NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Proposed Multiple Technology Appraisal

Therapeutics for people with COVID-19

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of remdesivir, tocilizumab, casirivimab and imdevimab, baricitinib, sotrovimab, molnupiravir, anakinra, lenzilumab and PF-07321332 and ritonavir within their proposed marketing authorisations for treating people with coronavirus disease 2019 (COVID-19).

Background

COVID-19 is predominantly an acute respiratory illness caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It varies widely in clinical severity. Symptoms can range from asymptomatic infection to severe pneumonia and respiratory failure with the need for mechanical ventilation. People who become critically ill may develop acute respiratory distress syndrome (ARDS), the leading cause of mortality among patients with COVID-19.

The COVID-19 pandemic rapidly evolved globally, with countries facing different stages of the spread of disease. In England and Wales between 1 March 2020 and 26 November 2021 153,179 deaths occurred involved COVID-19.[1] Data from the UK suggest that mortality due to COVID-19 is strongly associated with older age, male gender, deprivation and Black, Asian and minority ethnic family background.[2] Disabled people and people with a learning disability have a higher risk of dying from COVID-19.[3,4] People with pre-existing conditions, including people with dementia and Alzheimer's disease, diabetes, heart disease or obesity, are also more at risk from dying from COVID-19.[3] However, children and young people appear to be less affected by the virus, with low numbers of death in this age group.[5]

COVID-19 has a diverse range of clinical manifestations, ranging from mild infection to severe disease accompanied by high mortality.[6] It begins with infection, or the viral replication phase, with symptoms such as cough, fever and breathlessness. This disease stage is when viral shedding occurs and people are at the peak of infectiousness. At this stage anti-viral treatments may be the most beneficial because they inhibit viral replication. If the disease is not adequately controlled, excessive immune response can lead to more severe complications. This is part of the inflammatory phase of the disease, with symptoms that include ARDS, other organ failure and exacerbation of co-morbid conditions. At this stage, anti-inflammatory treatments are used to reduce inflammation in order to avoid these hyperinflammatory complications. Antibody treatments may also be used throughout the disease course to limit the potential for severe disease. Post-COVID-19 syndrome (also known as long COVID) also has a significant burden from some people, including longer-term effects on breathing, pain and variations in heart rate. It is defined as any signs or symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.

Currently, established clinical management for most people in hospital with COVID-19 is an appropriate level of respiratory support which may range from oxygen delivered by face mask or nasal canula to invasive mechanical ventilation and organ support. NICE's rapid guideline on managing COVID-19 recommends corticosteroids, including dexamethasone, or either hydrocortisone or prednisolone if dexamethasone cannot be used or is unsuitable, for people with COVID-19 who need supplemental oxygen.

The COVID-19 rapid guideline also recommends the following therapeutics for treating COVID-19 for people in hospital. Remdesivir is recommended for people who need low-flow supplemental oxygen. Tocilizumab and sarilumab are recommended for people that have completed a course of corticosteroids and need supplemental oxygen. However, sarilumab does not have a marketing authorisation and use of this treatment is off-label. A combination of casirivimab and imdevimab is recommended for people who have no detectable COVID-19 antibodies.

NHS England has an Interim Clinical Commissioning Policy on neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. This recommends sotrovimab for people with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID-19 infection. If sotrovimab is contraindicated or it is not possible to administer it, molnupiravir is recommended instead.

The technologies

Remdesivir (Veklury, Gilead) is a viral RNA polymerase inhibitor that interferes with the production of RNA, stopping the virus from multiplying inside cells. It is administered intravenously. Remdesivir has a conditional marketing authorisation for treating COVID-19 in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen.

Tocilizumab (Actemra, Roche) is a monoclonal antibody (MAb). MAbs are synthetic proteins that have been designed to recognise and attach to structures, specifically antigens. Tocilizumab attaches to the receptor for a messenger molecule, or 'cytokine', called interleukin-6. By preventing interleukin-6 attaching to receptors, tocilizumab reduces inflammation. It can be administered by subcutaneous injection or intravenously. Tocilizumab does not currently have a marketing authorisation in the UK for treating people with COVID-19. It has been recommended to be available as a treatment option through an interim clinical commissioning policy, for adult patients (aged 18 years and older) hospitalised with COVID-19.

Casirivimab and imdevimab (Ronapreve, Regeneron and Roche) are MAbs, used in combination. Casirivimab and imdevimab attach to the spike protein of the virus which causes COVID-19, limiting it from entering the body's cells. Casirivimab and imdevimab can be administered intravenously, together. Or they can be administered consecutively by subcutaneous injection. Casirivimab and imdevimab has a conditional marketing authorisation in the UK for the treatment of acute COVID-19 infection.

Baricitinib (Olumiant, Eli and Lilly) is an immunosuppressant. It works by blocking the action of enzymes known as Janus kinases. By blocking the actions of the enzymes it reduces joint and skin inflammation. It is administered orally. Baricitinib does not currently have a marketing authorisation in the UK for treating people with COVID-19 who have been hospitalised or in the community setting. It has been studied in clinical trials, alone, in people with COVID-19. It has been studied in clinical trials in

combination with remdesivir in people aged 18 years and older, hospitalised with COVID-19.

Sotrovimab (Xevudy, GlaxoSmithKline and Vir Biotechnology) is a MAb designed to attach to the spike protein of the virus which causes COVID-19, limiting it from entering the body's cells. It is administered intravenously. Sotrovimab has a conditional marketing authorisation in the UK for the treatment of symptomatic adults and adolescents (aged 12 years and over and weighing at least 40 kg) with acute COVID-19 infection who do not require oxygen supplementation and who are at increased risk of progressing to severe COVID infection.

Molnupiravir (Lagevrio, Ridgeback Biotherapeutics and Merck Sharp & Dohme) is an antiviral medication that interferes with the virus' replication, preventing it from multiplying, keeping virus levels low in the body and reducing the severity of the disease. It is administered orally. Molnupiravir has a conditional marketing authorisation in the UK for the treatment of mild to moderate COVID-19 in adults with a positive SARS-COV-2 diagnostic test and who have at least one risk factor for developing severe illness.

Anakinra (Kineret, Swedish Orphan Biovitrum) is an immunosuppressant. It is a copy of the natural human protein called 'human interleukin 1 receptor antagonist' that blocks the receptors for a chemical messenger in the body called interleukin 1. By attaching to the receptor that interleukin 1 would attach to, anakinra blocks the activity of interleukin 1, reducing symptoms of disease. It is administered by subcutaneous injection. Anakinra does not currently have a marketing authorisation in the UK for treating people with COVID-19. It has been studied in clinical trials, alone, in people hospitalised with COVID-19.

Lenzilumab (brand name unknown, Humanigen) is a MAb that targets and neutralises granulocyte-macrophage colony stimulating factor (GM-CSF). GM-CSF is an initiator in the systemic inflammatory pathway. It is administered intravenously. Lenzilumab does not currently have a marketing authorisation in the UK for treating people with COVID-19 who have been hospitalised or in the community setting. It has been given expediated consideration by the MHRA. It has been studied in a clinical trial, alone, in people aged 18 years and older, hospitalised with COVID-19.

PF-07321332 and ritonavir (Paxlovid, Pfizer) is an antiviral medication that interferes with the virus' replication. PF-07321332 blocks the activity of an enzyme needed by the virus to multiply, keeping virus levels low in the body and reducing the severity of the disease. Ritonavir is a protease inhibitor which slows the breakdown of PF-07321332, enabling it to remain in the body at levels that affect the virus for longer. PF-07321332 and ritonavir are administered orally, consecutively. PF-07321332 and ritonavir has a conditional marketing authorisation in the UK for treating adults with mild to moderate COVID-19, who are at high risk for progression to severe COVID-19.

Interventions	Remdesivir, tocilizumab, casirivimab and imdevimab, baricitinib, sotrovimab, molnupiravir, anakinra, lenzilumab and PF-07321332 and ritonavir

Populations	• People with COVID-19 who have not been hospitalised • People with COVID-19 who have been hospitalised.
Comparators	For people who have not been hospitalised: • Established clinical management For people who have been hospitalised: • Established clinical management with or without corticosteroids and appropriate respiratory support
Outcomes	The outcome measures to be considered include: • mortality • requirement for respiratory support • time to recovery • length of hospitalisation • time to return to normal activities • virological outcomes (viral shedding and viral load) • symptoms of post-COVID-19 syndrome • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	Related Guidelines: 'COVID-19 rapid guideline: Managing COVID-19' (2021).

	NICE guideline 191. Evidence summary 'COVID-19 rapid evidence summary: acute use of non-steroidal anti-inflammatory drugs (NSAIDs) for people with or at risk of COVID-19' (2020). NICE evidence summary 23. 'COVID-19 rapid evidence summary: angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) in people with or at risk of COVID-19' (2020). NICE evidence summary 24 'COVID-19 rapid evidence summary: Long-term use of non-steroidal anti-inflammatory drugs (NSAIDs) for people with or at risk of COVID-19' (2020). NICE evidence summary 25 'COVID 19 rapid evidence summary: Anakinra for COVID-19 associated secondary haemophagocytic lymphohistiocytosis' (2020). NICE evidence summary 26
Related National Policy	NHS England (2020) COVID-19 Clinical/medical management NHS England (2021) Interim Clinical Commissioning Policy: Neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19 NHS England (2021) Interim Clinical Commissioning Policy: Casirivimab and imdevimab for patients hospitalised due to COVID-19 NHS England (2021) Interim Clinical Commissioning Policy: Tocilizumab for hospitalised patients with COVID-19 pneumonia (adults) NHS England (2021) Interim Clinical Commissioning Policy: Sarilumab for critically ill patients with COVID-19 pneumonia (adults) NHS England (2020) COVID-19 therapy: corticosteroids including dexamethasone and hydrocortisone NHS England (2021) Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older) NHS England (2020) Acute use of non-steroidal anti-inflammatory drugs (NSAIDs) in people with or at risk of COVID-19 NHS England (2021) Rapid Clinical Policy development: COVID-19 The NHS Long Term Plan, 2019. NHS Long Term Plan

	NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health and Social Care, NHS Outcomes Framework 2016-2017: Domains 1,3. https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017

Questions for consultation

How many people who need supplemental oxygen progress to severe COVID-19?

Have all relevant interventions for these settings been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for treating people hospitalised with COVID-19?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom these technologies are expected to be more clinically effective and cost effective or other groups that should be examined separately?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatments are and will be licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider that the use of any of the technologies could result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculations? Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Multiple Technology Appraisal (MTA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction)

References

1. Office for National Statistics (2021) Deaths registered weekly in England and Wales, provisional. Accessed December 2021.

2. Government Actuary's Department (2020) Mortality Insights from GAD - December 2020. Accessed December 2021.

3. The King's Fund (2021) Deaths from Covid-19 (coronavirus). Accessed December 2021.

4. Public Health England (2020) Deaths of people identified as having learning disabilities with COVID-19 in England in the spring of 2020. Accessed December 2021.

5. Smith C, Odd D, Harwood R et al. (2021) Deaths in children and young people in England after SARS-CoV-2 infection during the first pandemic year. Nature Medicine.

6. Cevik M, Kuppalli K, Kindrachuk J et al. (2020) Virology, transmission, and pathogenesis of SARS-CoV-2. The BMJ.