RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V25.0 23-May-2022)

1 Introduction

The following medicines are listed as IMPs for this study. The supply arrangements for each arm is different (see table 1 below).

This clinical trial is being run to make it as easy as possible, while ensuring that the outcome data from the patients is collected to inform future care of patients with Covid-19.

Table 1: Medicines for RECOVERY Clinical Trial for Adults

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Randomisation Part E					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part F					
No additional treatment					
Empagliflozin	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part G					
No additional treatment					
Baloxavir marboxil	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part H					
No additional treatment					
Oseltamivir	Oral capsule, Oral suspension	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part I					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No

Randomisation Part J					
No additional treatment					
Sotrovimab	Solution for Intravenous Infusion	GSK trial specific stock	No	Yes	No
Randomisation Part K					
No additional treatment					
Molnupiravir	Oral capsule	See Section 7.1	No	Yes	No
Randomisation Part L					
No additional treatment					
Paxlovid	Oral tablet	See Section 8.1	No	Yes	No

The MHRA is aware and have approved the study to allow any doctor working within the hospital to prescribe for this study (this can include FY1 doctors under supervision as per local practice). Similarly GCP trained research staff to take consent of the patient for this trial is not required. However, it is expected that all staff will complete online Recovery study training.

Further information regarding paediatric dosing and administration can be found on a separate document (RECOVERY Paediatric Guidance Document)

2 Dexamethasone

2.1 Initial supply and re-ordering

Dexamethasone will be sourced by local pharmacy procurement team via their normal routes.

2.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

2.3 Dispensing quantities

Different randomisation parts have different doses and duration – please check carefully.

Randomisation Part **E**: Dexamethasone **20mg** (base) once daily by mouth, nasogastric tube or intravenous infusion for **5** days followed by dexamethasone **10mg** (base) once daily for **5** days. Treatment should be discontinued at 10 days or on discharge from hospital if sooner.

Randomisation Part **I**: Dexamethasone **6mg** once daily by mouth or intravenously for **10** days or discontinued on discharge from hospital if sooner.

2.4 Returns and Destructions

During the study any patient returns or if there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. No approval from Sponsor is required.

FAQs

Q. My patient is pregnant or breastfeeding can they be treated with dexamethasone?

A. No.

Randomisation Part **E**: Pregnant or breastfeeding women should be prescribed:
Prednisolone 130mg once daily orally or hydrocortisone (sodium succinate) 180mg three times a day or 135mg four times a day intravenously or methylprednisolone (sodium succinate) 100mg once daily intravenously for 5 days.
Followed by either prednisolone 65mg once daily orally or hydrocortisone (sodium succinate) 90mg three times a day or 70mg four times a day intravenously or methylprednisolone (sodium succinate) 50mg once daily intravenously for 5 days.
Sites are free to choose between three times a day or four times a day dosing for the hydrocortisone (sodium succinate) treatment course.
Administration: Hydrocortisone 70-180mg IV – give slowly over 5-10 minutes.
Methylprednisolone 50mg or 100mg IV – give slowly over 5 minutes.

Randomisation Part **I**: Pregnant or breastfeeding women should be prescribed oral prednisolone 40mg once a day or intravenous hydrocortisone (sodium succinate) 80mg twice daily.

Q. How is dexamethasone to be prescribed as there are different salts available?

A. To be prescribed as dexamethasone 6mg base

Q. Is the dose the same for oral and IV for dexamethasone despite differences in bioavailability?

A. Yes, the dose will be 6mg base for both IV and oral.

Q. How should the oral dose be taken?
Dexamethasone should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.

Q. The IV 6mg and 20mg dose of dexamethasone base of the 3.3mg/mL comes to 1.82mL or 6.06mL which cannot be measured accurately in a 2mL or 10mL syringe. What do we do?

A. Volume to be rounded to 6mg/1.8mL and 20mg/6mL, which is measurable.

Q. The IV 67.5mg dose of hydrocortisone (sodium succinate) comes to 1.65mL (50mg/mL) or 3.375mL (20mg/mL) which cannot be measured accurately in a 2mL or 5mL syringe. What do we do?

A. Volume to be rounded to 70mg/1.4mL or 70mg/3.5mL, which is measurable.

Q. Our normal hospital practice is to dissolve dexamethasone 2mg tablets instead of using soluble tablets or oral liquid, is this permitted?

A. Yes. If sites cannot source the soluble tablets or liquid, then the 2mg tablets can be dissolved in 10mL of water. There are no issues with this going down a fine bore nasogastric tubes (Reference: Handbook of Drug Administration via Enteral Feeding Tubes).

Q. Is IV dexamethasone to be given as an IV bolus or infusion?

A. Either is acceptable, treating clinician to decide.

Q. My patient has been randomised to receive Paxlovid, can they also receive corticosteroids?

A. Patients eligible for Paxlovid will be excluded from the high-dose corticosteroid arm (Randomisation Part E) due to the potential interaction between the two. If corticosteroids are indicated (ie, the patient is receiving oxygen) then prednisolone (oral) or hydrocortisone (IV) should be used instead of dexamethasone.

3 Empagliflozin

3.1 Initial supply and re-ordering

Empagliflozin will be sourced by local pharmacy procurement team via their normal routes. Empagliflozin is available as 10mg tablets in packs of 28 tablets.

In England, A Blueteq form will need to be completed for each patient to ensure that costs can be reimbursed to hospital trusts. The Blueteq form can be completed in retrospect. [Reimbursement arrangements are yet to be confirmed for the devolved nations.]

Please note that currently hospitals will only be reimbursed for treatment given. Therefore, it is not advised to overstock as any unused stock will not be reimbursed.

3.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

3.3 Dispensing quantities

Empagliflozin 10 mg once daily by mouth for 28 days in total or discontinued on discharge from hospital if sooner.

3.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any empagliflozin for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. Remaining stock that has been returned for non-trial use should only be dispensed to patients whom have prior approval to be treated with empagliflozin. No approval from Sponsor is required.

3.5 FAQs

Q. Can the dose be reduced at all for this study?

A. Dose reductions are not expected including for patients with renal impairment or who develop renal impairment.

Q. My patient has severe hepatic impairment, can they be randomised to receive empagliflozin?

A. Yes, they can, this would be at the treating doctor's discretion.

Q. My patient has diabetic ketoacidosis, can they be randomised to receive empagliflozin?

A. No; these patients should not be randomised to receive this medicine.

Q. Do I need to follow MHRA/CHM advise on risk of diabetic ketoacidosis with empagliflozin?

A. Yes. You must continue to monitor patients for the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat) and if suspected stop treatment and test for raised blood ketones even if plasma glucose levels are near-normal.

Q. My patient is volume depleted, can they still have empagliflozin?

A. Correct the fluid depletion and then randomise to treatment and continue to monitor fluid balance and renal function closely.

Q. Can empagliflozin tablets be cut or crushed for patients who have swallowing difficulties or who have a feeding tube?

A. No; these patients should not be randomised to receive this drug. The tablets must be swallowed whole with or without food. Please also note that these tablets contain lactose as an excipient, so patients who are lactose intolerant should not be randomised to receive this medicine.

Q. My patient is 85 years old or older, can they be randomised to receive empagliflozin in this trial?

A. Yes, they can, this would be at the treating doctor's discretion.

4 Baloxavir marboxil

4.1 Initial supply and re-ordering

For sites within England, Scotland and Wales: Baloxavir marboxil will be sourced by local pharmacy procurement team free of charge from Alliance Health Hospital system. Baloxavir is available as 40mg tablets in packs of 2 tablets.

For your initial order, order 10 packs of baloxavir 40mg using the PIP code provided in your site's activation e-mail (please ask your PI if you did not receive this) and NOT the usual PIP code for ordering normal hospital supplies.

Orders placed before 15:00 will be delivered to site the following working day.

For resupplies when sites are down to 2 packs of baloxavir, then place a re-order for a further supply of 10 packs. For your initial order and re-orders, then only order as 10 packs using the above PIP code to help Roche distinguish between commercial and stock for this trial.

For sites in Northern Ireland: Baloxavir tablets will be sourced by local pharmacy procurement team free of charge. For your initial order, order 10 packs of baloxavir tablets (2 x 40mg), complete the Recovery Drug Order Form and email the completed form to Movianto (form and e-mail address will be attached to your site's activation e-mail; please ask your PI if you did not receive this).

Orders placed before 15:00 will be delivered to site the following working day.

For resupplies, when sites are down to 2 packs of baloxavir, then place a re-order for a further supply of 10 packs. For your initial order and re-orders, then only order as 10 packs to help Movianto distinguish between commercial and stock for this trial.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating 'to be used in the RECOVERY trial only' and storing in different areas of pharmacy.

4.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

4.3 Dispensing quantities

Adults and adolescents (≥ 12 years of age)
<80kg Baloxavir 40mg once daily by mouth on day 1 and day 4 ie 1 x 2 x 40mg pack
≥80kg Baloxavir 80mg once daily by mouth on day 1 and day 4 ie 2 x 2 x 40mg packs

If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home.

4.4 Returns and Destructions

During the study any patient returns should be destroyed on site. If there is still stock at end of study, please seek guidance from the sponsor.

4.5 FAQs

Q. Can baloxavir tablets be cut or crushed for patients who have swallowing difficulties or who have a feeding tube?

A. The tablet must **not** be crushed or split. It can be dissolved if needed: Place tablet in 100ml medicine bottle, add 50ml of water for irrigation at ambient temperature and shake for 10 minutes. Add 50ml ORA-Blend to mask the taste, shake again to mix well. The mixture has not been tested for enteral administration. ORA-Blend is the only option: do NOT mix with food or juice.

If administering via a feeding tube (where taste is not an issue), the tablets can be dissolved in 100ml water. (While the company's in house data on dispersing tablet has not been tested for enteral administration, baloxavir suspension is licensed in the US for administration via enteral feeding tube, suggesting drug interaction with tubing is unlikely to be an issue. Given the licensed baloxavir 2mg/mL suspension is bioequivalent to baloxavir tablet, and the suspension is a simple suspension formulation (excipients: non-colloidal silicon dioxide, hypromellose, maltitol, mannitol, povidone

K25, sodium chloride, strawberry flavour, sucralose and talc), the administration of dispersed tablet suspension is likely to have minimal impact on bioavailability.)

Q. How should the tablets be taken?
A. The tablets must be swallowed whole with or without food.
Baloxavir should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium

Q. Do tablets contain lactose?
The tablets contain lactose as an excipient, so patients who are lactose intolerant should not be randomised to receive this medicine.

Q. My patient is pregnant or breastfeeding can they be treated with baloxavir?

A. Yes; pregnant or breastfeeding women can be randomised to receive baloxavir in this trial.

5 Oseltamivir

5.1 Initial supply and re-ordering

For sites within England, Scotland and Wales: Oseltamivir will be sourced by local pharmacy procurement team free of charge from Alliance Health Hospital system. Oseltamivir is available as 75mg capsules in packs of 10 capsules and as 6mg/mL powder for oral suspension (65mL = 390mg oseltamivir) in packs of 1 bottle per carton.

For your initial order please order 8 packs of oseltamivir 75mg capsules and 2 bottles of 6mg/mL powder for oral suspension using the PIP codes provided in your activation e-mail (please ask your PI if you have not received this directly), and NOT the usual PIP code for ordering normal hospital supplies.

Orders placed before 15:00 will be delivered to site the following day.

For resupplies when sites are down to 2 packs of oseltamivir 75mg capsules and/or 1 bottle of 6mg/mL powder for oral suspension, then place a re-order for a further supply of 8 packs of oseltamivir 75mg capsules and/or 2 bottles of 6mg/mL powder for oral suspension. For your initial order and re-orders, then only order pack quantities stated using the above PIP code to help Roche distinguish between commercial and stock for this trial.

For sites in Northern Ireland: Oseltamivir will be sourced by local pharmacy procurement team free of charge. For your initial order of 8 packs of oseltamivir capsules (10 x 75mg) and 2 bottles of oseltamivir 6mg/mL powder for oral suspension (65mL), complete the Recovery Drug Order Form and email the completed form to Movianto (form and e-mail address will be attached to your site's activation e-mail; please ask your PI if you did not receive this). .

Orders placed before 3pm will be delivered to site the following working day.

For resupplies, when sites are down to 2 packs of oseltamivir 75mg capsules and/or 1 bottle of

6mg/mL powder for oral suspension, then place a re-order for a further supply of 8 packs of oseltamivir 75mg capsules and/or 2 bottles of 6mg/mL powder for oral suspension. For your initial order and re-orders, then only order pack quantities stated to help Movianto distinguish between commercial and stock for this trial.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating 'to be used in the RECOVERY trial only' and storing in different areas of pharmacy.

5.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

5.3 Dispensing quantities

Adult or children over 40 kg:
Oseltamivir 75mg capsules twice daily by mouth for five* days.

Children or under 40kg:

Body Weight	Recommended dose for 5* days
10 kg to 15 kg	30 mg (5ml of 6mg/ml liquid) twice daily, 1 x 65ml bottle
> 15 kg to 23 kg	45 mg (7.5ml of 6mg/ml liquid) twice daily, 2 x 65ml bottle
> 23 kg to 40 kg	60 mg (10ml of 6mg/ml liquid) twice daily, 2 x 65ml bottles
> 40 kg	75 mg (12.5ml of 6mg/ml liquid) twice daily, 2 x 65ml bottles

Neonates (age <36 weeks corrected gestational age): 1 mg/kg twice daily for 5* days.

Infants (age 0-12 months and ≥36 weeks corrected gestational age): 3 mg/kg twice daily for 5* days.

*Course can be extended to 10 days for immunosuppressed patients at the managing clinician's discretion. If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home.

5.4 Returns and Destructions

During the study any patient returns or if there is still stock at end of study, please contact the sponsor.

FAQs

Q. My patient has renal impairment, can they receive oseltamivir?

A. Yes; 75mg twice a day dose should be reduced if their renal function is:

- eGFR ≥10 <30mL/min/1.73m^2 to 75mg once daily

- eGFR <10mL/min/1.73m^2 to 75mg as a single dose on day 1.

Q. My patient is pregnant or breastfeeding can they be treated with oseltamivir?

A. Yes; pregnant or breastfeeding women can be randomised to receive oseltamivir.

6 Sotrovimab

6.1 Initial supply and re-ordering

Sotrovimab is available as 500mg in 8mL vials, 1 vial per carton. The initial supply of sotrovimab will be sent by Fisher to each site for this arm (under instruction from the sponsor). The Principal Investigator will need to have completed the necessary training for this arm and the site activated before IMP is shipped.

Sites are to re-order supplies of sotrovimab when stock levels are running low by emailing the RECOVERY trial team: recoverytrial@ndph.ox.ac.uk

6.2 Receipt and Storage

As per SmPC.
Pharmacy department should receive all shipments.

All shipments will come with a temperature monitoring device. Follow the temperature monitoring device instructions included in the shipment. Please email the shipment temperature data to the RECOVERY trial team (see below) to confirm receipt. Discard the temperature monitoring device after the temperature readout report has been downloaded and emailed.

During storage only temperature excursions (i.e. temperatures outside of 2 – 8^{o}C) for more than 1 hour are considered reportable to the RECOVERY trial team only.

If there has been a temperature excursion during shipping or during storage at site, then affected stock must be physically quarantined until further guidance is given. Sites will need to complete the 'Clinical Investigational Medicinal Product (IMP) Temperature Excursion or Damage Form'. Send the completed form to the RECOVERY trial team only: recoverytrial@ndph.ox.ac.uk

All sites will need to ensure clear storage separation between stock for this study and general stock, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating 'To be used in the RECOVERY trial only' and storing in different areas of pharmacy.

Please note that the expiry date on the carton is not accurate. A batch specific variation for the following Lots: **2T8F** and **UK3F** have been approved by the MHRA which extends their expiry date by 12 months (Lot 2T8F to February 2023 and Lot UK3F to March 2023). It will be necessary to re-label all stock at the point of receipting from March 2022 onwards to indicate the change in expiry date. All stock previously held from before March 2022 should have already been expiry date extended. Please see Appendix 2 for a worksheet to support this.

6.3 Dispensing quantities

Sotrovimab dispense 2 x 500mg vials for a single **1000mg dose** to be administered as an intravenous infusion over **60 minutes** using a 0.2micron low protein binding in-line filter.

Note: *The dose and duration are different to SmPC license.*

6.4 Preparation Guidance

Doses of Sotrovimab may be made on the ward as per individual Trust guidance and risk assessment for monoclonal antibodies. Trust must have an IV monograph available on the wards where doses will be prepared (see Appendix 1 for an example)..

Preparation steps

1. Remove **TWO** vials of sotrovimab from the refrigerator to allow the vials to equilibrate to room temperature, protected from light, for approximately 15 minutes
2. Obtain one **100mL** sodium chloride 0.9% or glucose 5% infusion bag
3. Visually inspect each vial to ensure it is a clear, colourless or yellow to brown solution, free from visible particles and that there is no visible damage to the vial
4. Gently swirl each vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vials
5. Withdraw **16mL** of sotrovimab from the two vials
6. Add **16mL** of sotrovimab to a 100mL sodium chloride 0.9% or glucose 5% infusion bag
7. Gently rock the infusion bag back and forth 3 to 5 times. Do NOT invert the infusion bag. Avoid forming air bubbles

The stability concentration range is 1 – 10mg/mL. Sites must ensure that the brand of IV bag being used can hold this additional volume safely and that there is no additional risk of spillage/inadvertent loss when the ward nurse spikes the bag. The diluted solution should be administered immediately. If not possible then it may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2 – 8°C) for up to 24 hours from the time of dilution.

Please ensure the time of infusion is recorded in the medical records (if not done routinely).

6.5 Returns and Destructions

During the study if there is any damaged or expired stock, or if there is still stock at end of study, this can be destroyed on site. No approval from Sponsor is required.

FAQs

Q. My patient has renal impairment and/or hepatic impairment, can they be treated with sotrovimab?

A. Yes, no dose adjustment is required.

Q. My patient weighs less than 40kg, can they be treated with Sotrovimab?

A. Yes, unless they are ≥12 <18 years old in which case they must weight >40 kg.

Q. Can adolescents under 12 years receive sotrovimab?

No, and see protocol for other arms.

Q. My patient is pregnant or breastfeeding can they be treated with sotrovimab?

A. Yes; pregnant or breastfeeding women can be randomised to receive sotrovimab, but the consent process must explain the risks and benefits.

7 Molnupiravir

7.1 Initial supply and re-ordering

Molnupiravir is available as 200mg capsules, 40 capsules per bottle.

For England:

Molnupiravir has been purchased by DHSC Antiviral Task Force. It is supplied into hospital pharmacy departments free of charge via the COVID-19 vaccination programme delivery route. The current supply route is a "push" model with COVID-19 Medicine Delivery Unit (CMDU) host Trusts being allocated molnupiravir based on ICS population served.

The MHRA have approved molnupiravir for the RECOVERY trial as unmodified commercial stock. This means that no additional labelling is required other than a routine dispensing label in line with the trial protocol. Stock may be accessed from hospital pharmacy departments aligned to the CMDUs. Sites should be registered as a trial site and a trial prescription should be supplied. As the RECOVERY trial requires molnupiravir for inpatient use it and it may be required out of hours, a process of holding stock in locations outside of the pharmacy department may be required and such arrangements should be agreed with the Trust's Chief Pharmacist. Trusts should consider maintaining minimal stocks in these locations. Whilst there is no requirement to specifically hold RECOVERY stock within a clinical trials location, all stock must be visible on Exend with regular physical stock balances checks. This is essential to support the on-going replenishment of stock.

For sites that are not aligned to CMDUs, the hospital pharmacy department must be registered as a trial site. In order for these organisations to receive a supply of stock, the RECOVERY trial team will ask sites to provide the name and telephone number of a pharmacy contact and the address of the Pharmacy Stores to which stock will be delivered and receipted. These organisations will then be registered with the logistic provider commissioned to delivery molnupiravir. Organisations are requested to manage stock in the same way as CMDU sites.

Ordering for Northern Ireland, Scotland and Wales: to be sourced by local pharmacy procurement team via their normal routes.

7.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

7.3 Dispensing quantities

Molnupiravir 800mg twice daily for 5 days orally ie 40 capsules = one bottle.

Note: Women of child-bearing potential **must** have a negative pregnancy test before being randomised to molnupiravir.

If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home. Please ensure the provision of such medication does not delay the discharge.

7.4 Returns and Destructions

During the study ward returns from trial patients or if the Trust chooses to ring fence any molnupiravir for the study, it can be returned to stock in the usual way or destroyed on site. Remaining stock that has been returned for non-trial use should only be dispensed to patients whom have prior approval to be treated with molnupiravir. No approval from Sponsor is required.

FAQs

Q. My patient has renal impairment and/or hepatic impairment, can they receive molnupiravir?

A. Yes, and no dose adjustment is required.

Q. My patient is pregnant or breastfeeding can they be treated with molnupiravir?

A. No; pregnant or breastfeeding women cannot randomised to receive molnupiravir. Women of child-bearing potential should be advised not to get pregnant while taking molnupiravir or for 4 days after completing the course.

Q. Can adolescents under 18 years receive molnupiravir?

No, and see protocol for other arms.

Q. My patient has swallowing difficulties or has a nasogastric tube, can they receive molnupiravir?

A. No; the capsules should not be opened, crushed or chewed. Molnupiravir can be taken with or without food and swallowed whole with a glass of water.

8 Paxlovid

8.1 Initial supply and re-ordering

Paxlovid is available as 1 x 150mg nirmatrelvir (PF-07321332) tablet and 1 x 100mg ritonavir tablet; it is a combination product, but the constituents are in separate tablets.
The carton contains 5 foils strips each containing morning and evening doses - 2 sets of 2 x 150mg nirmatrelvir tablets and 1 x 100mg ritonavir tablets ie 20 nirmatrelvir 150mg tablets and 10 ritonavir 100mg tablets per carton.

For England:

Paxlovid has been purchased by DHSC Antiviral Task Force. It is supplied into hospital pharmacy departments free of charge via the COVID-19 vaccination programme delivery route. The current supply route is a "push" model with COVID-19 Medicine Delivery Unit (CMDU) host Trusts being allocated Paxlovid based on ICS population served.

The MHRA have approved Paxlovid for the RECOVERY trial as unmodified commercial stock. This means that no additional labelling is required other than a routine dispensing label in line with the trial protocol. Stock may be accessed from hospital pharmacy departments aligned to the CMDUs. Sites should be registered as a trial site and a trial prescription should be supplied. As the RECOVERY trial requires Paxlovid for inpatient use it and it may be required out of hours, a process of holding stock in locations outside of the pharmacy department may be required and such arrangements should be agreed with the Trust's Chief Pharmacist. Trusts should consider maintaining minimal stocks in these locations. Whilst there is no requirement to specifically hold RECOVERY stock within a clinical trials location, all stock must be visible on Exend with regular physical stock balances checks. This is essential to support the on-going replenishment of stock.

For sites that are not aligned to CMDUs, the hospital pharmacy department must be registered as a trial site. In order for these organisations to receive a supply of stock, the RECOVERY trial team will ask sites to provide the name and telephone number of a pharmacy contact and the address of the Pharmacy Store to which stock will be delivered and receipted. These organisations will then be registered with the logistic provider commissioned to delivery Paxlovid. Organisations are requested to manage stock in the same way as CMDU sites.

Ordering for Northern Ireland, Scotland and Wales: to be sourced by local pharmacy procurement team via their normal routes.

8.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

8.3 Dispensing quantities

Paxlovid 300mg/100mg (2 tablets of 150mg nirmatrelvir with 1 tablet of 100mg ritonavir) twice daily for 5 days orally ie one carton.

If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home. Please ensure the provision of such medication does not delay the discharge.

Please note that Paxlovid contains ritonavir, therefore be aware of drug-drug interactions. Paxlovid is contraindicated with medicinal products that are potent CYP3A inducers and also with medicinal products that are highly dependent on CYP3A for clearance (see SmPC for further details).

8.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any Paxlovid for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. Remaining stock that has been returned for non-trial use should only be dispensed to patients whom have prior approval to be treated with Paxlovid. No approval from Sponsor is required.

FAQs

Q. My patient has renal impairment and/or hepatic impairment, can they receive Paxlovid?

A. For mild – moderate renal impairment the dose should be reduced to 150mg/100mg (1 tablet of 150mg nirmatrelvir with 1 tablet of 100mg ritonavir) twice daily for 5 days. Patients with severe renal and/or hepatic impairment Paxlovid is contra-indicated.

For these patients who complete the course at home, the pharmacist **MUST** remove the additional nirmatrelvir tablet from the foil blister strips before giving the remaining tablets to the patient to take home. The nirmatrelvir tablet can be safely removed from the blister strip by either cutting the tablet out or by carefully opening the well in which the tablet sits in and popping the tablet out. The excess tablets must be disposed on into medicine waste. Record the number of tablets supplied on the TTO/TTA prescription.

Q. My patient is pregnant or breastfeeding can they be treated with Paxlovid?

A. If the patient is in their first trimester (i.e. first 12 weeks) then they should NOT be randomised to receive Paxlovid. If the patient is in their second or third trimester they can be randomised to receive Paxlovid, but the consent process must explain the risks and benefits.
There is no data available regarding Paxlovid in breastfeeding. The SmPC states that breastfeeding should be discontinued during treatment with Paxlovid and for 7 days after the last dose of Paxlovid.

Q. Can adolescents under 18 years receive Paxlovid?

A. No, and see protocol for other arms.

Q. My patient has swallowing difficulties or has a nasogastric tube, can they receive Paxlovid?

A. No; the tablets should not be opened, crushed or chewed. Paxlovid can be taken with or without food and swallowed whole with a glass of water.

Q. My patient has been randomised to receive Paxlovid, can they also receive corticosteroids?

A. Patients eligible for Paxlovid will be excluded from the high-dose corticosteroid arm (Randomisation Part E) due to the potential interaction between the two. If corticosteroids are indicated (ie, the patient is receiving oxygen) then prednisolone (oral) or hydrocortisone (IV) should be used instead of dexamethasone.

9 General FAQs

Q. What happens if our site does not have one of the medications used in the study in stock?

A. The co-ordinating centre should be informed (e-mail to recoverytrial@ndph.ox.ac.uk). It is possible to indicate on the randomisation form if a treatment is unavailable (and this can be set at a site level), so participants would not be assigned it.

Q. How will the cost of IMPs be covered?

A. Trusts will be able to recoup the costs of empagliflozin from NHS England by completing a Blueteq form for each patient. Baloxavir and oseltamivir will be free of charge from Alliance (or Movianto in NI). Sotrovimab will be free of charge from GSK. Molnupiravir and Paxlovid will be free of charge from DHSC. Dexamethasone, hydrocortisone, methylprednisolone and prednisolone could be covered by assigning to the government's COVID-19 cost centre as part of their overall treatment costs. Please liaise with your finance department to identify the mechanism set-up on how to claim for these extra COVID-19 costs.

Q. Can patients treated according to local pathway/protocol guidance still be considered for the RECOVERY trial further down the line?

A. All patients should receive standard care according to their local protocol. Randomisation is in addition to that.

Q. Are you allowing co-enrolment into other clinical trials of COVID-19?

A. Yes, as long as the clinical trial does not directly conflict with RECOVERY. Please see the trial website for further information.

Q. To ensure consistency for all patients, can the sponsor provide some guidance on how urgent (hours) the trial patient needs to receive the first dose of treatment?

A. We have no specific guidance on this, but within 6 hours would be ideal.

Q. Is Sponsor happy for sites to 'pre-pack' tablets into patient courses?

A. Yes

Q. If patients are discharged early are pharmacy expected to use the left over medication to maximise stock (if sites SOPs allow)?

A. Yes if local site SOPs allow

Q. Are sites able to add their own dispensing/additional labels to manage the study as they feel is most appropriate?

A. Yes

Q. Can non-medical prescribers be utilised to prescribe trial medications?

A. Yes if local SOPs allow

10 Appendix 1: Worksheet for sotrovimab preparation

See next page.

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Clinical Area Preparation Record – Sotrovimab 1000mg in 100mL Sodium Chloride 0.9% Infusion Bag (Total volume = 116 mL)

Set up

Step 1
Remove from the refrigerator:
- 2 x Sotrovimab 500mg (62.5mg/mL) Concentrate for Solution for Infusion vial.

Select:
- 1 x Sodium Chloride 0.9% 100mL Infusion Bag
- 1 x 20mL luer lock syringe
- 1 x drawing up needle
- 1 x 0.2 micron administration filter

Step 2
Visually inspect the Sotrovimab vials
- The solution should be clear, colourless or yellow to brown and free from visible particles

Should particulate matter or discoloration be observed, the vial must be discarded and replaced with a new vial.

Step 3
Place to the left side of the preparation area:
- 2 x Sotrovimab 500mg vial
- 1 x Sodium Chloride 0.9% 100ml Infusion Bag

Step 4
Prepare an infusion additive label with the following details:
- Sotrovimab 1000mg in Sodium Chloride 0.9% (Total volume = 116 mL)
- Date and time prepared
- [Additional details as required by local label format]

Preparation of Infusion Bag

Step 1
Bring the Sodium Chloride 0.9% 100mL Infusion Bag from the left side of the preparation area into the middle, swab the bung with a sterile 70% alcohol wipe and allow to dry.

Step 2
Bring the Sotrovimab 500mg vials from the left side of the preparation area into the middle, swab the bungs with sterile 70% alcohol wipe and allow to dry.

Step 3
Gently swirl the vials several times before use without creating air bubbles. **Do not shake or vigorously agitate the vial.**

Step 4
Attach a drawing up needle to a 20mL luer lock syringe and draw up **1 x 16mL** of Sotrovimab 500mg (62.5mg/mL) from the 2 vials

Step 5
Add **16mL** of Sotrovimab (62.5mg/mL) to the Sodium Chloride 0.9% 100mL Infusion Bag. Discard the syringe and needle into a yellow lidded sharps bin

Step 6
Gently rock the infusion bag back and forth 3 to 5 times.
NB: Do not invert the infusion bag. Avoid forming air bubbles. Do not shake

Step 7
Attach the pre-prepared label to the bag

Step 8
Ensure the product is administered using an [Insert local in-line or add-on 0.2µm filter used] as a single IV infusion for 60 minutes

Step 9
Record details of the patient who will receive the bag below, and file the completed *Clinical Area Preparation Record* in accordance with local guidance

Patient Name		Hospital No		Date of Birth	

11 Appendix 2: Worksheet for sotrovimab expiry extension

See next page.

RECOVERY Trial Pharmacy Expiry Extension Labelling Worksheet SOTROVIMAB 500mg in 8mL Concentrate solution for infusion

Site:	
Date of over-labelling operation:	
Storage conditions whilst over-labelling:	Sotrovimab vials may be out of the fridge (2 – 8ºC) for no more than 60 minutes
GSK/Vir confirmation of shelf-life expiry extension	Attach a copy to this work sheet

Product	Qty	Batch Number	Expiry	Assembled By:	Checked By:
Sotrovimab 500mg in 8mL Solution for Infusion (1 vial per carton)		UK3F			
		2T8F			
Upon completion of this exercise, supplies will be labelled with an expiry date of:					

Label Production	
Master Label:	Sample Label:
	Affix the last label printed here

Method		
	Performed By:	Checked By:
1. Ensure the work area is clean and free from all materials not required in this process		
2. Calculate number of labels need A = (no. of vials x 2) +1, print the labels		
3. Remove sotrovimab vials from the fridge Record time removed: ……		
4. Apply label to the carton and vial		
5. Replace sotrovimab vials back in the carton and into the fridge Record time replaced: ……		
6. Calculate total time removed from fridge ……. minutes		
7. Check that this is less than 60 minutes		

Label Reconciliation			
	No. of Labels	Performed By:	Checked By:
No. of labels printed (A)			
No. of sample labels attached to worksheet (B)			
No. of labels attached to vials (C)			
No. of labels attached to carton (D)			
No. of excess labels destroyed (E)			
Total number of labels accounted for A = B + C + D + E	Y / N		

Approvals:
The above product has been over-labelled with new expiry extension labels according to the instructions above. Any remaining labels have been destroyed.

Actions completed by:

_____ (Print Name) _____ (Sign) _____ (Initials) _____ (Date)

Actions Pharmacist checked by:

_____ (Print Name) _____ (Sign) _____ (Initials) _____ (Date)

Comments / Deviations

Storage of document:
Completed worksheet must be retained in the RECOVERY pharmacy site file, along with evidence of expiry date extension.