NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Therapeutics for people with COVID-19

Pre-invite scope

Remit/appraisal objective

To appraise the clinical and cost effectiveness of remdesivir, tocilizumab, casirivimab and imdevimab, baricitinib, sotrovimab, molnupiravir, anakinra, lenzilumab and nirmatrelvir 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). The disease refers to any symptom resulting from the infection and these can vary widely in clinical severity. 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 involving COVID-19.[1] The gradual mutation of SARS-CoV-2 has led to various variants of concern, each with different transmissibility, morbidity, and mortality effects. 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]

COVID-19 has a diverse range of clinical manifestations, ranging from mild infection to severe disease accompanied by high mortality.[5] 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 and neutralising monoclonal antibodies (mABs) are expected to be more beneficial because they inhibit viral replication, which may reduce severity of symptoms. 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 and immunomodulatory mAbs, which target responses to the inflammatory pathway, may be more beneficial to reduce inflammation and avoid these hyperinflammatory complications. Anti-viral treatments can also be useful during the inflammatory stage of the disease, to reduce ongoing viral replication. Post-COVID-19 syndrome (also known as long COVID) also has a significant burden for 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.

The COVID-19 rapid guideline for people who are not in hospital but are thought to be at high-risk of progression to severe COVID-19 is a neutralising mAb, including sotrovimab and casirivimab plus imdevimab. NHS England also has an Interim Clinical Commissioning Policy on neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19. This recommends nirmatrelvir plus ritonavir or 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 nirmatrelvir plus ritonavir is contraindicated or if it is not possible to administer it, and clinical judgment deems an antiviral is the preferred option remdesivir is recommended. If nirmatrelvir plus ritonavir, sotrovimab and remdesivir are contraindicated or it is not possible to administer it, molnupiravir is recommended instead.

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 antivirals or neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients. This separates treatments for people hospitalised for COVID-19 and treatments for people with hospital-onset COVID-19.

The technologies

Remdesivir (Veklury, Gilead) is a viral RNA polymerase inhibitor. It is administered intravenously. Remdesivir has a conditional marketing authorisation in the UK 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. It also has a conditional marketing authorisation in the UK for treating COVID-19 in adults with pneumonia not requiring supplemental oxygen.

Tocilizumab (Actemra, Roche) is a mAb. It can be administered by subcutaneous injection or intravenously. Tocilizumab has a marketing authorisation in the UK for treating COVID-19 in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation.

Casirivimab and imdevimab (Ronapreve, Regeneron and Roche) are mAbs, used in combination. Casirivimab and imdevimab can be administered intravenously, together. Or they can be administered consecutively by subcutaneous injection. Casirivimab and imdevimab has a marketing authorisation in the UK for the treatment of acute COVID-19 infection.

Baricitinib (Olumiant, Eli and Lilly) is an immunomodulator. Baricitinib 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 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. 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. It is administered orally. Molnupiravir has a 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 administered by subcutaneous injection. Anakinra does not currently have a marketing authorisation in the UK for treating people with symptomatic COVID-19. It has been studied in clinical trials in combination with standard of care, 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). It is administered intravenously. Lenzilumab does not currently have a marketing authorisation in the UK for treating people with COVID-19. 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.

Nirmatrelvir and ritonavir (Paxlovid, Pfizer) is an antiviral medication. Ritonavir is a protease inhibitor. Nirmatrelvir and ritonavir are administered orally, consecutively. Nirmatrelvir and ritonavir has a conditional marketing authorisation in the UK for treating COVID-19 in adults who do not require supplemental oxygen and who are increased risk for progression to severe COVID-19.

Interventions	Remdesivir, tocilizumab, casirivimab and imdevimab, baricitinib, sotrovimab, molnupiravir, anakinra, lenzilumab and nirmatrelvir and ritonavir
Populations	• People with mild COVID-19 at high risk of progressing to severe COVID-19 • People with severe COVID-19
Comparators	• Established clinical management with or without corticosteroids and appropriate respiratory support • The interventions will be compared to each other

Outcomes	The outcome measures to be considered include: • mortality • requirement for respiratory support • time to recovery • hospitalisation (requirement and duration) • 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. The impact of vaccination status or SARS-CoV-2 seropositivity on the clinical evidence base of each intervention, generalisability to clinical practice and interaction with other risk factors will be considered in the context of the appraisal. The impact of different variants of concern of COVID-19 on the clinical evidence base of each intervention will be considered in the context of the appraisal.
Related NICE recommendations	Related Guidelines: 'COVID-19 rapid guideline: managing COVID-19' (2021). NICE guideline 191. 'COVID -19 rapid guideline: managing the long-term effects of

	COVID-19' (2022). NICE guideline 188. 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 (2022) UK Interim Clinical Commissioning Policy: Therapies for symptomatic non-hospitalised patients with COVID-19 NHS England (2022) UK Interim Clinical Commissioning Policy. Therapies for patients with symptomatic hospital-onset COVID-19 NHS England (2022) Interim Clinical Commissioning Policy: Remdesivir for patients hospitalised due to COVID-19 (adults and adolescents 12 years and older) NHS England (2022) Interim Clinical Commissioning Policy: neutralising monoclonal antibodies or antivirals for non-hospitalised patients with COVID-19 NHS England (2022) Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of hospital-onset COVID-19 NHS England (2022) Interim Clinical Commissioning Policy: Antivirals or neutralising monoclonal antibodies in the treatment of COVID-19 in hospitalised patients NHS England (2021) Interim Clinical Commissioning Policy: IL-6 inhibitors (tocilizumab or sarilumab) for hospitalised patients with COVID-19 (adults) NHS England (2020) COVID-19 therapy: corticosteroids including dexamethasone and hydrocortisone 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)

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