RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V16.1 08-Jul-2021)

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 A					
No additional treatment					
Dimethyl Fumarate	Oral tablets or capsules	NHS Stock. Licensed product – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part D					
No additional treatment					
Baricitinib	Oral tablet	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

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 Dimethyl Fumarate

2.1 Initial Supply and Re-Ordering

Dimethyl Fumarate will be sourced by local pharmacy procurement team via their normal routes. For the purpose of this study dimethyl fumarate 120mg capsules or tablets may be used. Tecfidera® are capsules from Biogen and Skilarance® are tablets from Alimirall.

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.

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.

2.2 Storage

As per SmPC
Keep the blisters in the outer carton in order to protect from light.
No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

2.3 Dispensing quantities

Dimethyl Fumarate dosage is 120mg every 12 hours for 4 doses followed by 240mg every 12 hours for 8 days (total 10 days or discontinued on discharge from hospital if sooner). If 240mg every 12 hours cannot be tolerated, the dose may be reduced (see below).

The dose should be swallowed whole and taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking with food may improve tolerability. Please also be aware the tablets contain lactose and that the capsules contain gelatin.

Biogen and Almirall do not have any additional stability data regarding cutting blister strips. Each capsule/tablet appears to be heat sealed individually. Therefore, the expiration date should not be affected by cutting the blister strip as long as the seal around the capsule/tablet is not broken when cutting through the blister strip sites can pack down to minimise waste. The Tecfidera® capsules must be packed down into a carton which will protect the capsules from light. As good practice we would recommend sites to write the batch number and expiry on the dispensing label.

2.4 Returns and Destructions

During the study any patient returns or if a Trust chooses to ring fence any dimethyl fumarate 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 dimethyl fumarate. No approval from Sponsor is required.

2.5 FAQs

Q. Can the dose be reduced for this study?

A. Yes at the discretion of the treating doctor. The dose can be reduced from 240mg twice daily to 120mg twice daily or 120mg once daily.

Q. Can the capsules be opened for patients who have swallowing issues or require nasogastric administration?

A. No; these patients should not be randomised to this receive this drug. As per the Tecfidera ® SmPC the contents of the capsule should **not** be crushed, divided, dissolved, sucked or chewed as the enteric coating of the micro-tablets prevents irritant effects on the gut. This is the same for Skilarence® where the coating of the gastro-resistant tablet is designed to prevent gastric irritation.

Q. Should participants have their liver function tests monitored?

A. The protocol for participants in this comparison (including those allocated to the usual care arm) requires ALT to be checked on day 3, 5 and 10 (but not required if they have been discharged sooner).

3 Baricitinib

3.1 Initial supply and re-ordering

Baricitinib will be sourced by local pharmacy procurement team via their normal routes. Baricitinib is available as 2mg and 4mg film coated tablets.

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.

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

Baricitinib 4 mg once daily by mouth or nasogastric tube for 10 days in total or discontinued on discharge from hospital if sooner.

Eli Lilly have confirmed that from a stability standpoint the tablet expiration date will not be affected by cutting the blister strip as long as long as the tablet remains sealed in the strip. Therefore, sites can pack down to minimise waste.

3.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any baricitinib 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 baricitinib. No approval from Sponsor is required.

3.5 FAQs

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

A. Yes. Dose should be reduced in presence of renal impairment:

- eGFR ≥30 <60 mL/min/1.73m^2: 2 mg once daily
- eGFR ≥15 <30 mL/min/1.73m^2: 2 mg alternate days

Dose should be halved in patients also taking an organic anion transporter 3 (OAT3) inhibitor such as probenecid.

At a local level, if the treating doctor feels that a dose reduction due to side effects is required then this is allowed.

Q. Can the Baricitinib tablets be cut in half?

A. Eli Lilly do not advise cutting the baricitinib tablets in half as these tablets are not scored.

Q. Can the Baricitinib tablets be dispersed in water for NG administration?

A. Yes. For patients unable to swallow whole baricitinib tablets – tablet(s) can be dispersed in a container with 10mL (5mL minimum) of room temperature water and dispersed with gently swirling. Take the contents orally immediately. The container should be rinsed with an additional 10mL (5mL minimum) of room temperature water and the entire contents swallowed by the patient.

For patients with a gastrostomy feeding tube – tablet(s) should be dispersed in a container with 15mL (10mL minimum) of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw entire contents from the container into an appropriate syringe and immediately administer. The container should be rinsed with 15mL (10mL minimum) of room temperature water, withdraw the contents into the syringe and administer through the tube

For patients with an enteral feeding tube – tablet(s) should be dispersed in a container with 30mL of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes (smaller than 12 Fr) the syringe can be held horizontally and shaken during administration. Rinse container with sufficient amount (minimum of 15mL) of room temperature water, withdraw the contents into the syringe and administer through the tube.

Tablets may be crushed to facilitate dispersion. It is not known if powder from the crushed tablets may constitute a reproductive hazard to the preparer. Use proper control measures (e.g. ventilated enclosure) or personal protective equipment (i.e. N95 respirator)

Dispersed tablets are stable in water for up to 4 hours.

Q. If patients are already on an immunosuppressive drug can they also be randomised to receive baricitinib?

A. Yes they can.

4 Empagliflozin

4.1 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.

4.2 Storage

As per SmPC

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

4.3 Dispensing quantities

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

4.4 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.

4.5 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.

5 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 baricitinib, dimethyl fumarate and empagliflozin from NHS England by completing a Blueteq form for each patient.

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 earlier than 10 days 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

Q. If a patient has suspected COVID-19, but the test results come back negative are they expected to come off the study?

A. If COVID swabs come back negative, but the treating clinician feels that clinically the patient does have COVID-19 then the patient can continue on study. However, the patient should stop if it is thought that the symptoms are due to another cause.

Q. What do we do with the remaining stock of dexamethasone, hydroxychloroquine, lopinavir/ritonavir and azithromycin?

A. The remaining stock of dexamethasone, hydroxychloroquine, azithromycin and tocilizumab can be moved into hospital's own stock, if appropriate. The remaining stock of lopinavir/ritonavir needs to be ring fenced and kept for now as there may be future UPH trials which may require it.

Q. What do we do with the remaining stock of REGN10933 and REGN10987?

A. All remaining stock of REGN10933 and REGN10987 should be returned to Regeneron. This includes stock which is beyond its given 'expiry' date. Contact the RECOVERY trial team for further instructions.