NICE National Institute for Health and Care Excellence

NICE guidance

Nirmatrelvir plus ritonavir and tocilizumab for treating COVID-19

Technology appraisal guidance
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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance is at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:

- do not need supplemental oxygen for COVID-19 and
- have an increased risk for progression to severe COVID-19, as defined in section 5.

1.2 This recommendation has been deleted because the company has discontinued manufacturing, supply, distribution and marketing of sotrovimab in the UK.

1.3 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:

- are having systemic corticosteroids and
- need supplemental oxygen or mechanical ventilation.

Tocilizumab (branded or biosimilar) is only recommended if the companies provide it according to the commercial arrangement.

1.4 This recommendation has been deleted because the conditional marketing authorisation for casirivimab plus imdevimab for treating COVID-19 was withdrawn.

Why the committee made these recommendations

About this evaluation

This evaluation reviews the clinical and cost effectiveness of:

- nirmatrelvir plus ritonavir for mild COVID-19
- tocilizumab for severe COVID-19.

Most of the clinical evidence for these treatments is highly uncertain because it comes from studies done before the dominant Omicron variants of SARS-CoV-2 (the virus that causes COVID-19).

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.

Clinical and cost effectiveness

Clinical evidence suggests that:

- nirmatrelvir plus ritonavir is effective at treating mild COVID-19 compared with standard care
- tocilizumab is effective at treating severe COVID-19 compared with standard care.

The independent advisory group report commissioned by the Department of Health and Social Care defines people with the highest risk of progression to severe COVID-19 (see section 5). Nirmatrelvir plus ritonavir is recommended in these groups because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources.

Tocilizumab is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources.

2 Information about the treatments

Marketing authorisation indications

2.1 Nirmatrelvir plus ritonavir (Paxlovid, Pfizer) is 'indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19'.

2.2 Tocilizumab (RoActemra, Roche Products) is indicated 'for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation'.

Dosage in the marketing authorisation

2.3 The dosage schedule for nirmatrelvir plus ritonavir is available in the summary of product characteristics for nirmatrelvir plus ritonavir.

2.4 The dosage schedule for tocilizumab is available in the summary of product characteristics for tocilizumab.

Price

2.5 The list price for nirmatrelvir plus ritonavir is £829 per pack containing 20 nirmatrelvir tablets (150 mg) and 10 ritonavir tablets (100 mg).

2.6 The list price for tocilizumab is £256 per 200 mg/10 ml and £512 per 400 mg/20 ml concentrate for solution for infusion vial (excluding VAT; BNF online, accessed October 2022). The company of branded tocilizumab (RoActemra, Roche Products) has a commercial arrangement. This makes tocilizumab available to the NHS with a discount. The size of the discount is commercial in confidence. NHS England has completed a national procurement for tocilizumab, which includes the biosimilar versions of tocilizumab. Prices paid for the

originator or biosimilar tocilizumab should be in line with the national procurement outcome and should be no higher than that provided through the original commercial arrangement.

3 Committee discussion

The evaluation committee considered evidence from several sources. See the committee papers and the committee papers for the partial review of nirmatrelvir plus ritonavir for full details of the evidence.

This evaluation reviews:

- nirmatrelvir plus ritonavir (antiviral) in the mild COVID-19 setting
- tocilizumab (anti-inflammatory) in the severe COVID-19 setting (with and without supplementary oxygen).

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, and that severely impact a person's physical and mental health and potentially affect their ability to work, attend school or do their usual activities. During draft guidance consultation, consultees highlighted the treatment gap for children. At the second evaluation committee meeting (referred to as 'second meeting' from now on) one clinical expert explained that COVID-19 rarely makes children unwell. But, there is a small proportion of children with underlying conditions who have an increased risk of severe COVID-19 comparable with adults who have underlying conditions. Many people are at increased risk of hospitalisation or death from COVID-19, including people who are immunosuppressed (for example, people with primary immunodeficiency, people having chemotherapy, or people who have had a transplant) or who have

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

The rapidly evolving SARS-CoV-2 virus

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

3.3 At the time of the first evaluation committee meeting (referred to as 'first meeting' from here on), the dominant variant of concern in the UK was the Omicron 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 people with COVID-19 having different characteristics than seen earlier in the pandemic. At the second meeting, the committee saw the updated Omicron variant data

published in the UK Health Security Agency's (UKHSA's) technical briefing 49. Based on all the UK sequenced samples between 26 December 2022 and 1 January 2023, BQ.1 was the dominant 'designated variant'. BQ.1 was not expected to increase the risk of severe COVID-19 compared with BA.5. The committee understood from this data that the BQ.1 subvariants account for a large proportion of the currently circulating variants in the UK. The committee noted the XBB.1.5 and CH.1.1 subvariants are some of the fastest growing variants in the UK. The clinical experts explained that people presenting at hospital with COVID-19 are mainly either unvaccinated or immunocompromised, or did not have an immune response to vaccines. They reported that 'viral persistence' from chronic infection is a concern in immunocompromised people because new variants or subvariants can develop if the viral infection persists. They also noted that offering a clinically ineffective treatment unable to clear the infection may increase the risk of future variants developing. 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, but noted that the context and relevant variants are still changing at a fast pace.

Defining high risk

Key definitions

3.4 The committee noted that the marketing authorisation for the treatment that lowers the risk of progression to severe COVID-19 (nirmatrelvir plus ritonavir) was based on evidence from populations with slightly different definitions of high risk. For example, some trials included people with at least 1 risk factor for severe COVID-19 whereas some had specific age requirements. Understanding of the prognostic effects of risk factors has developed throughout the pandemic, and therefore the available evidence may represent a heterogeneous population. The committee acknowledged the potential limitations of the available evidence but considered it was important to clearly define high risk and therefore treatment eligibility. PANORAMIC was a large UK platform trial that included people with

many different potential risk factors, including chronic conditions and immunosuppression, and allowed enrolment of people aged over 50 years. It also allowed for clinical judgement of clinical vulnerability. The independent advisory group report commissioned by the Department of Health and Social Care ('the McInnes report' from here on) defined groups of people at highest risk for adverse COVID-19 outcomes, including hospitalisation and death. The 'UK interim commissioning policy on treatments for non-hospitalised patients with COVID-19' 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 immunocompromised people, including people with inflammatory arthritis, liver disease and kidney disease. OCTAVE showed differential antibody reactivity depending on disease group. The committee considered how this may affect who is at high risk. This is because people with a lower vaccine response have increased risk of adverse outcomes from COVID-19 infection compared with the general population, particularly if they are having rituximab.
- They cited an OpenSAFELY cohort analysis study that assessed the risk of severe COVID-19 in people with immune-mediated inflammatory diseases. This showed that people with inflammatory diseases who are having systemic therapies had similar rates of hospitalisation and death as people having targeted therapies, except for rituximab. The committee considered the different risk of progressing to severe COVID-19 may be related to which immunosuppressant drugs are being taken, but the relationship may be

complex and differ in other disease areas.

At the second meeting, the committee noted the draft guidance consultation comments highlighted the need for separate 'high-risk' and 'highest-risk' groups, or a separate high-risk group contraindicated to nirmatrelvir plus ritonavir. The committee saw examples on how the risk group could be split based on Patel et al. (2022). The clinical experts explained that there is a small group of children who are also at high risk of severe COVID-19 and may not be able to access treatment. The committee noted that the McInnes report has made additional consideration for people 12 years and over in its definition of high risk. The committee concluded that it would expect clinicians to offer treatments using the McInnes high-risk criteria when applicable across all age groups, in line with product marketing authorisations.

Age as an independent risk factor

3.6 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, which defined age over 50 years as a risk factor (Knight et al. 2020). They noted that age over 70 years may be an important determinant of mortality but also considered that the relationship between age and comorbidities is complex, particularly for immunocompromised people. One of the companies considered that age was an important risk factor but noted an ongoing debate about what age is appropriate for inclusion in the high-risk group. The clinical experts agreed it was challenging to define an exact age that defines high risk. The committee was concerned that making a recommendation based on age might cause inequality, given that age is a protected characteristic. For this reason, NICE technology appraisal guidance on medicines for cardiovascular disease do not include criteria based on age, despite it being a well-recognised risk factor. The committee noted that age is a protected characteristic and any recommendation including age would need to be assessed for impact on equity of treatment. At the first meeting, the

committee concluded that more evidence was needed on the impact of age to justify including it as an independent factor that increases risk at similar levels to other risk factors defined in the McInnes report. This should include evidence, adjusted for these risk factors, from a vaccinated population who are infected with the Omicron variant. At the second meeting, the committee noted the additional evidence provided by consultees 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 that could also contribute to increased risk of severe COVID-19. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. It said the evidence should include age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects. The committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor. This was explored as part of the broader definition of risk in the partial review of the guidance (see section 3.8).

High-risk definition conclusion

3.7 The assessment group (AG) explained the approach used to model high-risk groups in its economic model (see section 3.28). At the first meeting, it assumed that people had general population survival, with a starting age of 56.6 years and the same hospitalisation rate as PANORAMIC. Therefore, no individual high-risk subgroups were modelled based on specific baseline characteristics, and these characteristics were explored in sensitivity analyses that represented the entire group eligible for treatment. The clinical experts acknowledged the difficulties of defining high risk by separate subgroups. The committee recognised that the decision problem for this evaluation required a definition of who has a high risk for progressing to severe COVID-19. It recognised the limitations of the model in characterising a group at high risk but considered the hospitalisation rate to be the most important variable for sensitivity to the clinical inputs (see sections 3.27 and 3.29). At the second meeting, the committee repeated these limitations of

modelling separate high-risk groups and concluded that a single definition of high risk should be used. The committee noted that evidence at a subgroup level is limited and too uncertain to parameterise the model. For example, additional functionality, clinical or cost inputs and treatment-effectiveness assumptions would be required to make differential subgroup recommendations and this would not be practical or aligned with the decision problem. The committee did not see additional evidence to justify splitting the high-risk group. The committee considered that the McInnes report's definition of high risk was based on the most robust evidence of people who have a high risk for progression to severe COVID-19, and this did not include age as an independent risk factor. Another benefit of using this definition is that outcomes data has been collected on this well-defined cohort over the course of the pandemic, providing some evidence from vaccinated people who were infected with Omicron variants. The committee considered the use of the Q-COVID risk calculator in clinical practice but concluded it had limited applicability because of the limitations of the model. The committee noted a wider definition of risk, from PANORAMIC, was included in the marketing authorisations for each of the treatments (see section 3.4). However, it concluded that the definition of risk in the McInnes report is the most robust definition. The committee acknowledged that the McInnes definition of high risk may be revised over time. Depending on the nature of the revisions, this guidance may need to be reviewed if a difference in clinical or cost effectiveness is expected.

Partial review considering broader high-risk population

3.8 NICE were made aware of the Therapeutics Clinical Review Panel (TCRP) modelling group findings: risk of severe COVID-19 outcomes ('the Edmunds report' from here on) and a company request to submit additional evidence supporting the cost effectiveness of nirmatrelvir plus ritonavir in a broader population than the McInnes-defined high-risk group. The Edmunds report considered if any other groups of people have an equivalent risk to people with any condition in the McInnes-defined high-risk group. The Department of Health and Social Care considered that based on the report, age 70 and over, diabetes, and obesity were important risk factors that should be taken into account in a cost-effectiveness analysis. The committee therefore considered the findings of the report in detail and the additional evidence submitted by the company (see

section 3.30).

3.9 The Edmunds report included analysis of 3 sources of evidence on outcomes of people with COVID-19, comprising large datasets from UK observational studies: OpenSAFELY (18.7 million people), Agrawal (30 million people) and Hippisley-Cox (1.3 million people). The OpenSAFELY data was collected during the Delta wave, while the Agrawal and Hippisley-Cox datasets were mostly collected during the Omicron wave. The OpenSAFELY data included unadjusted mortality rates whereas the other datasets included adjusted mortality and hospitalisation rates. The Edmunds report concluded that there was some evidence suggesting additional groups have an equivalent or greater risk of severe COVID-19 than people with certain autoimmune or inflammatory conditions such as rheumatoid arthritis or inflammatory bowel disease (the lowest risk level for people included in the McInnes high-risk definition). These additional groups included people aged 70 and over, people with diabetes or living with obesity, and people with other conditions. The committee noted feedback received at consultation on the partial review that people with heart failure also have increased risk of severe COVID-19 outcomes. It was aware that the McInnes report identified heart failure as an additional risk factor but had not made any specific recommendation for this group. It was also aware that the Hippisley-Cox and Agrawal studies showed higher risk for people with heart failure compared with people with rheumatoid arthritis or lupus. The committee considered that people with heart failure likely have a similar risk to the additional high-risk groups identified in the Edmunds report (age 70 and over, diabetes and obesity).

3.10 The introduction to the Edmunds report noted 'the methods used are crude and any groups identified through this process would require closer scrutiny to better understand their risk and to what extent this might be modified by improved access to antivirals and therapeutics'. The Edmunds report also noted the limitations of the analysis in that the 3 sources of evidence used different definitions of risk groups and outcomes, adjusted for different variables, and collected evidence during different waves of the pandemic. The committee considered the evidence underpinning the Edmunds report's findings. It noted that the OpenSAFELY data had been collected during the Delta wave. The committee was aware that the Omicron variant and its sublineages, which have been dominant since December 2021, are less virulent than the Delta variant. However, while this would impact absolute risks, the information on relative risks

between population groups was still relevant to the decision problem of the partial review. The committee noted that the aims of the independent advisory group (McInnes) and the TCRP modelling group (Edmunds) were slightly different. The McInnes group considered which groups are at highest risk from COVID-19 and therefore most likely to benefit from treatment. The Edmunds group addressed whether there are additional groups with a risk level at least as high as those who are already eligible for treatment. The committee noted the Edmunds group's comment that the extent to which risk may be modified by improved access to treatments for these additional groups would need close scrutiny. The committee was also aware that different methodology underpinned both reports. The McInnes group included more granular information on patient groups by specifying whether certain autoimmune or inflammatory conditions are active or uncontrolled, and when people are taking specific medications likely to affect their immune response to vaccination. The analysis underpinning the Edmunds report had used diagnosis codes to identify people with certain conditions. The committee considered that this would result in the groups having more heterogeneity in terms of risk by, for example, including people not currently taking immunosuppressants because of disease remission. The committee had previously discussed that COVID-19 risk may be more related to medication than diagnosis (see section 3.5). It considered that this heterogeneity would cause the overall risk estimate to mask a significant proportion of people who have much lower risk and are therefore less likely to benefit from treatment. The committee concluded that although there was some evidence to suggest that the broader population identified by the Edmunds report had a similar risk to the group defined in the McInnes report, it was uncertain whether they have an equivalent likelihood to benefit from treatment.

Current clinical management of COVID-19

Treatments for mild COVID-19

3.11 Current clinical management of mild COVID-19 in people who have a high risk for progression to severe COVID-19 includes treatments commissioned through a UK interim commissioning policy (see section 3.4). In May 2023, the policy was:

- first-line treatment: nirmatrelvir plus ritonavir (antiviral)

- second-line treatment: sotrovimab (neutralising monoclonal antibody)
- third-line treatment: remdesivir (antiviral)
- fourth-line treatment: molnupiravir (antiviral).

People who have symptoms and are not showing signs of a clinical recovery must start treatment as soon as possible after testing positive for COVID-19. The professional organisations explained there are different aims of treatments at this stage of COVID-19. Antivirals aim to reduce viral load and viral replication, which may reduce risk of severe disease. They are administered orally or intravenously. Neutralising monoclonal antibodies also aim to do this by binding to specific viral proteins to block viral infection. They are administered as injections or infusions (intravenously, intramuscularly or subcutaneously, depending on the treatment).

Treatments for severe COVID-19

3.12 For people hospitalised with severe COVID-19, anti-inflammatories are used along with antivirals, based on the UK interim clinical commissioning policies for secondary care. Anti-inflammatories treat the multisystem inflammation that develops later in the COVID-19 disease pathway. The clinical experts said a hierarchical flow of treatments is followed in hospital and recommending one treatment over another is challenging. The suitability of certain interventions can vary based on respiratory support requirements, minimum COVID-19 symptom duration or renal impairment status, but is generally as follows:

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

care.

- For people admitted to hospital with COVID-19 who need high-flow oxygen, baricitinib or tocilizumab are offered, subject to eligibility criteria, through the UK interim clinical commissioning policies for secondary care.

Clinical effectiveness

Assessment group's indirect comparison approach

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

- mild COVID-19 setting:
  - relative risk of hospitalisation or death
  - relative risk of all-cause mortality at 28 days
- severe COVID-19 setting:
  - hazard ratio of time to death
  - hazard ratio of time to discharge
  - relative risk of clinical improvement at 28 days.

The AG highlighted some significant limitations of their approach, because of the changing nature of COVID-19 (see section 3.2). Each trial included in the analysis was done at a different time in the pandemic. Most trials compared an individual treatment against the standard care at the time. Standard care has evolved in response to better understanding of the disease course, and changes in respiratory support and use of dexamethasone. The context of the disease has also changed with different circulating variants of concern, and changes in protection

through vaccinations and greater natural immunity over time. Each of these limitations were compounded by significant differences in trial design, baseline characteristics and geographical locations. The AG explained that the analysis assumed any relative effect of treatment is transferable to current clinical management. The clinical experts commented that meta-analysing the trial results may not be appropriate. This is because the weighting of each trial in a meta-analysis may not consider the relevance of the context of each trial within the analysis, for example, with different variants. The committee recognised the high levels of uncertainty with each treatment effect and the context-specific nature of the evidence. To characterise the uncertainty, rather than use probabilistic sensitivity analysis, the AG ran scenarios using the mean and the upper and lower confidence limits of each efficacy estimate. This provided scenarios showing 'mean-efficacy', 'lower-efficacy' and 'higher-efficacy' estimates. The AG cautioned the committee that the lower-efficacy and higher-efficacy scenarios had limitations because they represented a different uncertainty to that in the evidence base; they represented uncertainty on the estimates in the trial and were therefore sensitive to the number of events in each trial, rather than the context in which the trial was done. Therefore, they would not be sensitive to changes in efficacy against new circulating variants of concern. The committee understood the limitations of the scenario analysis. The committee considered it represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty. At draft guidance consultation, consultees highlighted that the lower-efficacy scenarios were arbitrary and a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The committee noted that the heterogeneity in the trial populations and the generalisability issues across the trials made the uncertainty challenging to parameterise. Therefore, the appropriate type of uncertainty would not have been captured in the probabilistic sensitivity analysis. 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 lower-efficacy scenario. The AG also included the updated COVID-19 NMA results for tocilizumab in the economic model.

Observational evidence

3.14 The committee considered the latest data from OpenSAFELY (non-randomised observational evidence from 40% of English GP practices). The OpenSAFELY database links with other national databases including the Office for National Statistics (ONS), inpatient hospital records, renal registries and Covid Medicines Delivery Units (CMDUs). The dataset is granular, updated regularly and reflective of the McInnes high-risk group during the Omicron wave in the UK. The committee acknowledged that this analysis of OpenSAFELY was done well and made efforts to account for confounding bias when possible. The analysis was done in a dynamic environment with changing treatment practices and linkages with various data sources that can increase risk of confounding bias. The committee noted the results of Hill and Mirchandani (2022), which compared the outcomes of a randomised controlled trial with non-randomised studies on COVID-19 treatments. The authors questioned the validity of non-randomised studies when their outcomes contradict the outcomes from a randomised controlled trial. The authors cautioned against using non-randomised evidence independent of randomised evidence for regulatory decisions. The committee was willing to accept the OpenSAFELY data on relative treatment effectiveness as supplementary evidence to the trial evidence and for modelling estimates for hospitalisation rates. The committee cautioned against solely relying on non-randomised evidence when making conclusions on treatment effect.

Generalisability of trial evidence to current endemic context

3.15 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. Clinical experts said extrapolating data from past trials was misleading because epidemiology and virus characteristics have changed (see section 3.2). The clinical experts and the committee considered it appropriate to consider how the clinical evidence would generalise to the endemic setting. It considered the main generalisability concerns to be:

- changes in population immunity through natural immunity and vaccination
- changes in the pathogenicity of the virus

- increased effectiveness of supportive care as knowledge of the virus evolved
- other differences that were specific to the context of a pandemic setting.

The absolute changes in these settings were considered in the economic modelling when possible. However, the committee considered the relative risks from these trials would also lack generalisability because there would be interaction between some of these concerns and treatment effect in the trial. This would likely favour the treatments compared with standard care, because the trials were done when key outcomes of hospitalisation and mortality were significantly higher. Therefore, the committee considered that the mean-efficacy scenarios from these trials likely reflect the highest clinical effectiveness or 'ceiling efficacy' of the treatment. The committee concluded that changes in best supportive care and higher vaccination rates mean that any limited relative treatment effects seen during the pandemic setting would have less effect in an endemic setting. This is because any limited benefit in the pandemic setting would likely be further limited or potentially have no difference in treatment effect compared with standard care (hazard ratios would tend towards 1) in an endemic setting.

3.16 The committee recognised that the treatment effects needed to be considered separately as follows:

- **Antiviral (nirmatrelvir plus ritonavir) – mild COVID-19 setting**: Evidence on nirmatrelvir plus ritonavir was more recent and captured the Delta wave.
- **Anti-inflammatory (tocilizumab)**: Clinical trial evidence on tocilizumab was collected before the Omicron wave. The committee considered the corroborating clinical evidence from multiple trials with evidence on outcomes pooled from multiple studies. The key trial, REMAP-CAP, included multiple UK sites and RECOVERY was reflective of standard care in NHS clinical practice. The committee also considered the relative treatment benefit of tocilizumab largely generalisable because the mechanism of action regulates hyperinflammation, which it did not expect would change based on variants, vaccination or natural immunity.

In vitro evidence

3.17 In vitro (laboratory) evidence may provide additional information on whether there is a realistic clinical possibility that a treatment retains efficacy against currently circulating variants. In vitro neutralisation assays can be used to assess if treatments can neutralise new variants, which can then be used to infer whether they retain clinical effectiveness over time as the virus evolves. An advantage of in vitro evidence is that it can be generated much faster than clinical trial evidence. A large body of in vitro evidence suggests that specific COVID-19 treatments may no longer show neutralisation activity against some circulating Omicron variants. In the first meeting, the committee could not comment on the validity of in vitro data and welcomed comments in response to consultation. Because of this, NICE commissioned an 'in vitro expert advisory group' made up of experts in infectious disease, virology, vaccine epidemiology, immunology and pharmacology (see the in vitro expert advisory group report in the committee papers). The group developed a decision framework to link in vitro neutralisation data to clinical outcomes and helped the committee use the framework to interpret the in vitro evidence. The committee understood this framework and also noted the latest in vitro evidence.

3.18 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 1 in vitro study (Imai et al. 2023) that investigated the effectiveness of the antivirals against BQ.1.1 and XBB. The in vitro study 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 in prevalence. 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 public committee slides in vitro presentation.

Generalisability of clinical effectiveness

3.19 By using the framework and the evidence, the committee concluded that the clinical effectiveness of anti-inflammatories (tocilizumab) are not variant-specific because of their mechanism of action. The committee concluded there was no in vitro evidence showing reduced clinical efficacy of antivirals (nirmatrelvir plus ritonavir) across the variants tested.

3.20 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.

Relative treatment effects for mild COVID-19

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

Nirmatrelvir plus ritonavir's relative treatment effect

3.22 The clinical experts considered that in clinical practice nirmatrelvir plus ritonavir appears to be the most effective at reducing progression to severe disease. But, they noted that there are many contraindications for nirmatrelvir plus ritonavir, including severe renal and hepatic impairment, and interactions with many common treatments. The committee noted that evidence on nirmatrelvir plus ritonavir was from 1 large randomised controlled trial (EPIC-HR) done in an unvaccinated population in an earlier wave of the pandemic. The committee concluded that OpenSAFELY data provided support for the continuous hospitalisation and mortality benefit of nirmatrelvir plus ritonavir seen from the

older trial. The committee was mindful not to make conclusions about relative treatment effects based solely on non-randomised evidence from OpenSAFELY. The committee noted the subgroup analysis from the recent EPIC-SR trial that included people who were vaccinated and had at least 1 risk factor for severe COVID-19. The committee acknowledged the EPIC-SR enrolment was stopped early and the results were preliminary and published only on the company's website rather than a peer-reviewed journal. However, the committee noted the preliminary outcomes showed non-significant reduction in hospitalisation rates in this vaccinated high-risk subgroup, adding to the existing generalisability concerns for EPIC-HR. It still considered there to be substantial uncertainty because of generalisability concerns with the mean-efficacy estimate. Therefore, the committee considered the range between the mean- and lower-efficacy estimates for nirmatrelvir plus ritonavir from the trial to be more suited to the current endemic setting, despite the limitations with this approach (see section 3.13). It noted that PANORAMIC was also recruiting a nirmatrelvir plus ritonavir treatment arm that could answer questions about effectiveness for people who have a high risk of progressing to severe COVID-19 but are not defined in the McInnes high-risk group.

Partial review: nirmatrelvir plus ritonavir's relative treatment effect

3.23 In the partial review, the committee noted that it did not have direct evidence of relative treatment effect for nirmatrelvir plus ritonavir in a vaccinated population of people aged 70 and over, or people with diabetes, heart failure or living with obesity. It noted PANORAMIC is expected to provide evidence to inform this consideration when results become available. Because of the generalisability concerns with EPIC-HR, the committee had previously concluded that efficacy could only be extrapolated cautiously to people with the very highest risk of adverse outcomes because of conditions or medications that affect vaccination response. These people could be considered to have similar risk to unvaccinated people included in EPIC-HR. Older age, diabetes, heart failure and obesity were not considered to impact vaccination response in the same way as the conditions and medications identified in the McInnes report. The committee was also mindful of the current endemic setting, with high background vaccination, less severe disease and much lower risk of hospitalisation and mortality. OpenSAFELY data showed that the absolute risk of death had decreased markedly between

wave 1 of the pandemic and wave 3 (the Delta variant). This decreased for many of the highest-risk population groups included in the McInnes report, with the notable exception of people who have had transplants. The committee considered that the lower hospitalisation and mortality rates expected in the current endemic setting were better reflected by the available results from the EPIC-SR trial. It considered that the EPIC-SR results may be more appropriate because this trial considered a more heterogenous population than EPIC-HR that may include people with much lower levels of risk and without attenuated antibody response to vaccination. The committee noted that the 721 people included in the relevant subgroup was a reasonably large sample to give an estimation of relative efficacy. The committee agreed to consider the mean- and low-efficacy estimates from EPIC-SR alongside the mean- and low-efficacy estimates from EPIC-HR in its decision making for the population of interest.

3.24 During consultation on the partial review, the company expressed concern about using EPIC-SR as the main source of efficacy estimates. Because it stopped early, it was not adequately powered to show efficacy in reduced hospitalisation or deaths in the full population and especially not the subgroup of interest. The committee recognised the limitations of EPIC-SR but noted that uncertainty around estimates taken from an underpowered trial did not preclude their use in decision making. Also, the committee did not agree with the company that the limitations of EPIC-SR meant that EPIC-HR was the most robust source of efficacy estimates. The committee reaffirmed its previous conclusion that EPIC-HR was not the most appropriate source of evidence on nirmatrelvir plus ritonavir's efficacy in the population of interest. It acknowledged the company's argument that a change in absolute risk over time did not change the treatment's mechanism of action and its clinical effect. However, the committee did consider that a change in the trial population (including generalisability of the trial participants) and other factors (outlined in section 3.15) would modify the treatment effect in terms of relative risk. The committee concluded that efficacy estimates from EPIC-SR, while subject to significant uncertainty, were the most appropriate source available for use in decision making. This is because the population most closely matched the population of interest in the decision problem.

3.25 The committee noted the wide range of potential treatment effect sizes dependent on the source and uncertainty of relative effect. It considered the

different efficacy analyses for the randomised data from EPIC-SR and EPIC-HR. The committee considered that when using EPIC-SR estimates, the mean-efficacy scenario was reasonable because the trial population was more representative of the current endemic context. The committee also recognised supplementary evidence on the relative effect of nirmatrelvir plus ritonavir from a selection of real-world studies from the US, Israel, Hong Kong and Canada. It considered NICE's real-world evidence framework and noted that these studies had neither been assessed for risk of bias nor identified in a systematic way. The committee noted that assessment for risk of bias is essential in non-randomised studies because choice of treatment is affected by unknown prognostic factors. The methods of adjustment performed in each of the studies may not fully account for the bias. But it considered that these non-randomised studies were important as supplementary evidence of continued efficacy in populations broader than that defined in the McInnes criteria. The committee noted that the relative treatment effect estimates from these observational studies mostly lay between the mean-efficacy estimate from EPIC-SR and the low-efficacy estimate from EPIC-HR for reducing hospitalisation or mortality. The committee considered that there were many factors and complexities that may modify the treatment effect, including time to starting treatment from symptom onset, that had not been assessed in many of the real-world studies. Also, there may be considerable selection, information and confounding bias present in the studies and there were low numbers of hospitalisations and deaths despite the large sample sizes, meaning the uncertainty was not reduced compared with EPIC-SR. The committee concluded that the randomised evidence had priority over the non-randomised real-world evidence for establishing treatment effect and the real-world evidence did not fully support the effect size of EPIC-HR over EPIC-SR. So, the mean-efficacy estimate from EPIC-SR was considered the most reliable estimate of treatment effect size, despite considerable uncertainty.

Relative treatment effects for severe COVID-19

3.26 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. For the

anti-inflammatory immunomodulator treatment, tocilizumab, the committee noted statistically significant clinical-effectiveness results. The clinical expert considered that tocilizumab should be used with caution in clinical practice and noted uncertainty with relative effect in the changing context of COVID-19. The committee noted that the virus is changing and there is bound to be some uncertainty in the clinical evidence. Tocilizumab acts on the complications caused by the virus, rather than attempting to neutralise the virus itself. Tocilizumab's mechanism of action is more robust to changes in the variants than neutralising monoclonal antibodies. The committee concluded that it was more confident in the mean-efficacy results because of tocilizumab's mechanism of action and clinical trial evidence base (see section 3.16).

Economic model

Model structure and key drivers of cost effectiveness

3.27 The economic model for this appraisal was developed by the AG and informed by a publication (Rafia et al. 2022) that 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 offered to people with COVID-19. People were hospitalised at a baseline standard care rate, or not hospitalised. Those 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, the level of respiratory support was assumed based on COVID-19 severity, with associated costs and disutilities by health state. The clinical inputs for each of the clinical efficacy scenarios were from the indirect treatment comparison (see section 3.13). The AG fitted parametric distributions to long COVID data from the ONS. Consultees highlighted that the long COVID duration was underestimated and should be higher than the 108.6 weeks used by the AG. In response, the AG updated the model, which estimates that 30% of people will still have symptoms at 2 years, 10% at 5 years and 3% at 10 years. The AG assumed that 100% of people in the severe COVID-19

setting and 10% in the mild COVID-19 setting would have long COVID. Consultees noted that the proportion should be reduced for the severe COVID-19 setting and increased for the mild COVID-19 setting. The AG considered its original assumption to be conservative and therefore appropriate because alternative evidence was not available at the time of the second meeting. The committee noted that the treatment efficacy was highly uncertain and the most important driver of cost effectiveness, but also noted the following other key drivers of model outputs:

- The key driver of the outputs in the mild COVID-19 setting was the baseline rate of hospitalisation. This is because it determined how many people were included in the high-cost and low-utility hospital setting.
- The key drivers of the outputs in the severe COVID-19 setting were the baseline standard care assumptions for overall survival and time to discharge. The model was adjusted so the baseline standard care assumptions were reflective of current UK clinical practice. NICE's rapid guidelines on COVID-19 were used to make this adjustment.

  The clinical experts commented that, because of changes to the disease, the outcomes for these treatments are now more nuanced than hospitalisation and mortality. The committee considered that relative treatment effect, and reduced hospitalisation and mortality rates, are key drivers of benefit but acknowledged that the model was not sensitive to other benefits of treatment like faster resolution of symptoms (hospital setting). The committee considered the model appropriate to capture the most important outcomes and appropriate for decision making given the available evidence base for COVID-19.

Hospitalisation rates

3.28 The rate of hospitalisation is a key driver of model outputs (see section 3.27) 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 incremental cost-effective ratios (ICERs). PANORAMIC was reflective of the

current COVID-19 landscape, including the Omicron variant. However draft guidance consultation comments further highlighted that PANORAMIC would have excluded people at higher risk who were eligible for treatment through the UK interim clinical commissioning policy (see section 3.4). Consultees provided a range of hospitalisation rates identified through targeted reviews. The committee saw overall hospitalisation rates defined by the McInnes high-risk definition including: OpenSAFELY 2.41% (untreated but eligible using McInnes definition), 1.37% (untreated but eligible group without contraindications to nirmatrelvir plus ritonavir) and 2.82% (DISCOVER-NOW database, UK observational study of people covered in the McInnes report). Hospitalisation rates also varied across different conditions, including between 4.15% and 4.40% for advanced renal kidney diseases and 15.90% (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 because the highest risk group may have been underrepresented in PANORAMIC (see section 3.4). They acknowledged the difficulty of determining hospitalisation rate without analysing the baseline population and all appropriate groups at risk. The rate is likely to vary substantially based on types of underlying conditions in the high-risk group, with potentially higher rates for severely immunocompromised people, such as people who have had a transplant and people having chemotherapy. The committee acknowledged significant uncertainty in estimating the hospitalisation rate for the population who have a high risk of progression to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.82% from the DISCOVER-NOW database. The committee concluded that the hospitalisation rate for the McInnes high-risk group is between 2.41% and 2.82% based on OpenSAFELY and DISCOVER-NOW. For people 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 a proxy from OpenSAFELY.

Assessment group analysis for partial review

3.29 In the partial review, the broader population of people aged 70 and over was represented in the AG's model by adjusting the mean age and baseline hospitalisation rates. These were both informed by data provided in confidence

by the PANORAMIC trial team, so cannot be reported here. It was noted that changing the mean age for hospitalised and non-hospitalised patients had little impact on the cost-effectiveness estimates. The AG modelled 3 scenarios:

- 1) baseline hospitalisation rate from people aged 70 and over in PANORAMIC and relative treatment effect from COVID-NMA (which only included published data from EPIC-HR on relative treatment effect for nirmatrelvir plus ritonavir)
- 2) baseline hospitalisation rate from PANORAMIC and relative treatment effect from EPIC-SR
- 3) baseline hospitalisation rate for the McInnes highest-risk group and relative treatment effect from COVID-NMA.

The committee considered that PANORAMIC was the most appropriate source for the baseline hospitalisation rate for people aged 70 and over because it reflects the current endemic context and is the only study that provides specific data for this age group. It did not consider that the baseline hospitalisation rate accepted for the McInnes highest-risk group was an appropriate reflection of the risk for people aged 70 and over. This is because it had concluded that this was a more heterogenous group that would include people at lower levels of risk (see section 3.10), and is therefore more closely aligned with the PANORAMIC trial population. The committee noted it was not presented with cost-effectiveness analyses for people with diabetes or living with obesity. It considered whether the analysis of people aged 70 and over could be extrapolated to people with diabetes or living with obesity, based on baseline hospitalisation rate. The committee considered it might be reasonable to expect that baseline hospitalisation rates would be similar. But, without a way to specifically parameterise this population in the model (for example, by taking into account the effects of other treatments that these groups may be having that may reduce their risk of hospitalisation over time), this assumption was associated with substantial uncertainty.

Company analysis for partial review

3.30 The company had provided a range of cost-effectiveness analyses for different

populations. It did not include an analysis for people aged 70 and over. Instead, it presented an analysis of people aged 70 and over and people aged 18 to 69 with at least 1 pre-existing condition. The company used the baseline hospitalisation rate from PANORAMIC for people aged 70 and over and people aged 18 to 69 with at least 1 pre-existing condition. It also assumed that the relative risk of hospitalisation or death with nirmatrelvir plus ritonavir was zero, because there were no events in the age 70 and over subgroup of the nirmatrelvir plus ritonavir arm in the EPIC-HR trial. The AG noted this was methodologically incorrect because it assumes there will never be any COVID-19-related hospitalisations or deaths for people aged 70 and over and having nirmatrelvir plus ritonavir. It noted this should have a continuity correction in the model to adjust for small numbers of events. In addition, because the company's analysis included people aged under 70, the mean age modelled was much lower than that modelled by the AG. The AG noted that this would reduce cost-effectiveness estimates because more quality-adjusted life years (QALYs) will be gained per death avoided. The committee concluded that the analysis provided by the company was not relevant to the decision problem of the partial review and it preferred to use the AG's cost-effectiveness estimates in its decision making.

3.31 During consultation on the partial review, the company reproduced the AG's cost-effectiveness estimates using a different statistical method to account for low event rates (the method for continuity correction). The AG noted that there were 3 different recognised methods that could be applied to the evidence and provided analyses that used the Wald, score and likelihood ratio tests. The committee noted that the different methods did not have a large impact on the ICERs. But, they had a larger impact on the EPIC-SR efficacy estimates compared with the EPIC-HR efficacy estimate because of the much lower number of events. The committee considered it was reasonable to use any of these methods to account for low event rates but acknowledged the additional uncertainty to the ICER calculation.

Time to discharge

3.32 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. The AG had previously noted the time to discharge

evidence was collected during the early stages of the pandemic, which could lead to substantial generalisability concerns because the context of care has changed in the endemic setting. The committee noted that in clinical practice, time to discharge can sometimes overestimate time in high-cost health states because it can depend on multiple factors (for example, waiting for a negative COVID-19 test). Time to discharge was also considered more important for people who are being discharged to a care home. The committee also noted that clinical experts in both meetings explained that people hospitalised with COVID-19 have very different symptoms at present (the time of this evaluation) compared with early stages of the pandemic. It also noted that the population is heterogeneous (see sections 3.2 and 3.3). The AG included scenarios that removed treatment effects on time to discharge and clinical improvement at 28 days to try and account for these potential uncertainties. At the first meeting the committee considered these scenarios to be plausible but conservative if treatments had effects outside of hospitalisation and mortality. The committee was not presented with additional evidence on time to discharge or clinical improvement and was uncertain about the treatment benefit in the endemic setting. The committee concluded it was reasonable to remove these treatment effects.

Utility values

Utility value assumptions

3.33 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 recently

published 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 postdischarge long COVID utility decrements from Evans et al. (2022). The same utility decrement was assumed regardless of ordinal scale status at hospital admission. At AG report consultation, stakeholders suggested an alternative source of postdischarge utility decrements split by history of ordinal scale status. The AG explained that the model structure was unable to allocate postdischarge utility based on historical ordinal scale admission status. It also said that these utility decrements are only applied for the duration of long COVID and are not a key driver of ICERs. The committee agreed with the AG's rationale and the long COVID utility decrement assumptions.

Costs

Long COVID costs

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

yearly costs (£2,500). The committee agreed these scenarios had minimal effect on the cost-effectiveness estimates but considered that any new UK-specific evidence on long COVID costs should be included if available. During draft guidance consultation a consultee said the AG's base-case long COVID cost underestimates the true burden of long COVID and provided an alternative higher cost from Vos-Vromans et al. (2017). The AG accepted this new evidence and inflated the cost to £2,267 per year (to reflect 2021/2022). The committee agreed with the updated base-case value.

Administration costs

3.35 The AG did not originally include administration costs for oral or subcutaneous treatments. For intravenous treatments, a cost of £221 was assumed based on NHS reference code SB12Z. After consultation, the AG updated the assumptions in the model with costs provided by NHS England. NHS England provided a CMDU deployment cost for the administration of oral antivirals (£410). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care. However, future delivery may be in primary care, which would likely reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs. They also noted that these costs were calculated before implementation of nirmatrelvir plus ritonavir, which may increase resource use because of expected requirements to assess contraindications. During draft guidance consultation, consultees did not agree with the administration costs used in the AG base case. Some consultees said additional pharmacist per hour costs (about £352.49) should be added for assessment of nirmatrelvir plus ritonavir interactions with other treatments. Other consultees argued that the prescribing cost for nirmatrelvir plus ritonavir should be lower and between £75 to £117 because e-consultations and telephone triage options factor in the assessment of contraindications by clinicians already familiar with doing them. 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.

Partial review: nirmatrelvir plus ritonavir administration costs

3.36 In the partial review, the committee was mindful that with the end of free testing and the closure of CMDUs, there may be challenges around patient identification and delivering treatment to a broader population. These could have cost and resource implications for the healthcare system that were not fully captured in the model. Although these could not be quantified, the committee considered that they were likely to increase the cost-effectiveness estimates.

3.37 During consultation on the partial review, the company submitted evidence of administration costs from a survey of UK healthcare professionals with experience of drug–drug interaction assessment for oral antivirals. The survey elicited estimates of clinician type, grade and time spent on medical review for both standard and complex patients and converted these to an average cost by applying the time requirements to the specialty and banding of the healthcare professionals doing the assessment. Based on the survey results the company presented cost-effectiveness analyses that assumed an administration cost of £117. The clinical expert noted that during the setup of the CMDUs, higher-cost consultants initially made decisions but this has now changed and lowered costs. They also highlighted that the costs for people who are not prescribed treatments in the CMDUs are included in these administration costs and may be higher than for people who are prescribed nirmatrelvir plus ritonavir. This is because non-prescription often took longer than a decision to prescribe. The committee considered it was plausible that administration costs may now be lower than the cost of £410 derived from CMDU delivery models used during the pandemic. This is because it included costs such as consumables and room hire that would not necessarily be incurred when delivering these medicines as part of business-as-usual services. But it was also aware that the £410 estimate did not include the time needed for medical review of drug–drug interactions. NHS England said that some integrated care boards were intending to replicate the CMDU delivery model once responsibility for COVID-19 antiviral treatment transferred over to them. So, costs may be more variable than those assumed in the company's analysis. The committee considered the clinical expert's comments about costs for people who were assessed but not prescribed nirmatrelvir plus ritonavir in clinical practice and whether these costs should be included in the analysis. It recognised that, from an NHS perspective (as in the NICE reference case), the costs of consultations not resulting in prescription may

form part of the conceptual cost of assessment and diagnosis when prescribing the treatment. Therefore, it would be appropriate to include the costs in line with the CMDU cost analysis. However, not all these costs would be attributable to nirmatrelvir plus ritonavir, because other medicines, treatments and advice can be delivered through the CMDUs. Therefore, the committee concluded there may be a proportion of costs that would increase those identified in the company's survey, as well as additional uncertainty from variable methods of implementation within the NHS. The committee concluded overall that it was appropriate to consider the range of administration costs between the £117 and £410 estimates.

Hospitalisation costs

3.38 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 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 further adjustments that were applied).
- Ordinal scale 5: weighted average cost of DZ19N to DZ19Q (lobar, atypical or viral pneumonia, with single intervention) for non-elective long stay (see the AG report in the committee papers for further adjustments that were applied).
- Ordinal scale 6: using XC07Z (adult critical care, 0 organs supported).
- Ordinal scale 7: weighted average cost for adult critical care, 1 or more organs supported (XC01Z to XC06Z).

  The committee acknowledged the changes implemented by the AG and agreed with the AG's final approach.

Cost-effectiveness estimates

Treatment for mild COVID-19

3.39 For the mild COVID-19 setting, ICERs and net monetary benefits were calculated for nirmatrelvir plus ritonavir for the McInnes group. The committee looked at the pairwise ICERs compared with standard care presented by the AG. The committee reviewed results for the low-efficacy, mean-efficacy and high-efficacy scenarios (see section 3.13). The committee noted its preferred assumptions to include combinations of the following:

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

The ICERs for nirmatrelvir plus ritonavir compared with standard care using a) mean-efficacy treatment effect and b) low-efficacy treatment effect and a 2.41% hospitalisation rate were both below £20,000 per QALY gained. Based on the committee's preferred assumptions, it considered that nirmatrelvir plus ritonavir was likely a cost-effective use of NHS resources compared with standard care, for people with high risk of severe COVID-19, as defined by the McInnes report's criteria. This includes people in hospital with mild COVID-19 who have a high risk of progressing to severe COVID-19. The committee also considered the mean-efficacy and low-efficacy scenarios using a hospitalisation rate of 0.77% from PANORAMIC, which more closely approximated the marketing authorisation population for nirmatrelvir plus ritonavir. The ICERs were above £20,000 per QALY gained and nirmatrelvir plus ritonavir was likely not a cost-effective use of NHS resources in this broader lower-risk population.

Partial review of nirmatrelvir plus ritonavir

3.40 The committee considered the ICER estimates using the efficacy estimates from EPIC-SR with the range of potential corrections for low event rates (see

section 3.30) and supported by the estimates from the real-world evidence studies. The analyses used the hospitalisation rate from people aged 70 and over in PANORAMIC and the range of administration costs (see section 3.37). At the list price of £829, the most likely ICERs were above £30,000 using an administration cost of £117 and substantially above £30,000 using an administration cost of £410. The committee preferred to use a threshold of £20,000 per QALY gained because of the remaining uncertainties associated with the clinical data (see sections 3.23 to 3.25) and the costs of testing (see section 3.35). The committee concluded that nirmatrelvir plus ritonavir was not a cost-effective use of NHS resources in the broader population identified in the Edmunds report. So, it could not be recommended for this broader population.

Severe COVID-19 and supplemental oxygen

3.41 For the severe COVID-19 with supplemental oxygen setting, ICERs were calculated for tocilizumab. Pairwise ICERs compared with standard care were presented. The committee reviewed results for the low-efficacy and mean-efficacy scenarios (see section 3.13).

The ICERs for tocilizumab cannot be reported here because of confidential prices. The ICERs for tocilizumab compared with standard care were below £20,000 per QALY gained for the mean-efficacy scenario. The committee considered tocilizumab likely to be a cost-effective use of NHS resources compared with standard care.

Other factors

Uncaptured benefits

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

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

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

3.43 At the second committee meeting for the partial review, the clinical expert noted that some people, particularly older people with dementia symptoms, may experience step-changes in progression of cognitive symptoms because of hospitalisation with COVID-19. They considered this is not currently captured in the model. This population correlates with the over 70 population of interest in the broader risk population. The committee noted that dementia and neurodegenerative disorders associated with severe frailty are included in the revised McInnes criteria (March 2023). It also noted that progression of cognitive symptoms is increased in people with baseline dementia, so nirmatrelvir plus ritonavir would already be suitable for these people. The clinical expert also noted that some older people hospitalised with COVID-19 are hospitalised for substantially longer than other patients. The committee considered it was

possible there may be uncaptured benefit in terms of the reduced costs and additional benefits of avoiding hospitalisation. But it was aware that the assumed length of hospital stay included in the model was based on the distribution from the RECOVERY trial, adjusted to evidence between March 2020 and December 2021, before the less severe Omicron variant. This included a significant proportion of people who had stays longer than 5 days. So, the model may already overestimate length of stay for the target population in the partial review. The committee considered it was unclear to what extent the length of stay was increased for older people and to what extent any benefits would be uncaptured in the model. This was because of the substantial uncertainty in the available evidence and heterogeneous populations.

Equality issues

3.44 The committee considered potential equality issues, including:

- **Disability – people for whom nirmatrelvir plus ritonavir is contraindicated**: The committee noted nirmatrelvir plus ritonavir was contraindicated for concomitant use with many medicinal products. The committee originally evaluated alternative treatments for people who cannot take nirmatrelvir plus ritonavir. The committee considered whether, by recommending nirmatrelvir plus ritonavir, without recommending an alternative for people in whom nirmatrelvir plus ritonavir is contraindicated, it would be indirectly discriminating against people in these groups. Indirect discrimination means producing guidance that appears to apply to all but has a disproportionate adverse impact on those with a protected characteristic. The committee took this into account and considered a higher hospitalisation rate of 4% for the McInnes-defined high-risk group who were also contraindicated to nirmatrelvir plus ritonavir. Assuming the higher hospitalisation rate meant that sotrovimab (originally included in this evaluation) was considered a cost-effective use of NHS resources, for people in whom nirmatrelvir plus ritonavir is contraindicated. As of February 2026, sotrovimab was no longer available to the NHS because it was discontinued by the company.
- **Disability – optimised recommendation on nirmatrelvir plus ritonavir**: The committee noted the marketing authorisation for nirmatrelvir plus ritonavir is broader and included people at lower risk of severe COVID-19 compared with

the optimised recommendation (see section 1). The committee acknowledged that the optimised recommendation may exclude some people in certain high-risk groups who were included in the marketing authorisation and who have disability, which is a protected characteristic (see section 3.4).

- **Race**: The committee was aware that people from minority ethnic family backgrounds were more likely to be diagnosed with COVID-19. Also, the risk of dying from COVID-19 was disproportionately higher in people from Black, Asian and other minority ethnic family backgrounds. The committee further noted that nirmatrelvir plus ritonavir was contraindicated in people with hepatic and renal impairments. The prevalence of certain comorbidities including renal impairment are known to be higher in people from these family backgrounds. Differences in prevalence cannot usually be resolved in a technology appraisal, although the committee did not consider that family background has a significant impact on access to treatment. However, the committee noted that certain minority ethnic populations suffered worse health outcomes. The committee concluded that it would consider these issues in its decision making.

- **Treatment for children**: The committee noted that the summary of product characteristics for nirmatrelvir plus ritonavir (mild COVID-19 setting) and tocilizumab (severe COVID-19 setting) do not recommend these treatments in people under 18 years. By only recommending tocilizumab in the severe COVID-19 setting there is a risk of indirectly discriminating against children and young people.

- **Pregnancy and maternity**: The committee noted that the summary of product characteristics for tocilizumab states it should not be used during pregnancy unless clearly necessary. By recommending tocilizumab there is a risk of indirectly discriminating against people who are pregnant. The committee considered that in the context of acute hospital treatment, no other alternative treatments for treating hyperinflammation were included in the scope of this appraisal. It considered that clinicians should use independent judgement when considering the risk factors of tocilizumab in people who are pregnant.

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 (29 March 2023).

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 a patient has COVID-19 and the doctor responsible for their care thinks that nirmatrelvir plus ritonavir or tocilizumab is the right treatment, it should be available for use, in line with NICE's recommendations.

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

5 Supporting information on risk factors for progression to severe COVID-19

This section provides supporting information for recommendations 1.1 and 1.2. Box 1 and box 2 present risk factors for progression to severe COVID-19 defined by the independent advisory group commissioned by the Department of Health and Social Care. Box 1 details risk factors in adults and box 2 details risk factors in young people aged 12 to 17 years. The information presented in box 1 and box 2 was provided by the independent advisory group and has not been independently reviewed or verified by NICE. See the Department of Health and Social Care webpage on the independent advisory group report for the background to this work.

Box 1 Risk factors for progression to severe COVID-19 in adults

Risk factors for progression to severe COVID-19 in adults defined by the independent advisory group commissioned by the Department of Health and Social Care (June 2023)

Down's syndrome and other genetic disorders

All individuals with Down's syndrome or other chromosomal disorders known to affect immune competence

Solid cancer

- Metastatic or locally advanced inoperable cancer
- Lung cancer (at any stage)
- People receiving any chemotherapy (including antibody-drug conjugates), PI3K inhibitors or radiotherapy within 12 months
- People who have had cancer resected within 3 months and who received no adjuvant chemotherapy or radiotherapy
- People who have had cancer resected within 3 to 12 months and receiving no adjuvant chemotherapy or radiotherapy are expected to be at less risk (and thus less priority) but still at increased risk compared with the non-cancer populations

Haematological diseases and recipients of haematological stem cell transplant (HSCT)

- Allogeneic HSCT recipients in the last 12 months or active graft versus host disease (GVHD) regardless of time from transplant (including HSCT for non-malignant diseases)
- Autologous HSCT recipients in the last 12 months (including HSCT for non-malignant diseases)
- Individuals with haematological malignancies who have received CAR-T cell therapy in the last 24 months, or until the lymphocyte count is within the normal range

- Individuals with haematological malignancies receiving systemic anti-cancer treatment (SACT) within the last 12 months, or radiotherapy in the last 12 months
- All people who do not fit the criteria above, and are diagnosed with:
  - myeloma (excluding monoclonal gammopathy of undetermined significance [MGUS])
  - AL amyloidosis
  - chronic B-cell lymphoproliferative disorders (chronic lymphocytic leukaemia, follicular lymphoma)
  - myelodysplastic syndrome (MDS)
  - chronic myelomonocytic leukaemia (CMML)
  - myelofibrosis
  - any mature T-cell malignancy
- All people with sickle cell disease
- People with thalassaemia or rare inherited anaemia with any of the following:
  - severe cardiac iron overload (T2 * less than 10 ms)
  - severe to moderate iron overload (T2 * greater than or equal to 10 ms) plus an additional comorbidity of concern (for example, diabetes, chronic liver disease or severe hepatic iron load on MRI)
- Individuals with non-malignant haematological disorders (for example, aplastic anaemia or paroxysmal nocturnal haemoglobinuria) receiving B-cell depleting systemic treatment (for example, anti-CD20, anti-thymocyte globulin [ATG] and alemtuzumab) within the last 12 months

Renal disease

- Renal transplant recipients (including those with failed transplants within the past 12 months), particularly those who have:

  - received B-cell depleting therapy within the past 12 months (including alemtuzumab, rituximab [anti-CD20], ATG)
  - an additional substantial risk factor that would in isolation make them eligible for monoclonals or oral antivirals

- Non-transplant renal patients who have received a comparable level of immunosuppression
- People with chronic kidney disease (CKD) stage 4 or 5 (an estimated glomerular filtration rate [eGFR] less than 30 ml per min per 1.73 m^2) without immunosuppression

Liver diseases

- People with cirrhosis Child-Pugh (CP) class A, B and C, whether receiving immune suppressive therapy or not. Those with decompensated liver disease (CP B and C) are at greatest risk
- People with a liver transplant
- People with liver disease on immune suppressive therapy (including people with and without cirrhosis)

Solid organ transplant recipients

Solid organ transplant recipients not in any of the above categories.

Immune-mediated inflammatory disorders (diseases in which autoimmune or autoinflammation-based pathways are implicated in disease, for example, inflammatory arthritis, connective tissue diseases, inflammatory skin diseases, inflammatory gastrointestinal disease)

- People who have received a B-cell depleting therapy (anti-CD20 drug, for example, rituximab, ocrelizumab, ofatumumab, obinutuzumab) in the last 12 months
- People who have been treated with cyclophosphamide (IV or oral) in the

6 months prior to positive PCR or relevant COVID test

- People who are on corticosteroids (equivalent to 10 mg or more per day of prednisolone) for at least the 28 days prior to positive PCR or relevant COVID test
- People who are on biologics or small molecule JAK inhibitors
- People who are on current treatment with mycophenolate mofetil, oral tacrolimus, azathioprine, mercaptopurine, or similar agents (for major organ involvement such as kidney, gastro-intestinal tract, liver, lung, brain), methotrexate (for interstitial lung disease or asthma only) and/or ciclosporin. No minimum dose threshold is suggested
- People who are on current treatment (or within the last 6 months) with S1P modulators (fingolimod, ponesimod or siponimod), or alemtuzumab or cladribine within the last 12 months
- People who exhibit at least one of: (a) uncontrolled or clinically active disease (that is, required recent increase in dose or initiation of new immunosuppressive drug or IM steroid injection or course of oral steroids within the 3 months prior to positive PCR or relevant COVID test); and/or (b) other high risk comorbidities (for example, body mass index [BMI] greater than 30, diabetes mellitus, hypertension, major organ involvement such as significant kidney, liver, nervous system or lung inflammation or significantly impaired renal, liver, nervous system and/or lung function)

Respiratory

- Asthma in people on oral corticosteroids (defined above). Any asthma patient taking immunosuppressants for their asthma including but not exclusively methotrexate, ciclosporin. Frequent exacerbations requiring 4 or more courses of prednisolone per year, usually 40 mg per day for 5 days or more
- COPD on long term home non-invasive ventilation (NIV). Patients on long term oxygen therapy. People with moderate or severe disease (FEV1 less than or equal to 50% predicted) who have required 4 or more courses of prednisolone 30 mg for 5 days or greater in last 12 months

- Interstitial lung disease (ILD) – all patients with idiopathic pulmonary fibrosis
- Sub-types of ILD, for example, connective tissue disease related, sarcoidosis, hypersensitivity pneumonitis, NSIP (non-specific interstitial pneumonia) who have received a B-cell depleting therapy in last 12 months, or IV or oral cyclophosphamide in the 6 months prior to testing positive for COVID-19. Any ILD patient on current treatment with corticosteroids, mycophenolate mofetil, azathioprine, tacrolimus, cyclosporin or methotrexate. No minimum dose criteria
- Any people with any type of ILD who may not be on treatment due to intolerance but has severe disease with an FVC predicted less than 60%
- NIV and tracheostomy ventilated – all patients requiring this type of support regardless of the underlying disorder (which might include COPD, obesity hypoventilation syndrome, scoliosis, bronchiectasis, neurodisability and genetic muscular diseases [refer to neurology section]).
- Lung cancer patients, refer to 'Solid cancer' section above
- Lung transplant patients (refer to solid organ transplant section)
- Pulmonary hypertension (PH): groups 1 and 4 from PH classification

Immune deficiencies

- Common variable immunodeficiency (CVID)
- Undefined primary antibody deficiency on immunoglobulin (or eligible for Ig)
- Hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- Severe combined immunodeficiency (SCID)
- Autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- Primary immunodeficiency associated with impaired type 1 interferon signalling

- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)
- Any person with secondary immunodeficiency receiving, or eligible for, immunoglobulin replacement therapy

HIV/AIDS

- People with high levels of immune suppression, have uncontrolled or untreated HIV (high viral load) or present acutely with an AIDS defining diagnosis
- People on treatment for HIV with CD4 less than 350 cells per mm^3 and stable on HIV treatment or CD4 greater than 350 cells per mm^3 and additional risk factors (for example, age, diabetes, obesity, cardiovascular, liver or renal disease, homeless, alcoholic dependency)

Neurological disorders

- Conditions associated with neuromuscular respiratory failure requiring chronic ventilatory support:
  - motor neurone disease
  - Duchenne muscular dystrophy
- Conditions that require use of specific immunotherapies:
  - multiple sclerosis (MS)
  - myasthenia gravis (MG)
  - other immune-mediated disorders
- Dementia, neurodegenerative and neuroimmune disorders when associated with severe frailty (for example, levels 7 or 8 on Clinical Frailty Scale, as part of a personalised care plan):
  - Alzheimer's disease, vascular disease, Lewy body disease, or frontotemporal atrophy
  - Parkinson's disease

- Huntington's disease
- progressive supranuclear palsy and multiple system atrophy
- motor neurone disease
- multiple sclerosis and other immune-mediated neurological disorders

Box 2 Risk factors for progression to severe COVID-19 in young people aged 12 to 17 years

Pathway for PCR(or relevant COVID test) positive symptomatic cases aged older than 12 and younger than 18 years, greater than 40 kg weight, and clinical concern: defined by the independent advisory group commissioned by the Department of Health and Social Care (March 2023)

Children and young people (CYP) at substantial risk

Complex life-limiting neurodisability with recurrent respiratory infections or compromise.

CYP at significant risk if 2 or more of these risk factors are present

Primary immunodeficiency:

- common variable immunodeficiency (CVID)
- primary antibody deficiency on immunoglobulin (or eligible for immunoglobulin replacement)
- hyper-IgM syndromes
- Good's syndrome (thymoma plus B-cell deficiency)
- severe combined immunodeficiency (SCID)
- autoimmune polyglandular syndromes or autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy (APECED syndrome)
- primary immunodeficiency associated with impaired type 1 interferon signalling
- X-linked agammaglobulinaemia (and other primary agammaglobulinaemias)

Secondary immunodeficiency:

- HIV CD4 count less than 200 cells per mm^3
- solid organ transplant
- haematological stem cell transplant (HSCT) within 12 months, or with graft versus

host disease (GVHD)

- CAR-T cell therapy in last 24 months
- induction chemotherapy for acute lymphoblastic leukaemia (ALL), non-Hodgkin's lymphoma, chemotherapy for acute myeloid leukaemia (AML), relapsed and/or refractory leukaemia or lymphoma

Immunosuppressive treatment:

- chemotherapy within the last 3 months
- cyclophosphamide within the last 3 months
- corticosteroids greater than 2 mg per kg per day for 28 days in last 4 weeks
- B-cell depleting treatment in the last 12 months

Other conditions:

- high body mass index (BMI; greater than 95th centile)
- severe respiratory disease (for example, cystic fibrosis or bronchiectasis with FEV1 less than 60%)
- tracheostomy or long-term ventilation
- severe asthma (paediatric intensive care unit [PICU] admission in 12 months)
- neurodisability and/or neurodevelopmental disorders
- severe cardiac disease
- severe chronic kidney disease
- severe liver disease
- sickle cell disease or other severe haemoglobinopathy
- trisomy 21

- complex or chromosomal genetic or metabolic conditions associated with significant comorbidity
- multiple congenital anomalies associated with significant comorbidity
- bronchopulmonary dysplasia – decisions should be made taking into account degree of prematurity at birth and chronological age

6 Evaluation committee members and NICE project team

Evaluation committee members

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

Committee members are asked to declare any interests in the technology being evaluated. If it is considered there is a conflict of interest, the member is excluded from participating further in that evaluation.

The minutes of each evaluation committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

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
Technical lead

Adam Brooke
Technical adviser

Louise Jafferally
Project manager

Associate director
Ross Dent

7 Update information

February 2026

We removed the recommendation on sotrovimab. This is because GlaxoSmithKline has discontinued manufacturing, supply, distribution and marketing of sotrovimab in the UK. The 'why the committee made these recommendations' section and committee discussion section have also been amended to reflect the updated recommendation.

We also included information in section 1 explaining why the recommendation on casirivimab plus imdevimab was removed in March 2024.

May 2025

The recommendation for nirmatrelvir plus ritonavir was updated. The recommendation made in March 2024 after a partial review of the guidance was based on a confidential price offered by the company to the NHS. In May 2025, the company set a new list price of £829. This was because NICE was considering if the recommendation needed to be reviewed due to the evolving COVID-19 landscape and emerging data from NHS England. Nirmatrelvir plus ritonavir is no longer cost effective for the groups evaluated in the partial review (people with diabetes, obesity or heart failure, or aged 70 years or over). So, these groups were removed from the recommendation.

Nirmatrelvir plus ritonavir remains cost effective for the highest-risk group, so this recommendation remains in place.

We also:

- updated the list price in section 2.7
- updated sections 3.42 and 3.46 to reflect the updated recommendation
- removed sections 4.5 to 4.15 because the funding variation for nirmatrelvir plus ritonavir related to the recommendation that has been withdrawn.

June 2024

The wording of the recommendation describing the commercial arrangement (see section

1.3), and in section 2.9, has been updated to include procurement information about tocilizumab biosimilars.

March 2024

After a partial review of this guidance, we updated the recommendation on nirmatrelvir plus ritonavir to include additional groups eligible for treatment (people with diabetes, obesity or heart failure, or aged 70 years or over).

We removed the recommendation on casirivimab plus imdevimab because the conditional marketing authorisation for casirivimab plus imdevimab for treating COVID-19 was withdrawn.

June 2023

We added a section with supporting information on risk factors for progression to severe COVID-19. This supporting information was provided by the independent advisory group commissioned by the Department of Health and Social Care.

April 2023

We updated the recommendations on nirmatrelvir plus ritonavir and sotrovimab to link to the updated independent advisory group report commissioned by the Department of Health and Social Care.

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