COVID-19 Therapeutic Alert

CEM/CMO/2020/025

Issue date: 26 May 2020

Early Access to Medicines Scheme for remdesivir in the treatment of COVID-19. Implementation of the scheme and management of supply.

Summary

A positive Scientific Opinion for remdesivir in the treatment of COVID-19 has been published by the Medicines and Healthcare Products Regulatory products Agency (MHRA) https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions. It advises on the conditions where the technology will be used and commissioned by the NHS.

Hospitals who have registered an interest in participating in COVID-19 Early Access to Medicines Scheme (EAMS) should use the country specific EAMS application process to apply for access to remdesivir for eligible patients.

The MHRA Early Access to Medicines Scheme (EAMS) aims to give patients with life-threatening or seriously debilitating conditions access to medicines that do not yet have a marketing authorisation when there is a clear unmet medical need. The MHRA will give a scientific opinion on the benefit/risk balance of the medicine, based on the data available; this opinion does not replace the normal licensing procedures for medicines but supports the prescriber and patient to make a decision on whether to use the medicine before its licence is approved. It will also enable companies to gain additional knowledge and experience of these medicines in clinical use in a real world setting. (More information about the scheme can be found here: https://www.gov.uk/apply-for-the-early-access-to-medicines-scheme-eams)

There are two parts to the scheme. Step 1 is to designate a product with a “promising innovative medicine” (PIM) designation. This gives an indication that a product may be eligible for the Early Access to Medicines Scheme (based on early clinical data). In Step 2 the MHRA issues a scientific benefit/risk opinion, following the assessment of quality, safety and efficacy data. This describes the benefits and risks of the medicine, based on the information submitted to MHRA by an applicant after sufficient data have been gathered from clinical trials and other studies. The EAMS scientific opinion assessment report and EAMS treatment protocols can be found on the website above.

Further to the designation of Promising Innovative Medicine (PIM) status for remdesivir on 19 May 2020 (EAMS Step 1), MHRA issued a positive Scientific Opinion on 26 May 2020 which supports remdesivir for the following:

- Remdesivir is indicated for the treatment of adults and adolescent patients aged ≥ 12 years and weighing at least 40 kg hospitalised with suspected or laboratory confirmed SARS-CoV-2 infection and severe disease.
- Patients with severe disease are those with an $SpO_2 \leq 94\%$ on room air or requiring supplemental oxygen, or requiring non-invasive or invasive ventilation or extracorporeal membrane oxygenation (ECMO).

Note that due to supply constraints further access criteria are listed below (see: Interim Access Criteria).

Medicine supply

Remdesivir is supplied to the UK by Gilead. The medicine comes in two forms:

- Remdesivir 100 mg concentrate for solution for infusion (each vial contains 100 mg of remdesivir, each mL of concentrate contains 5 mg of remdesivir).
- Remdesivir 100 mg powder for concentrate for solution for infusion (each vial contains 100 mg of remdesivir, after reconstitution, each vial contains 5 mg/mL of remdesivir solution).

The supply to the UK will be determined by Gilead on a weekly basis informing the RAPID-C19-Delivery team in the NHS. It is expected that the supply will not initially be sufficient for all patients meeting the MHRA scientific opinion. Distribution of supply to the 4 nations will follow the Barnet Formula. Allocation of supply will follow country specific procedures, see below.

Remdesivir is made available free of charge for EAMS patients during the EAMS period with associated activity costs covered by the appropriate commissioner. Patients must be informed that remdesivir is being made available ahead of a Marketing Authorisation decision through EAMS.

To support the clinical decision making of which patients should access the limited supply a set of access criteria has been defined based upon the best available evidence and from expert clinical advice. It is expected that these criteria will be amended as further evidence is made available and as experience increases in using the medicine.

The supply allocation to individual NHS hospitals in each country will be determined each week by the respective NHS national body. Once this information has been provided to Gilead, with the name and contact details for the COVID-19 clinical lead and COVID pharmacy lead, the Gilead medical department will make contact to arrange an EAMS initiation teleconference. During this teleconference the process and documentation for the EAMS will be explained to ensure local clinical staff are aware of the requirements of the programme and key safety information.

In parallel with the EAMS onboarding process, each hospital should raise an open Purchase Order with the title “Remdesivir EAMS” clearly marked to ukcustomer.services@gilead.com (or fax: 01223 897291). To assist with the delivery of the product under controlled cold chain storage conditions, you must include:

- Contact Name/Alternative contact
- Contact Number(s)
- Confirmed delivery address

Interim access criteria

The patients most likely to benefit from remdesivir are those patients at the early stage of a COVID-19 infection who have a high probability of developing severe disease putting their lives at risk. To support clinicians to identify patients the following access criteria should be used. As the demand vs supply improves these criteria will be reviewed on a weekly basis and take into account any further emerging evidence and if amended circulated to Trusts by the pharmacy network to inform staff.

There are ethical considerations to the prioritisation involved in setting clinical criteria in the context of a scarce resource (such as with the limited supply of remdesivir), and due to the emergency context and time constraints it has not been possible to attend to these comprehensively. Such ethical considerations in resource prioritisation would normally include:

ensuring the process is as transparent, inclusive, and openly available for comment; and discussing the ethical criteria behind the clinical criteria and the relative merits of each. Planned regular review of the clinical criteria provides an opportunity to develop these criteria further.

EAMS criteria

These criteria are defined within the EAMS:

- Age 12 years or older on the date of starting treatment
- Weight ≥40kg on the date of starting treatment
- Creatinine clearance above 50ml/min (upper level defined)
- AST/ALT below 5 times upper limit of normal and no history of chronic liver disease defined as Childs Pugh C

Risk Score

Access will follow the TACTIC trial protocol methodology (link), a risk count identifies patients admitted with a diagnosis of COVID19, who are at increased risk of developing severe COVID19-related disease. A risk count is calculated by summing (i.e. patients receive 1 point for) each of the following features on admission:

- Radiographic severity score >3
- Male gender
- Non-white ethnicity
- Diabetes
- Hypertension
- Neutrophils >8.0 10 /L
- Age >40 years
- CRP >40 mg/L

For access a severity of 4 or higher is required or 3 if the radiographic severity score threshold is reached. EAMS registered hospitals will receive information on the application of the scoring.

Diagnostic criteria

- Less than 10 days from onset of symptoms
- Hospitalised with SARS2-CoV infection confirmed by PCR collected in preceding 72 hours

Illness severity and organ support criteria

- Discussion about the eligibility for escalation to critical care including invasive mechanical ventilation, multi-organ support and CPR should be considered through shared decision making in line with the NICE guidance NG159 (link). Some patients not eligible for escalation may be suitable for access to remdesivir as determined by mutildisciplinary assessment.
- Patient who require FiO_2 ≥ 0.4% to maintain O_2 sats >94% with standard oxygen therapy (Hudson mask) measured on 2 occasions at least 1 hour apart; OR who are within 24h of commencing CPAP or $HFNO_2$ to maintain O_2 sats >94% and have not been previously mechanically ventilated for treatment of COVID19
- Not requiring invasive mechanical ventilation, ECMO, cardiovascular support (pressor, inotrope or mechanical) at the time of drug initiation. Those starting on the drug should continue if they subsequently need invasive mechanical ventiltation. The evidence of benefit has not been demonstrated for those on ventilation. There may be some patients just starting on ventilation in the early phase of the infection who may be suitable for access to remdesivir as determined by mutildisciplinary assessment.

Additional notes:

- Children aged 12 and under and pregnant mothers are able to access remdesivir through a separate compassionate use scheme operated by Gilead.
- The suggested dosage in adults and adolescents not requiring invasive ventilation and/or ECMO is a single dose of remdesivir 200 mg on Day 1 followed by once-daily maintenance

doses of remdesivir 100 mg for 4 days. If a patient does not demonstrate clinical improvement, treatment may be extended for up to 5 additional days (i.e. up to a total of 10 days). Whether to use the additional 5 days of treatment should determined by mutildisciplinary assessment.

Data collection

The reporting of safety and clinical outcome data is required as part of the EAMS process and to fulfil regulatory requirements.

Safety reporting

- Adverse Events (AEs), Serious Adverse Events (SAEs) and Special Situation reports (SSRs) (including pregnancies) are recorded on a paper reporting form and submitted to Gilead Pharmacovigilance & Epidemiology (PVE): Email: Safety_FC@gilead.com; Fax: +1-650-522-5477
- Any suspected adverse drug reactions (ADRs) for patients receiving remdesivir can also be reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus-yellowcard.mhra.gov.uk/

Clinical Outcome reporting

The Deputy Chief Medical Officer for Her Majesty's Government has mandated that data on all patients that receive remdesivir through the EAMS must be captured through the ISARIC 4C Clinical Characterisation Protocol (CCP) case report forms (CRFs), as coordinated by the COVID-19 Clinical Information Network (CO-CIN). Completion of the mandatory fields of the ISARIC WHO CCP-UK CRFs is required, to support ongoing implementation, including determination of future drug allocations between NHS hospitals, and evaluation (link to forms).

NHS England implementation

In order to access any medicine approved under COVID-19 EAMS Trusts must first register their interest and commit to collect required data. In order to register your trust as a site to access treatments for COVID-19, an application form must be completed via the Blueteq system. The form asks applicants to confirm the registration has been approved by the trust's medical director and that the trust will comply with other conditions of the MHRA EAMS scheme. This form is now available on the Blueteq system to register your Trust.

For this exercise, a dummy patient has been added to the system that has been made accessible for all trusts in England. It is through this patient that all applications should be completed and once a form has been approved for your trust, you will be added to the list of approved sites. The dummy patient can be found by searching for 'NHSE' as the patient's initials. The relevant form can be found by searching under the drug name 'Covid-19 registration'. A user guide will be circulated to the Hospital Chief Pharmacist. Once registered the remdesivir Blueteq form will become accessible.

Trusts will initially be allocated stock up front based on COVID-19 bed occupancy on a regional basis. Regions will then allocate this stock to those Trusts who have completed the Blueteq site registration form. Subsequently, Trusts must retrospectively complete a remdesivir Blueteq form in order to register patients who have received remdesivir and in order to receive further allocated stock.

As with all unlicensed medicines, individual Trusts should have local governance arrangements in place to authorise medicines supplied via an EAMS. This review should be expedited as a rigorous risk/ benefit assessment has already been conducted by MHRA and can be accessed in the Public Assessment Report (PAR) from the relevant link at https://www.gov.uk/government/collections/early-access-tomedicines-scheme-eams-scientific-opinions/

Hospitals should register patients and provide pharmacovigilance data and data collection as agreed. Specific details relating to pharmacovigilance can be found in the Treatment Protocol – Information on the pharmacovigilance system and requirements for reporting safety data. Pharmacovigilance should be approached as described in the Treatment Protocol.

Allocation

1. Hospitals will be allocated a supply of remdesivir by NHSE&I. The quantity allocated will be based on the previous week's sitrep data for NIV and V beds occupied by COVID-19 patients as a proxy measure of the severe patient population.

Ordering

2. Regional procurement pharmacists will notify hospitals to order a specified quantity of remdesivir.
3. All orders should be placed by the Hospital Pharmacy Department's procurement team.
4. To place an order for remdesivir via the Gilead EAMS scheme an open purchase order with the title "Remdesivir EAMS" clearly marked should be emailed to Gilead Customer Services: Email: ukcustomer.services@gilead.com, Fax: 01223 897291
5. Hospital Pharmacy Departments will receive a direct supply of remdesivir from Gilead. Two preparations of remdesivir (100mg) are available which have different storage conditions. These are a liquid preparation which requires cold chain storage and a dry powder formulation which can be stored at room temperature. Hospitals will be advised in advance which preparation they will receive.
6. To assist with the delivery of the product under controlled cold chain storage conditions, the open purchase order must include: contact name/alternative contact; contact number(s); confirmed delivery address.
7. For any queries regarding the order, please contact 0203 681 4681.
8. Monday to Friday (9am to 5pm), orders placed before 12 noon will usually be delivered the next working day. Orders placed after 12 noon will usually be delivered 2 working days later.
9. All orders should be receipted onto the Pharmacy dispensing system and remdesivir dispensed according to local procedures. Pharmacy dispensing system records must be kept up to date promptly.

Mutual Aid

10. Limited supplies of remdesivir are available and it may be necessary for mutual aid to be applied.
11. To agree mutual aid, the hospital pharmacy requiring additional stock should contact their Regional Pharmacy Procurement Specialist (RPPS).
12. The RPPS will access RxInfo and identify where within their region unused stocks of Remdesivir are held.
13. The RPPS will contact the Regional Chief Pharmacist to inform them that a request has been made for Mutual Aid.
14. The Regional Chief Pharmacist will authorise the supply.
15. The Regional Chief Pharmacist and the Hospital Chief Pharmacist will agree the arrangements for transfer of stock.
16. NHSE&I will be informed via an email to england.spoc-c19therapeutics@nhs.net that a transfer of stock between sites has occurred.
17. Further information regarding the application of this EAMS can be requested from the dedicated COVID-19 EAMS email address: england.spoc-c19therapeutics@nhs.net

NHS Scotland implementation

In order to access any medicine approved under COVID-19 EAMS, hospitals must first register their interest and commitment to collect the required data. Please contact: hcis.adtc-collaborative@nhs.net in order to register as a site to access treatments for COVID-19.

Allocation

1. Health boards will be allocated a supply of remdesivir; this will be communicated to health boards weekly by NSS National Procurement. The quantity allocated will be based on the most up-to-date published figure available for people in hospital with COVID-19.

Ordering

2. Health Boards need to raise an open purchase order for remdesivir with Gilead, following the steps outlined in points 3 to 9 above.

Mutual Aid

3. Limited supplies of remdesivir are available. If necessary, the process for sharing medicines across Scotland during the COVID-19 pandemic should be followed to seek access to stock from other health boards.

Healthcare Improvement Scotland, via the Area Drugs and Therapeutics Committee Collaborative (ADTCC), will separately issue all the EMAS documentation and any guidance on the data collection arrangements, as per standard process.

As with all unlicensed medicines, individual Health Boards will also have local governance arrangements in place to authorise medicines supplied via an EAMS. This review should be expedited as a rigorous risk/ benefit assessment has already been conducted by MHRA and can be accessed in the Public Assessment Report (PAR) from the relevant link at https://www.gov.uk/government/collections/early-access-tomedicines-scheme-eams-scientific-opinions/

Hospitals should register patients and provide pharmacovigilance data and data collection as agreed. Specific details relating to pharmacovigilance can be found in the Treatment Protocol – Information on the pharmacovigilance system and requirements for reporting safety data. Furter guidance will follow from the Area Drug and Therapeutoc Committee Collaborative (ADTCC). Pharmacovigilance should be approached as described in the Treatment Protocol.

Health and Social Care Northern Ireland implementation

Allocation

1. Supplies of remdesivir will be allocated by the Regional Pharmaceutical Procurement Service.

Ordering

2. Trusts need to raise an open purchase order for remdesivir with Gilead, following the steps outlined in points 3 to 9 above.

Mutual Aid

3. Limited supplies of remdesivir are available and if necessary, the process for sharing medicines across Northern Ireland will be managed by Trusts working with the Regional Pharmaceutical Procurement Service.

Further information including all the EMAS documentation will issue separately and any guidance on the data collection arrangements, as per standard process.

As with all unlicensed medicines, Trusts will also have local governance arrangements in place to authorise medicines supplied via an EAMS. This review should be expedited as a rigorous risk/ benefit assessment has already been conducted by MHRA and can be accessed in the Public Assessment Report (PAR) from the relevant link at

https://www.gov.uk/government/collections/early-access-tomedicines-scheme-eams-scientific-opinions/

Trusts should register patients and provide pharmacovigilance data and data collection as agreed. Specific details relating to pharmacovigilance can be found in the Treatment Protocol – Information on the pharmacovigilance system and requirements for reporting safety data. Furter guidance will follow from the Area Drug and Therapeutoc Committee Collaborative (ADTCC). Pharmacovigilance should be approached as described in the Treatment Protocol.

NHS Wales implementation

Allocation

1. Health boards will be allocated a supply of remdesivir; this will be communicated to health boards weekly by the NHS Wales Procurement Service. The quantity allocated will be based on the most up-to-date published figure available for people in hospital with COVID-19.

Ordering

2. Health Boards need to raise an open purchase order for remdesivir with Gilead, following the steps outlined in points 3 to 9 above.

Mutual Aid

3. Limited supplies of remdesivir are available. If necessary, the process for sharing medicines between health boards during the COVID-19 pandemic are well established and should be followed to seek access to stock from other health boards.

As with all unlicensed medicines, individual health boards will also have local governance arrangements in place to authorise medicines supplied via an EAMS, details of local arrangements should be discussed with the health board Chief Pharmacist. This review should be expedited as a rigorous risk/ benefit assessment has already been conducted by MHRA and can be accessed in the Public Assessment Report (PAR) from the relevant link at https://www.gov.uk/government/collections/early-access-tomedicines-scheme-eams-scientific-opinions/

Hospitals should register patients and provide pharmacovigilance data and data collection as agreed. Specific details relating to pharmacovigilance can be found in the Treatment Protocol – Information on the pharmacovigilance system and requirements for reporting safety data. Pharmacovigilance should be approached as described in the Treatment Protocol

Action

Clinical Teams should:

- work with their hospital pharmacy to secure readiness to offer the treatment as part of an EAMS;
- identify patients who may meet the access criteria in Annex A;
- complete the data entry requirements of those who have initiated treatment.

Regional Pharmacy leads/Directors of Pharmacy should:

- work with the national team to complete the allocation process;
- work with Trusts who have stock holding beyond projected their demand to re-distribute this stock across their region;

Trust/hospital pharmacy leads should:

- work with regional chief pharmacists and regional procurement pharmacists to manage stock appropriately and ensure Blueteq forms are completed in a timely manner;

Deadlines for actions

- Actions underway: on receipt of this alert.
- Actions complete: as soon as possible.

Supporting Information
More detailed information on the the use of remdesivir with COVID-19 infection can be found at the following locations:

A summary of the MHRA EAMS Public Assessment Report (PAR) is available here: https://www.gov.uk/government/collections/early-access-to-medicines-scheme-eams-scientific-opinions

New England Journal Medicine https://www.nejm.org/doi/full/10.1056/NEJMoa2007764

Requests for further information on remdesivir can be submitted to UKICOVID-19@gilead.com

The ISARIC 4C (Coronavirus Clinical Characterisation Consortium) can be found at: https://isaric4c.net/

Distribution

NHS Trusts (including NHS boards in Scotland and Wales)
Regional Medical Directors
Regional Chief Pharmacists
Lead/senior pharmacists
Trust/hospital medical directors to circulate to medical and nursing staff managing COVID-19 patients.

Enquiries

England
Enquiries from NHS Trusts in England should in the first instance be directed to your trust pharmacy team who will escalate issues to the Regional Pharmacist and national teams if required. Further information regarding the application of this EAMS can be requested from the dedicated COVID-19 EAMS email address: england.spoc-c19therapeutics@nhs.net.

Northern Ireland
Enquiries from hospitals in Northern Ireland should in the first instance be directed to your hospital pharmacy team.

Scotland
Enquiries from hospitals in Scotland should in the first instance be directed to your hospital pharmacy team who will escalate issues to the Scottish Government's Medicines Policy Team if required. Contact should be made using the email address - CPO-COVID19@gov.scot.

Wales
Enquiries from hospitals in Wales should in the first instance be directed to the health board's Chief Pharmacist who will escalate issues to the Pharmacy and Prescribing Team at Welsh Government if required. Enquiries to the Welsh Government should be directed to: COVID-19.Pharmacy.Prescribing@gov.wales.