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Rapid Policy Statement

Interim Clinical Commissioning Policy: remdesivir and molnupiravir for non-hospitalised patients with COVID-19

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Commissioning position

This interim policy applies in England from the date of publication until the date on which the appeals lodged against NICE's draft MTA recommendations for molnupiravir and remdesivir are determined. Access to these medicines will then be subject to the outcome of the appeal process.

The National Institute for Health and Care Excellence (NICE) Multiple Technology Appraisal (MTA) guidance on therapeutics for people with COVID-19 [TA878] recommends nirmatrelvir plus ritonavir (Paxlovid) or sotrovimab as treatment options for patients with COVID-19 who do not need supplemental oxygen and have an increased risk for progression to severe COVID-19.

Appeals are underway against NICE's draft MTA recommendations for remdesivir and molnupiravir. This policy therefore aims to provide clarity on access to remdesivir and molnupiravir for the period during which the appeal process is being conducted. Access should be guided both by this policy and the published NICE COVID-19 rapid guideline until the outcomes of the appeals are determined.

This policy specifically outlines the treatment options for remdesivir and molnupiravir in non-hospitalised adults and children aged 12 years and older with COVID-19 who are symptomatic and showing no evidence of clinical recovery in accordance with the criteria set out in this document. The options are:

- First-line**:** nirmatrelvir plus ritonavir (as per the published NICE MTA)
- Second-line: sotrovimab (as per the published NICE MTA)
- Third-line: remdesivir[1] (where supply is available)
- Fourth-line: molnupiravir

Combination treatment with an antiviral and a neutralising monoclonal antibody (nMAB) is **NOT** routinely recommended.

Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

[1] For remdesivir use in patients with hospital-onset COVID-19 please refer to the legacy hospital-onset policy: Coronavirus » Interim Clinical Commissioning Policy: Treatments for hospital-onset COVID-19 (england.nhs.uk)

Remdesivir

Evidence

A three-day intravenous course of remdesivir within 7 days of COVID-19 symptom onset for non-hospitalised patients with risk factors for disease progression, resulted in a relative risk reduction of 87% in hospitalisation or death at day 28 (Gottlieb et al, 2021). The WHO has made a conditional recommendation for remdesivir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).

The draft NICE MTA [TA878] provides a negative recommendation for remdesivir. An appeal has been commenced and final recommendations are expected to be published later in 2023, once the appeal process has been concluded.

Marketing authorisation

Remdesivir delivered intravenously has been granted a conditional marketing authorisation in Great Britain (England, Scotland and Wales; under the Medicines and Healthcare Products Regulatory Authority (MHRA) and a full marketing authorisation in Northern Ireland (under the European Medicines Agency (EMA)) for the following indications:

- treatment of COVID-19 in adults and paediatric patients (weighing at least 40 kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19 within 7 days of symptom onset, for a treatment duration of 3 days.
- treatment of COVID-19 in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen (low- or high- flow oxygen or other non-invasive ventilation at start of treatment), for a treatment duration of 5-10 days.

Molnupiravir

Evidence

Final results from the Phase 3 MOVe-OUT trial show that the oral antiviral molnupiravir administered within 5 days of COVID-19 symptom onset to high-risk, non-hospitalised patients resulted in a relative risk reduction of 30% in the composite primary outcome of hospitalisation or death at day 29 (Bernal et al, 2021). The WHO has made a conditional recommendation for molnupiravir for patients with non-severe COVID-19 at highest risk of hospitalisation (WHO, September 2022).

The draft NICE MTA [TA878] provides a negative recommendation for molnupiravir. An appeal has been commenced and final recommendations are expected to be published later in 2023, once the appeal process has been concluded.

Marketing authorisation

Molnupiravir administered orally has been granted a marketing authorisation in Great Britain (England, Scotland and Wales) for use in the treatment of mild to moderate COVID-19 in adults (aged 18 years and over) with a positive SARS-CoV-2 diagnostic test and who have at least one risk factor for developing severe illness. Access to molnupiravir in Northern Ireland for this indication is through a Regulation 174 approval.

Eligibility criteria

Treatments subject to positive recommendations (paxlovid, sotrovimab) in the published NICE MTA should be followed.

Where these medicines are contraindicated or otherwise clinically unsuitable for an individual, the following treatment choices may be considered.

Non-hospitalised patients are eligible for treatment with remdesivir or molnupiravir if the following

initial criteria are met:

- SARS-CoV-2 infection is confirmed by either:
    - Lateral flow test (registered via gov.uk or NHS 119) OR
    - Polymerase chain reaction (PCR) testing

AND

- Symptomatic with COVID-19 and showing no signs of clinical recovery

AND

- The patient is a member of a 'highest' risk group (as defined in the updated Department of Health and Social Care commissioned Independent Advisory Group Report)

Combination treatment with an antiviral and nMAB is **NOT** routinely recommended.

Patients who have previously received treatment with an antiviral or nMAB, and who have been considered for treatments subject to positive recommendations in the published NICE MTA, may receive treatment under this policy for a subsequent (new) infective episode, if clinically appropriate.

Remdesivir may be used in all children weighing over 40kg, in patients with no supplemental oxygen requirement.

For paediatric/adolescent patients, paediatric multi-disciplinary team (MDT) assessment should be used to determine clinical capacity to benefit from a treatment. Additional criteria can be found in the Department of Health and Social Care commissioned Independent Advisory Group Report

Where patients are ineligible for treatment under this policy, recruitment to the PANORAMIC trial, which is building the evidence for novel oral antivirals in a broader cohort of at risk patients, should be supported.

Exclusion criteria

- Patients would not be eligible for treatment if any of the following apply: new supplemental oxygen requirement specifically for the management of COVID-19 symptoms
- Known hypersensitivity reaction to the active substances or to any of the excipients of the medications below as listed in their respective Summary of Product Characteristics.

Remdesivir

If the initial criteria above are met, patients may be considered for treatment with **remdesivir**, where available, if:

- Treatment with nirmatrelvir/ritonavir, and sotrovimab, are both

contraindicated or not clinically suitable AND

- Treatment is commenced within 7 days of symptom onset.

The following additional **exclusion criteria** apply if considering treatment with remdesivir:

- Children weighing less than 40kg
- Estimated glomerular filtration rate (eGFR) <30 mL/min (except in patients with end-stage renal disease on haemodialysis)
- Alanine transaminase (ALT) ≥ 5 times the upper limit of normal.

Remdesivir should be discontinued in patients who develop **any** of the following:

- ALT ≥ 5 times the upper limit of normal during treatment with remdesivir (remdesivir may be restarted when ALT is < 5 times the upper limit of normal)
- ALT elevation accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or international normalised ratio (INR).

An individual clinical decision should be made as to whether pre-treatment urea and electrolytes and liver function tests are required based upon whether recent bloods are available or the patient is considered at risk of undiagnosed liver or kidney disease.

If the patient experiences clinical deterioration such that hospitalisation and low-flow supplemental oxygen is required, the patient may be considered for treatment with a 5-day course of remdesivir as outlined in the UK Clinical Commissioning Policy for remdesivir in patients hospitalised due to COVID-19.

Molnupiravir

If the initial criteria above are met, patients should only be considered for treatment with molnupiravir if:

- Treatment with nirmatrelvir/ritonavir or sotrovimab are contraindicated or not clinically suitable.

AND

- Treatment with remdesivir is contraindicated, not clinically suitable or not available.

AND

- Treatment is commenced within 5 days of symptom onset[1].

The following additional **exclusion criteria** applies if considering treatment with molnupiravir:

- Children aged less than 18 years
- Pregnancy.

Dose and administration

Remdesivir

The recommended dose of remdesivir for this cohort is 200mg intravenously on day 1 followed by 100mg intravenously on days 2 and 3. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 7 days of symptom onset.

200mg of remdesivir (day 1 loading dose) and 100mg of remdesivir (days 2 and 3 maintenance doses) should be diluted in either a 250ml or 100ml pre-filled bag of 0.9% sodium chloride solution and infused over a minimum of 30 minutes.

Molnupiravir

The recommended dose of molnupiravir is 800mg (four 200mg capsules) taken orally every 12 hours for 5 days. Treatment must not be extended beyond 5 days. Molnupiravir should be commenced as soon as possible after a diagnosis of COVID-19 has been made and within 5 days of symptom onset[1]. Clinicians should assure themselves that patients are able to swallow the oral capsules.

To reduce the possibility of emerging resistance, patients should be advised to complete the whole course of treatment even if their symptoms improve and/or they feel better. If a patient requires hospitalisation due to severe or critical COVID-19 after starting treatment with molnupiravir, the patient should complete the full 5-day treatment course at the discretion of his/her healthcare provider.

Cautions

Please refer to the Summary of Product Characteristics (SmPC) for remdesivir (Great Britain and

Northern Ireland) and molnupiravir for special warnings and precautions for use.

Remdesivir

Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed during and following administration of remdesivir. Signs and symptoms may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnoea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, and shivering. Slower infusion rates, with a maximum infusion time of up to 120 minutes, can be considered to potentially prevent these signs and symptoms. Patients should be monitored for hypersensitivity reactions during and following administration of remdesivir as clinically appropriate. If signs and symptoms of a clinically significant hypersensitivity reaction occur, administration of remdesivir should be discontinued immediately and appropriate treatment initiated.

Patients receiving remdesivir in an outpatient setting should be monitored according to local medical practice.

Molnupiravir

The most common adverse reactions (≥1% of subjects) reported during treatment and during 14 days after the last dose of molnupiravir were diarrhoea (3%), nausea (2%), dizziness (1%) and headache (1%) all of which were Grade 1 (mild) or Grade 2 (moderate).

Pregnancy and women of childbearing potential

Clinicians should refer to the SmPCs for the relevant products for further information on use in pregnancy and women of childbearing potential. All healthcare professionals are asked to ensure that any patients who receive a COVID antiviral while pregnant are reported to the UK COVID-19 antivirals in pregnancy registry on 0344 892 0909 (available 9:00am to 5:00pm, Monday to Friday, excluding bank holidays) so that they can be followed up. For more information, go to https://www.medicinesinpregnancy.org/COVID-19-Antivirals-Pregnancy-Registry/. Clinicians are advised to refer to the SmPC nirmatrelvir/ritonavir and molnupiravir for more information on use during pregnancy or lactation.

Remdesivir

There are no or limited amount of data from the use of remdesivir in pregnant women. Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual (please see SmPC for further information).

Molnupiravir

There are no data from the use of molnupiravir in pregnant women. Studies in animals have shown reproductive toxicity. Molnupiravir is **not recommended** during pregnancy. Individuals of childbearing potential should use effective contraception for the duration of treatment and for 4 days after the last dose of molnupiravir.

Co-administration

There is no interaction expected between remdesivir or molnupiravir and other commissioned treatments for COVID-19. For further information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Safety reporting

It is vital that any suspected adverse reactions (including congenital malformations and/or neurodevelopmental problems following treatment during pregnancy) are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/.

Governance

Data collection requirement

Provider organisations in England should register all patients using prior approval software (Blueteq) and ensure monitoring arrangements are in place to demonstrate compliance against the criteria as outlined.

Effective from

This policy will be in effect from the 11 May 2023.

Policy review date

This is an interim rapid clinical policy statement, which means that the full process of policy production has been abridged: public consultation has not been undertaken. A National Institute for Health and Care Excellence (NICE) Technology Appraisal or Scottish Medicines Consortium (SMC) Health Technology Assessment or All Wales Medicines Strategy Group (AWMSG) appraisal of antivirals and/or nMABs for COVID-19 would supersede this policy. Access to the medicines covered by this policy will subsequently be determined subject to the outcome of the appeal process.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the four nations' values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus
Neutralising monoclonal antibody	Synthetic antibodies that bind to a virus and inhibit its ability to infect host cells and replicate
Spike protein	The part of the SARS-CoV-2 virus that binds to the host cell, which then facilitates its entry into the cell

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