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 that 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 that 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

3.13 The committee acknowledged that most trials informing the clinical efficacy data predated the Omicron variant, which was the dominant circulating variant of concern at the time of this evaluation. The clinical experts said that 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

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- 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. But 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 substantially higher. So, 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.

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 including 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

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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. 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. It also concluded that there was no clinical trial 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
  - the particular sensitivity of these antibodies to changes in variants.

In vitro evidence

3.14 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

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whether treatments can neutralise new variants. This 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.

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

3.15 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. But, as discussed in the first meeting and based on the in

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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.

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. 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. They 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 an 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, 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

3.16 For the mild COVID-19 setting (considered at the first and second meetings), 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).

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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. The clinical experts also noted that multiple interventions could be needed, 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

3.17 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 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% confidence interval [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

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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 compared with 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 confidence 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 3.13). So, the committee 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 3.13). The committee noted that any mortality benefit is likely to be minimal when the hazard ratios 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 compared with standard care.

Subgroup analyses for remdesivir

3.18 For the third and fourth meetings, 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 3.3).

Low-flow oxygen at baseline subgroup

3.19 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

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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 substantial 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 statistically 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, including real-world evidence data generated in the US during the Omicron period, submitted by Gilead in response to the second draft guidance consultation. Additional benefits for remdesivir in adults having low-flow oxygen noted by Gilead included:

- an increased likeliness of achieving clinical improvement by 28 days compared with standard care (adjusted hazard ratio of 1.23, 95% CI 1.19 to 1.27), reported by Garibaldi et al. (2022) based on people hospitalised in a private healthcare network in the US from February 2020 to February 2021
- improved early (day 14/15) and late (day 28/29) recovery compared with standard care (risk ratios of 1.22, 95% CI 1.09 to 1.38; and 1.17, 95% CI 1.09 to 1.28, respectively), reported by Beckerman et al. (2022) based on NMAs of studies included in targeted searches done from February 2021 to April 2021
- lowered 30-day post-discharge readmission compared with the non-remdesivir group, reported by Caffrey et al. (2023) based on people hospitalised in the US Veterans Affairs healthcare system from May 2020 to November 2021
- reduced likelihood of long COVID-19, reported by Boglione et al. (2022) based on people hospitalised in Italy between March 2020 and January 2021.

The committee recognised that the evidence showed clinical benefit for remdesivir in the treatment for adults having low-flow oxygen. But it considered there were likely to be issues regarding generalisability resulting from the timing of the studies, the changing nature of SARS-CoV-2 and context of the pandemic, as well as issues of confounding that had not been fully explored.

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At the third meeting, Gilead preferred to use Huang et al. (2023) to inform 28-day mortality in the model. This was because the data searches by Huang et al. (2023) were done up to the most recent time period (February 2023). It was 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. (2022). The AG noted that Amstutz et al. (2023) reported results that either included or excluded data from the SOLIDARITY trial. Gilead noted that Amstutz et al. (2023) reported results for people with no oxygen and low-flow oxygen requirements. SOLIDARITY also did not differentiate between people needing low-flow or high-flow oxygen. So, Gilead was concerned that Amstutz et al. (2023) did not focus on the low-flow oxygen subgroup for which it was positioning remdesivir (see section 3.3). The AG explained that there were no statistically significant differences between the relevant comparisons by Amstutz et al. (2023). This was irrespective of whether SOLIDARITY was included or not, or whether people needed no or low-flow supplementary oxygen. 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. So, the AG preferred to use the individual patient-data meta-analysis results from Amstutz et al. (2023) including SOLIDARITY to inform efficacy for remdesivir. 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 it agreed 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. At the fourth meeting, Gilead considered that it was more appropriate to select the subgroup analysis by Amstutz et al. (2023) excluding SOLIDARITY because it better represents the low-flow oxygen population. Gilead also recalled that Amstutz et al. (2023) advised in the supplementary appendix of the publication that separate effects should be used for each subgroup. The committee recalled the consideration from earlier meetings, when evaluating a broader population with severe COVID-19, that including SOLIDARITY in the NMA was important and appropriate for remdesivir (see section 3.13). But it recognised that the appeal panel had since asked it to consider the subgroup of people with severe COVID-19 who need low-flow oxygen, and that

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SOLIDARITY did not distinguish between the levels of oxygen needed. The committee concluded that it preferred the Amstutz et al. (2023) meta-analysis including SOLIDARITY. This was because the SOLIDARITY trial included large numbers of people who did have low-flow oxygen. Also, it would not be appropriate to remove such a large source of evidence when trying to calculate small effect sizes. This decision was supported by the NICE rapid guideline, no statistically significant difference in including SOLIDARITY, and the reduction in the 95% confidence intervals. The committee recognised that including some people with high-flow oxygen requirements at baseline from SOLIDARITY may have been conservative for treatment effect. For that reason, the committee also considered the scenarios without SOLIDARITY. It recalled that confidence intervals measured by hazard ratios in the meta-analysis did not account for all types of uncertainties such as generalisability (see section 3.13). So, it maintained that the data including SOLIDARITY was appropriate to include in the analysis.

People who are immunocompromised

3.20 The committee noted that there was no clinical evidence from randomised controlled trials 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 that 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. (2023). The committee agreed with the AG, noting that using non-randomised evidence has substantial potential for risk of bias. But it noted substantial uncertainty with the AG's approach.

Children with severe COVID-19

3.21 The committee noted that there was no comparative clinical evidence provided for children with severe COVID-19. But limited evidence showed that remdesivir is safe and well tolerated. The AG considered that 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

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al. (2023) was appropriate for this population.

Economic model

Model structure and key drivers of cost effectiveness

3.22 The economic model for this appraisal was developed by the AG and informed by Rafia et al. (2022), which evaluated COVID-19 treatment in a prehospital 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 for people with COVID-19. People were hospitalised at a baseline standard care rate, or not hospitalised. People who 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 3.12). 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 that 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 but 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 it also noted the following other key drivers of model outputs at the first and second meetings:

- 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.

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- 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 it 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 AG'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. For the fourth meeting, the AG modelled the subgroup of people who are immunocompromised with no supplementary oxygen requirements, starting in ordinal scale 4. The AG 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. It also noted that 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

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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

3.23 The rate of hospitalisation was a key driver of model outputs (see section 3.22) at the first and second meetings, 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. But 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 England interim clinical commissioning policies (see section 3.10). Consultees provided a range of hospitalisation rates identified through targeted reviews. The committee saw overall hospitalisation rates defined by the McInnes high-risk definition. These included: 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 diseases and 15.9% in a 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 3.7), that 0.77% could be an underestimation. This was because the highest risk group may have been underrepresented in PANORAMIC (see section 3.4). They acknowledged the difficulty of determining the 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. Also, there are 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

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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 in whom nirmatrelvir plus ritonavir is contraindicated, the hospitalisation rate is assumed to be about 4% as an upper limit using advanced renal disease as proxy from OpenSAFELY.

Time to discharge

3.24 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. (2020) 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. (2020). The AG had previously noted the time to discharge evidence was collected during the early stages of the pandemic. This 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 (at the time of this evaluation) compared with early stages of the pandemic. Also, that the population is heterogeneous (see section 3.2). The AG included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try and account for these

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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. It was also 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. In the absence of stronger evidence of reducing time in hospital, the committee concluded that it was reasonable to remove any treatment effects on time to discharge for remdesivir from the base case. But it noted the potential for uncaptured benefits for people who are immunocompromised if this is a conservative assumption.

Relative efficacy for mortality

3.25 At the third and fourth meetings, the AG explored the uncertainty in the relative efficacy of remdesivir by modelling scenarios with:

- 3 assumed efficacy levels (mean, low and mean-low, see section 3.12)
- sources of mortality estimates for remdesivir (see section 3.19):
  - Huang et al. (2023), at the third meeting
  - Amstutz et al. (2023) with SOLIDARITY
  - Amstutz et al. (2023) without SOLIDARITY
  - real-world evidence generated during the Omicron period in the US (provided by the company in response to the second draft guidance consultation)
- pooled (combined evidence for the no oxygen and the low-flow oxygen groups) or group-specific (evidence aligned to the oxygen requirements of the subgroup being modelled) data.

  The committee considered that the pooled and group-specific data for the

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low-flow oxygen subgroup were similar. For the immunocompromised subgroup with no supplemental oxygen, the committee's preferred scenario was based on the pooled evidence. This was to reduce the uncertainty in the estimate of the efficacy of remdesivir. Gilead preferred the mean efficacy results. This was because it considered that, given the depth of available evidence for remdesivir, there was no reason to not apply mean efficacy levels as applied to other treatments evaluated in the multiple technology appraisal process. The committee understood that scenarios assuming high efficacy levels were not presented by the AG at the third and fourth meetings. This was because a greater mortality benefit than that seen in the studies was not expected in the current endemic setting (see section 3.13). It considered that the mean efficacy scenarios were also likely to overestimate the benefit of remdesivir compared with standard care in the current endemic setting (see section 3.13). So, it preferred the low and the mean-low efficacy scenarios.

In-hospital baseline mortality from COVID-19

3.26 For the third meeting, the underlying mortality rate used in the model was amended to account for the reduced severity of disease in people needing low-flow oxygen compared with 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 substantially 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. At the third meeting, 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

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needing low-flow oxygen, but the appropriate estimate was highly uncertain. It requested further investigation to give a more accurate estimate of mortality in this population because of the sensitivity of the cost-effectiveness estimates to this parameter.

Following the second draft guidance consultation, a range of sources for 28-day in-hospital mortality for people with low-flow oxygen requirements were considered by the committee, including:

- UKHSA dataset in 2023: a mortality rate of 9% (based on a crude estimate of total numbers of deaths and hospitalisations). The committee noted that the total number of deaths included any with COVID-19 on the death certificate. But a proportion of people may not have been hospitalised before death and so would be unable to benefit from remdesivir, so this figure would likely have overestimated 28-day mortality in the model.
- US-based real-world evidence study generated during the Omicron period (December 2021 to April 2023): a 28-day mortality rate of 9.80%. The AG was concerned that it had received limited information about the US real-world evidence dataset, so could not rule out confounding factors when generalising to the UK. The committee noted that this mortality rate based on the real-world study in the US was not peer-reviewed, which would have increased its credibility. The committee was also concerned about the generalisability of the US real-world evidence dataset to the clinical setting in the NHS, and the generalisability of data dating back to December 2021. The clinical members of the committee noted that this mortality rate did not reflect their experience of NHS clinical practice in the last 6 to 12 months, where mortality was not as high. Gilead agreed that the mortality rates for COVID-19 were worse at the end of 2021 than at the time of the fourth meeting, so generalisability of the data may be a concern.
- NHS Hospital Episode Statistics (HES) data: Gilead explained that it had begun exploring this source for estimating the underlying mortality rate but was not yet able to share reliable values with the committee.
- OpenSAFELY: 28-day mortality rates ranging from 1.32% to 4.15% were provided for all people hospitalised in 2023. These were stratified by intensive care admission, early and late 2023, and whether COVID-19 was coded as the primary reason for admission. Gilead was concerned that the

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OpenSAFELY data did not reflect the relevant low-flow oxygen subgroup and did not report on the use of previous medicines. So, it cannot be certain that the mortality rates did not include people who had used remdesivir. But the committee understood that remdesivir prescribing was low during the 2023 OpenSAFELY data period. It also noted that the 4.15% mortality rate for people categorised as needing intensive care unit admission, a setting in which a higher mortality rate was expected than for people having low-flow oxygen, was lower than the company's preferred estimates. Gilead acknowledged that OpenSAFELY was a useful dataset to explore but cautioned care in interpretating the coding of the dataset. It noted that the low mortality rates lacked face validity compared with the other data sources. The committee noted that the methodology of OpenSAFELY has been published and peer-reviewed, and considered that there are unlikely to be significant coding errors in the resulting evidence.

The committee considered the limitations of using each data set, and the additional mortality rate estimates provided in its decision making. It noted that the OpenSAFELY estimates closely aligned with the estimates for people in critical care and in the overall population hospitalised with COVID-19 provided by the clinical expert at the third meeting. It considered that OpenSAFELY was based on a large database in a setting with direct relevance and generalisability to UK clinical practice and that the mortality estimates were contemporary. But it acknowledged that the population was broader than the low-flow oxygen subgroup being considered, with limited evidence of baseline oxygen requirements at the point remdesivir would have been considered for use. The committee considered that the HES data would likely provide very similar evidence to OpenSAFELY because they would both be reporting rates for UK-specific hospitalisations and deaths. It concluded that, for the 28-day in-hospital mortality model input for those having low-flow oxygen, the OpenSAFELY dataset may be of most relevance and with fewest generalisability concerns. This is because baseline mortality is more likely to be driven by geography (population and health system characteristics) and timepoint in the pandemic than strict definition of the low-flow oxygen at baseline population. It also considered the UKHSA dataset and clinical consensus supported using OpenSAFELY as a relevant mortality estimate.

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For children, the AG modelled 2 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 committee concluded that the mortality rates for children were highly uncertain.

The AG originally assumed the probability of death for people who are immunocompromised to be 24.98% based on data from the Omicron period: the INFORM study reported by Evans et al. (2023). At the third meeting, 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 for low-flow oxygen. In response to the second draft guidance consultation, a consultation comment from AstraZeneca UK noted that the 24.98% mortality rate assumed by the AG was based on total COVID-19 deaths (including those not hospitalised). So, it overestimated mortality for people who are hospitalised and need low-flow oxygen. AstraZeneca UK estimated a mortality rate of 10.39% for people who were immunocompromised and hospitalised (for whom a general ward was assumed to be the highest level of care). This was based on unpublished data on file for the INFORM study. Gilead provided a 28-day mortality rate estimate of 19.2% for people who were hospitalised and immunocompromised. This was based on real-world evidence data generated during the Omicron period in the US. Limitations of the real-world evidence data provided by Gilead in response to the second draft guidance consultation are described in section 3.19. In addition, the immunocompromised population is difficult to define, so the generalisability of the population informing the mortality estimates may differ to the McInnes criteria. For the fourth meeting, the AG ran model scenarios using mortality rates of 10.39%, 14.00% and 19.20% for the immunocompromised subpopulation. The committee noted that the highest mortality rate reported from the 2023 OpenSAFELY data of 4.15% was for people hospitalised with an intensive care unit admission. But it acknowledged that the OpenSAFELY population did not reflect the immunocompromised subgroup being considered. The committee considered that the 10.39% rate from INFORM suggested that the committee's conclusion at the third meeting that the mortality rate could be around 14% for the immunocompromised subgroup

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was appropriate. It concluded that the estimate for mortality of people who are immunocompromised and in hospital is very uncertain, but the available evidence suggests it may be in the region of 10.39% and 14.00%. So, this range was considered in the cost-effectiveness estimates and the committee placed more weight on the lower rate of 10.39%.

Utility values

Utility value assumptions

3.27 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.

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(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 the ICERs. The committee agreed with the AG's rationale and the long-COVID utility decrement assumptions.

Costs

Long-COVID costs

3.28 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 that there were differences between people with long-COVID who were in and 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 that 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 that the AG's base-case long-COVID cost underestimates the true burden of long-COVID. They 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

3.29 The AG did not originally include administration costs for oral or subcutaneous treatments. For intravenous treatments, a cost of £221 was assumed based on

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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. But 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 implementing nirmatrelvir plus ritonavir (an oral antiviral). This treatment 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

3.30 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 TA878 for further adjustments that

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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

Acceptable ICER

3.31 NICE's manual on health technology evaluations notes that, above a most plausible ICER of £20,000 per quality-adjusted life year (QALY) gained, judgements about the acceptability of a technology as an effective use of NHS resources will take into account the degree of certainty around the ICER. The committee will be more cautious about recommending a technology if it is less certain about the ICERs presented, but will also take into account other aspects including uncaptured health benefits. The committee noted the high level of uncertainty, specifically:

- whether tixagevimab plus cilgavimab is effective against Omicron variants of COVID-19 (see section 3.13 and section 3.15)
- whether the evidence showing a relative effect of treatment is transferable to current clinical management, and whether it is appropriate to assume low or mean-low efficacy scenarios (see section 3.12, sections 3.16 to 3.19, and section 3.25)
- the heterogeneity of trial outputs and generalisability for mild COVID-19 (see section 3.16)

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- no randomised clinical evidence for remdesivir in people who are immunocompromised in the current endemic setting (see section 3.20)
- no comparative clinical evidence for remdesivir in children with severe COVID-19 (see section 3.21)
- the hospitalisation rate for the population who have high risk of progression to severe COVID-19 (see section 3.23)
- the underlying mortality rate for adults having low-flow oxygen (see section 3.26)
- the underlying mortality rate for children (see section 3.26)
- the underlying mortality rate for people who are immunocompromised (see section 3.26)
- the hospitalisation costs for the remdesivir subgroups of people who are immunocompromised and children, who may have longer hospital stays or higher costs (see section 3.30).

Given these uncertainties, the committee concluded that an acceptable ICER would be around £20,000 per QALY gained.

Treatments for mild COVID-19

3.32 For the mild COVID-19 setting considered at the first and second meetings, 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. It reviewed results for the mean, low and mean-low efficacy scenarios (see section 3.12). The committee noted its preferred assumptions to include combinations of the following:

- hospitalisation rates of between 2.41% and 2.82% for the McInnes high-risk group, 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 3.12).

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The committee noted substantial uncertainty with the relative treatment effects of tixagevimab plus cilgavimab. The committee concluded that tixagevimab plus cilgavimab has limited and uncertain clinical effectiveness in terms of reducing hospitalisation or mortality rate (see section 3.15). So, the ICERs were considered very uncertain. 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

3.33 For the third and fourth meetings, Gilead positioned remdesivir only for the subgroups of adults 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 scenarios exploring uncertainty in the efficacy estimates. All these ICERs 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 sources of relative mortality estimates for remdesivir (see section 3.19 and section 3.25). 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 source of underlying mortality rate and whether data was pooled for no and low-flow oxygen requirements were also explored. The committee noted its preferred assumptions included combinations of the following:

- not applying differences in clinical improvement or time to discharge (see section 3.24)
- mortality hazard ratios for remdesivir from Amstutz et al. (2023) with SOLIDARITY (see section 3.19)

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- mean-low and low efficacy relative treatment effects (see section 3.25)
- baseline mortality rate that is likely to be in the region of 10.39% for the immunocompromised subgroup (see section 3.26).

The ICERs using the committee's preferred assumptions for remdesivir in adults in hospital with COVID-19 who need low-flow supplemental oxygen were below £30,000 per QALY gained when a 14.00% underlying mortality rate was used. But the committee considered that the mortality rate would be considerably lower than 14.00% for people needing low-flow oxygen. The committee noted that lower underlying mortality rates increased the ICER for remdesivir. When using the underlying mortality rate of 9.80% from Gilead's US real-world evidence for the low-flow oxygen subgroup, the ICER for remdesivir was:

- above £20,000 per QALY gained in the mean-low efficacy scenario
- above £30,000 per QALY gained in the low efficacy scenario.

The committee recalled that the OpenSAFELY underlying mortality rates were substantially lower than 9.80%. So, the rates would increase the ICER for remdesivir to above £30,000 per QALY gained in both the low and mean-low efficacy scenarios. The committee considered that the ICER for remdesivir would be above £20,000 per QALY gained for any relevant source of relative efficacy (Amstutz et al. 2023, excluding SOLIDARITY and the US-based real-world evidence study generated during the Omicron period) and for the mean efficacy relative treatment effect scenarios. The committee preferred to see an ICER around £20,000 per QALY gained (see section 3.31). So, remdesivir could not be recommended for adults in hospital having low-flow oxygen.

At the fourth meeting, the committee considered that, for people who are immunocompromised, the most appropriate mortality rate was likely to be in the region of 10.39%. Using the committee's preferred assumptions for remdesivir in people who are immunocompromised when applying a 10.39% underlying mortality rate, the ICERs were in the range of around £20,000 to £40,000 per QALY gained for the low and mean-low efficacy scenarios. Considering the range of uncertainty in the mortality rate estimates and the potential for uncaptured benefits, the committee concluded that on balance

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remdesivir was likely to be a cost-effective treatment option for people who are immunocompromised.

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

3.34 The clinical experts said that 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:

- 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, doing 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.

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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.

Equality issues

3.35 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 people aged 12 years and over. So, this treatment is an option for this group if they have a high risk of progression to severe COVID-19, as defined by the McInnes report. For people under 12 years in the mild COVID-19 setting, the only option 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 3.32). No ICERs were presented for people under 12 years in this setting.

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 3.9 and section 3.21). But 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, so there is clinical rationale for why remdesivir, an antiviral, would be effective in this population (see section 3.9).

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Addressing health inequalities

3.36 The committee noted the equality issues outlined in section 3.35, 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. But 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

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

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 who have a high risk of serious illness (criteria as defined in section 5 of TA878). So, remdesivir is recommended in this population.

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. But 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.

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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, and considered these factors. To mitigate against the potential for indirect discrimination because there are no licensed treatments available for children, the committee considered it appropriate to recommend remdesivir for treating COVID-19 in children in hospital:

- with pneumonia who need supplemental oxygen
- at high risk of serious illness.

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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. Because remdesivir has been available through the early access to medicines scheme, NHS England and integrated care boards have agreed to provide funding to implement this guidance 30 days after 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 healthcare professional 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 The Scottish Medicines Consortium collaborated with NICE on this guidance. In Scotland, the advice will have the same status for health board consideration as other Scottish Medicines Consortium advice on new medicines.

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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.

Anuja Chatterjee, Rachel Ramsden
Technical leads

Adam Brooke
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