NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Final draft guidance

Nirmatrelvir plus ritonavir for treating COVID-19 (partial review of TA878)

This evaluation is a partial review of NICE technology appraisal guidance TA878, which recommends nirmatrelvir plus ritonavir for people with an increased risk of progression to severe COVID-19, as defined by the independent advisory group report commissioned by the Department of Health and Social Care. This partial review considers:

- the Therapeutics Clinical Review Panel modelling group findings on risk of severe COVID-19 outcomes that identify additional people with an increased risk of progression to severe COVID-19, and
- whether to recommend nirmatrelvir plus ritonavir for these additional risk groups.

Following the resolution of any appeals on the final draft guidance for this partial review, the final recommendations and relevant discussion will be incorporated into TA878, which will be reissued as updated guidance.

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

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

Issue date: January 2024

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
- they have any of the following:
  - an increased risk for progression to severe COVID-19, as defined in section 5 of the NICE technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab [TA878]
  - age 70 years and over
  - a body mass index (BMI) of 35 kg/m^2 or more
  - diabetes
  - heart failure.

Why the committee made this recommendation

This evaluation reviews the clinical and cost effectiveness of nirmatrelvir plus ritonavir for mild COVID-19. Most of the clinical evidence for this treatment 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 the 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. They also get lower as the risk of severe COVID-19 decreases. These lower rates increase the cost-effectiveness estimates.

Clinical evidence suggests that nirmatrelvir plus ritonavir is effective at treating mild 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 of TA878). Nirmatrelvir plus ritonavir is recommended for

treating COVID-19 in these groups because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources.

The Therapeutics Clinical Review Panel modelling group findings on risk of severe COVID-19 outcomes identify additional groups of people with an increased risk of severe COVID-19. This partial review evaluates whether nirmatrelvir plus ritonavir could also be recommended for some of these groups (age 70 years and over, BMI of 35 kg/m^2 or more, diabetes, and heart failure). The likely cost-effectiveness estimates for these groups are also within what NICE considers an acceptable use of NHS resources.

2 Information about nirmatrelvir plus ritonavir

Marketing authorisation indication

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'.

Dosage in the marketing authorisation

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

Price

2.3 The updated list price for nirmatrelvir plus ritonavir is confidential until released by the company and cannot be reported here.

3 Committee discussion

The evaluation committee considered evidence from several sources. For full details of the evidence, see the committee papers for NICE technology appraisal guidance TA878 and the committee papers for the partial review.

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 which severely impact a person's physical and mental health and potentially affect their ability to work, attend school or do their usual activities. During 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, 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 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 to 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 any treatment being evaluated. It agreed that the most appropriate approach would be to consider how relevant the clinical data are to the current endemic context of the disease at the time of this evaluation, 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 authorisations for the treatments which lower the risk of progression to severe COVID-19, including nirmatrelvir plus ritonavir, were based on evidence from populations with slightly different definitions of high risk. For example, some trials included people with at least 1 risk factor for severe COVID-19 whereas some had specific age requirements. Understanding of the prognostic effects of risk factors has developed throughout the pandemic, and therefore the available evidence may represent a heterogeneous population. The committee acknowledged the potential limitations of the available evidence but considered it 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 that defined age over 50 years as a risk factor (Knight et al. 2020). They noted that age over 70 years may be an important determinant of mortality but also considered that the relationship between age and comorbidities is complex, particularly for immunocompromised people. One of the companies considered that age was an important risk factor but noted 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 which showed a statistical relationship between age and comorbidities. The committee acknowledged that age is a risk factor for progression to severe COVID-19. The committee considered that the relationship between age and comorbidities can be important in explaining risk of severe disease. The committee concluded that age over 70 years is likely to be confounded by underlying conditions which could also contribute to increased risk of severe disease. The committee also noted that additional evidence is needed to model age over 70 years as an independent subgroup for the mild COVID-19 setting. It said the evidence should include age-adjusted hospitalisation and mortality rates for the untreated population and relative treatment effects. The committee concluded that the McInnes report's definition of high risk included the most robust evidence of people who have a high risk for progressing to severe COVID-19, and this did not include age as an independent risk factor. 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 3.19). 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 3.18 and 3.19). 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 economic 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 3.21).

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, different definitions of 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 (including hospital-onset 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 November 2022, the policy was:

- first-line treatment: nirmatrelvir plus ritonavir (antiviral)
- second-line treatment: remdesivir (antiviral)
- third-line treatment: molnupiravir (antiviral; not for hospital-onset COVID-19)

- sotrovimab (neutralising monoclonal antibody) to be considered when the above antivirals are contraindicated or unsuitable after a multidisciplinary assessment
- combination treatment with a neutralising monoclonal antibody and an antiviral is not routinely recommended.

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).

Clinical effectiveness

Assessment group's indirect comparison approach

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

The mild COVID-19 setting included these clinical endpoints:

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

The AG highlighted some significant limitations of its approach, because of the changing nature of COVID-19 (see section 3.2). Each trial included in the analysis was done at a different time in the pandemic. 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 happened. Therefore, they would not be sensitive to changes in efficacy against new circulating variants of concern. The committee understood the limitations of the scenario analysis. The committee considered it represented an attempt to address some aspects of uncertainty in the absence of alternative methods to model the uncertainty. At draft guidance consultation, consultees highlighted the lower-efficacy scenarios were arbitrary and a probabilistic sensitivity analysis would be a better way to capture the uncertainty. The 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 low-efficacy scenario.

Observational evidence

3.13 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-19 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 which can increase risk of confounding bias. The committee noted the results of Hill and Mirchandani (2022) that 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

3.14 The committee acknowledged that most trials informing the clinical efficacy data pre-dated the Omicron variant, which was the dominant circulating variant of concern at the time of this evaluation. Clinical experts

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

- changes in population immunity through natural immunity and vaccination
- changes in the pathogenicity of the virus
- increased effectiveness of supportive care as knowledge of the virus evolved
- other differences 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 [HRs] would tend towards 1) in an endemic setting.

In vitro evidence

3.15 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 for TA878). The group developed a decision framework to link in vitro neutralisation data to clinical outcomes and helped the committee use the framework to interpret the in vitro evidence. The committee understood this framework and also noted the latest in vitro evidence.

3.16 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. One in vitro study (Imai et al. 2023) investigated the effectiveness of the antivirals against BQ.1.1 and XBB. This 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 (at the time of the second meeting). The committee also considered the in vitro evidence that was systematically collected and summarised by multiple organisations including the 'Stanford Coronavirus Resistance Database'. For further details on the in vitro evidence, see the in vitro slides in the committee papers. By using the framework and the

evidence, the committee concluded that there was no in vitro evidence showing reduced clinical efficacy of nirmatrelvir plus ritonavir across the variants tested.

Relative treatment effects

3.17 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 3.12). The committee noted the potential for bias in all the comparisons because the indirect comparison used pairwise analysis rather than a network to produce its comparisons. They also noted that multiple interventions could be required and cautioned against the side-by-side comparison of treatment effects (as a fully incremental analysis). The committee considered that the heterogeneity of trial outputs and generalisability contributed greater uncertainty to the decision problem.

- **Discussion on nirmatrelvir plus ritonavir**: 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 study (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 one 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 3.12). 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.

- 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.

- 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 3.14) 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.

- 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.

Economic model

Model structure and key drivers of cost effectiveness

3.18 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 pre-hospital setting. The AG used a decision tree model structure for treatments in the mild COVID-19 (non-hospital) setting that joined with a partitioned survival model in the severe COVID-19 (hospital) setting. The decision tree had either an active treatment or standard care arm offered to people with COVID-19. People were hospitalised at a baseline standard care rate, or not hospitalised. Those that were hospitalised entered the partitioned survival model. This section of the model had 3 mutually exclusive health states: discharged from hospital and alive, hospitalised with or without COVID-19, and death (from COVID-19 or any other cause). For people in hospital, 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 3.12). 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

3.19 The rate of hospitalisation is a key driver of model outputs (see section 3.18) 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-effectiveness 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 UK interim clinical commissioning policies (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 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 high risk of progression to severe COVID-19. Based on the strength of the evidence it concluded that it was likely to fall between the underestimate of PANORAMIC at 0.77% and the estimate of 2.82% from the DISCOVER-NOW database. The

committee concluded that the hospitalisation rate for the McInnes high-risk group is between 2.41% and 2.82% based on OpenSAFELY and DISCOVER-NOW. For people contraindicated to nirmatrelvir plus ritonavir the hospitalisation rate is assumed to be about 4% as an upper limit using advanced renal disease as proxy from OpenSAFELY.

Assessment group's analysis for partial review

3.20 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

3.21 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 18 to 69-year-olds with at least 1 pre-existing condition. The company used the baseline hospitalisation rate from PANORAMIC for people aged 70 and over and 18 to 69-year-olds 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.

3.22 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 event rates. 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

3.23 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. Also that the population is heterogeneous (see sections 3.2 and 3.3). The AG included scenarios that removed treatment effects on time to discharge and clinical

improvement at 28 days to try and account for these potential uncertainties. At the first meeting the committee considered these scenarios to be plausible but conservative if treatments had effects outside of hospitalisation and mortality. The committee was 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

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

Costs

Long COVID costs

3.25 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

3.26 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 CMDU deployment costs for the administration of oral antivirals (£410) and neutralising monoclonal antibodies (£820). Some companies disagreed with using CMDU deployment costs because these include costs based in secondary care. However, future delivery may be in primary care, which would likely reduce these costs. The NHS England representative explained that the delivery of service is subject to change. In future, integrated care boards will be responsible for treatment delivery currently done by the CMDUs. They also noted that these costs were calculated before implementation of nirmatrelvir plus ritonavir 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. 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.

3.27 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 which 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 patients that 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

3.28 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

Nirmatrelvir plus ritonavir for mild COVID-19

3.29 ICERs and net monetary benefits were calculated for nirmatrelvir plus ritonavir in the mild COVID-19 setting 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-, mean- and high-efficacy scenarios (see section 3.12). The committee noted its preferred assumptions to include combinations of the following:

- hospitalisation rates between 2.41% and 2.82%, and 4.00% for people contraindicated to nirmatrelvir plus ritonavir
- mean and low efficacy relative treatment effects (noting the limitations of the scenarios in section 3.10).

The ICERs for nirmatrelvir plus ritonavir compared with standard care using a) mean 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 are at high risk of progressing to severe COVID-19.

The committee also considered the mean- 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.

3.30 In the second committee meeting for the partial review 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 3.22) 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 3.27). The most likely ICERs were around £20,000 (using an administration cost of £117) and £30,000 (using an administration cost of £410). The committee noted that using the lower administration cost, the ICER was close to its preferred threshold of £20,000 per QALY gained. The committee to preferred to use this threshold because of the remaining uncertainties associated with the clinical data (see section 3.17) and the costs of testing (see section 3.26). The committee concluded that nirmatrelvir plus ritonavir was a cost-effective use of NHS resources in the broader population identified in the Edmunds report. It could therefore be recommended for people aged 70 years and over or with a body mass index (BMI) of 35 kg/m2 or more, diabetes or heart failure.

Other factors

Uncaptured benefits

3.31 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.

3.32 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 that 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

3.33 The committee considered potential equality issues, including:

- **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 which was initially limited to the narrower McInnes high-risk definition. The committee acknowledged that the optimised recommendation may exclude some people in certain high-risk groups who were included in the marketing authorisation (see section 3.4) and who have disability, which is a protected characteristic. As a result of the partial review, the recommendation has been broadened to include additional high-risk groups. The committee considers that there is less chance of excluding people with disabilities from this broader population.

- **Age – optimised recommendation on nirmatrelvir plus ritonavir, inclusion of age 70 years and over as an independent risk factor:** The committee was aware that age is a protected characteristic and noted that it would not normally make a recommendation based on age. Age can interact with other protected characteristics such as ethnicity and disability, meaning recommendations based on age can inadvertently make it harder for people with protected characteristics to access treatment. However, the committee considered that the chance of this would be lower because of the large range of high-risk groups specified in the recommendation. Also, because of the partial review, the recommendation is expanded to a much wider population than the original recommendation based on the McInnes report. The committee had not seen evidence of clinical and cost effectiveness of nirmatrelvir plus ritonavir in age groups under 70 years. So, the committee considered that including age 70 years and over in the recommendation was a proportionate means of achieving the legitimate aim of only committing NHS resources to cost-effective treatments.

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 (ICBs), 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. For people with an increased risk for progression to severe COVID-19, as defined in section 5 of the NICE technology appraisal guidance on casirivimab plus imdevimab, nirmatrelvir plus ritonavir, sotrovimab and tocilizumab [TA878], this is 3 months after 29 March 2023. For people who are aged 70 years and over, or who have a body mass index (BMI) of 35 kg/m^2 or more, diabetes or heart failure, the normal period of compliance has been extended to 15 months to June 2025. This is because NHS England, on behalf of

ICBs, submitted a funding variation request for this expanded population, which was accepted by NICE after a period of public consultation. NHS England's justification for the funding variation request is that ICBs will need time beyond the usual 3 month implementation period to put in place the necessary treatment pathways and ensure the necessary capacity, knowledge and expertise is in place to support equitable access for the expanded population.

4.2 During the period of the variation, (that is, within 3 months of publishing final guidance) the NHS will rollout access to treatment to the following groups if they test positive for COVID-19:

- people aged 85 years and over
- people with end-stage heart failure who have a long-term ventricular assistance device
- people on the organ transplant waiting list
- people aged 70 years and over, or who have a BMI of 35 kg/m^2 or more, diabetes or heart failure, and:
  - are resident in a care home, or
  - are already hospitalised.

4.3 NICE has recommended nirmatrelvir plus ritonavir for people aged 70 years and over, or who have a BMI of 35 kg/m^2 or more, diabetes or heart failure because it is clinically and cost effective. Having done so, NICE should be cautious about introducing any delay in patients gaining access to treatments from which they may benefit. However, it should also avoid placing the NHS in a position of confronting substantial demand from patients for access to care which it has told NICE it cannot provide. To do so would risk sub-optimal treatment decisions and may subject the current NHS services to undue stress.

4.4 The responsibility for securing care for the NHS in England rests with NHS England and ICBs. NICE should be cautious and sure of its judgement before requiring NHS England and ICBs to provide services

that they do not consider that they can provide, or provide safely and efficiently. In effect, NICE would have to conclude that NHS England and ICBs were mistaken. NHS England has indicated that not all ICBs have in place the arrangements that it considers necessary to provide nirmatrelvir plus ritonavir, to the full extent recommended in this guidance, within 3 months. This is based on a consultation will ICBs and regional Senior Responsible Officers for COVID-19 treatments. Although the company has identified that some ICBs would be ready to implement the recommendation, NHS England, in setting out what it believes other ICBs need to do to put the necessary arrangements in place, has credibility. NICE needs to be wary of substituting its judgement for NHS England's in this respect.

4.5 NICE put to NHS England the question raised in consultation of whether ICBs that did consider they could implement the full recommendations sooner than the end of the funding variation period would be able to do so. NHS England responded that it did not consider that an approach during the variation, which sees some areas providing access sooner than others, is equitable or practicable. Such an approach would mean access was based on where someone lives. This could lead to confusion for patients and clinicians and would likely lead to an avoidable increase in pressure on services. In addition, access to testing would not be available. In the short term, NHS England is extending the arrangements already in place for the highest risk cohort, but will need to introduce new models to allow access for the full population. This will take the time requested in the funding variation and cannot be done in a phased way. NICE accepts these explanations.

4.6 NHS England provided an equality impact assessment which noted that the funding variation request could impact some groups. However, NHS England considers that the proposal to continue to provide access to nirmatrelvir plus ritonavir to treat mild COVID-19 in the highest risk groups

and to expand access to people aged over 85 years, people in care homes and hospital inpatients is a proportionate means of:

- protecting those at highest risk of severe COVID-19 outcomes and patients with protected characteristics who require primary care services for other health conditions. It is known from previous COVID-19 waves that risk of hospitalisation and death are closely associated with age.
- achieving the legitimate aim of maximising public health in the context of the availability of vaccination for the patients covered by this recommendation and of other COVID-19 treatments for hospital inpatients.
- ensuring access is provided in an equitable way across the whole NHS and not determined either by where someone lives or their ability to pay for a COVID-19 test.
- supporting the NHS to prepare for the implementation of NICE guidance in full as required by the legal funding requirement.

4.7 NICE fully understands the concerns put forward by consultees who object to the proposed extension to the funding period. Any additional delay in accessing recommended treatments is, undesirable. However, NHS England's request on behalf of ICBs reflects a real concern that the current arrangements expose existing services and other services to substantial risks from overwhelming demand.

4.8 An extension of the funding period is therefore granted under section 7(5) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013.

4.9 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. For people who are aged 70 years and over, or who have a BMI of 35 kg/m^2 or more, diabetes or heart failure, the normal period of compliance has been extended to 15 months to June 2025. This is for the reasons explained in section 4.1.

4.10 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 is the right treatment, it should be available for use, in line with NICE's recommendations.

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

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal evaluation committees are standing advisory committees of NICE. This topic was considered 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 and Anna Brett
Technical advisers

Louise Jafferally
Project manager

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