**RECOVERY TRIAL - CLINICAL INFORMATION**

Eligibility

* Adult patients (18+ years old) hospitalised with suspected or confirmed SARS-CoV-2 infection.

Prescriber

* Any doctor working within the hospital can prescribe for this study. They do not require GCP training and do not have to be on the delegation log; however they should have completed online Recovery study training.

Randomisation

* Randomisation will take place on a central web-based randomisation service and will be 2:1:1:1:1 to the following treatment arms
* The randomisation form should be **printed** and **attached** to the drug chart by the doctor or member of the research team doing the randomisation.

Prescription

* This will be prescribed on the drug chart using the stickers provided for standard dosing. Prescribers are permitted to modify or stop treatment if deemed to be in the patient’s best interest, this does not mean the patient must be withdrawn from the study as follow up can still continue.

Ordering a Supply

* Firstly check that the randomisation form matches the drug prescribed.
* Consider if a supply has been taken from the emergency drug cupboard (EDC) out of hours.
* If a supply needs to be ordered from the dispensary use the order form that has been created (unless there has been dose modification)
* Check the prescription on the drug chart matches the order form and tick the supply you need – send this to the dispensary
* Hospital stock of dexamethasone (all forms), hydrocortisone and prednisolone are to be used so if not already stock on the ward please request a supply of this – it does not need to be ordered via the order form or from dispensary. At some point trial specific dexamethasone will be provided at which point it will be ordered from dispensary.

Storage on the ward

* No temperature monitoring is required
* Keep IMPs (hydroxychloroquine, lopinavir/ritonavir, azithromycin) separate from ward stock to prevent RECOVERY medications being used for patients not part of the RECOVERY trial – this is not necessary for dexamethasone, hydrocortisone or prednisolone as using normal hospital stock (see above).

Out of Hours (On-Call)

* A small supply of all open treatment arms will be available in the EDC – this will be stored on the right hand side of the shelving, in a ‘RECOVERY’ box with a form for nursing staff to record what has been taken.
* Currently Kaletra liquid is not available therefore no items should be in the EDC fridge at this time however, once this becomes available a small supply will be available in a designated RECOVERY section of the EDC fridge.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Treatment Arm** | **Dose**  **All for 10 days or until discharge (whichever is sooner)** | **Notes** | **Contraindications & Cautions** | **Renal / Hepatic dose adjustments** | **Interactions** | **Side Effects** |
| **Arm 1 - Standard treatment** | n/a | n/a | n/a | n/a | n/a | n/a |
| **Arm 2 – Lopinavir/ Ritonavir** | 400mg / 100mg, BD, PO | If liquid is needed only 1 x 60ml bottle should be ordered and the patient should be switched to tablets as soon as possible due to stock shortages.  Tablets cannot be crushed and the liquid is incompatible with polyurethane feeding tubes so PVC or silicone tubes should be used (dieticians are aware of this).  Liquid contains 42% v/v alcohol – avoid metronidazole with this.  Liquid is stored in the fridge but once removed is stable for up to 42 days at <25oC.  Protocol states can be used in pregnancy. | C/I in severe liver impairment | No adjustment needed for renal impairment or dialysis.  No dose adjustment needed for mild – moderate hepatic impairment. | Lopinavir/Ritonavir should not be co-administered with medicines that are dependent on CYP3A for clearance.  Alfuzosin, amiodarone, ranolazine, neratinib, colchicine, quetiapine, simvastatin, sildenafil, midazolam, ergot alkaloids, St John’s wort. (see SmPC for full list)  **It is essential to check individual interactions**  **SEE LIVERPOOL DRUG INTERACTIONS &**  **http://www.covid19-druginteractions.org** | Common - diarrhoea, nausea, vomiting.  Upper respiratory infection, hypersensitivity, blood glucose and lipid disorders, anxiety, headache, dizziness, insomnia, hypertension, neuropathy, hepatitis, myalgia, fatigue. (see SmPC) |
| **Arm 3 –Azithromycin** | 500mg, OD, PO/IV | Protocol states can be used in pregnancy. | C/I in prolonged QT interval | No dose adjustment for renal impairment or patients on dialysis. | Antacids, digoxin (may increase levels).  Caution with other drugs that prolong QT interval. | Common – headache, diarrhoea, vomiting, abdominal pain, nausea, changes to WBC. |
| **Arm 4 - Dexamethasone** | 6mg, OD, IV/ PO | 6mg dose is of dexamethasone base therefore 6mg IV = 1.8ml of the 3.3mg/ml IV solution.  **In pregnant patients – PO prednisolone 40mg OD or IV hydrocortisone 80mg BD should be used.** | Patients on long term (2+ months) corticosteroids should be excluded from this arm as they may need increased dose due to sick day rules. | No dose adjustments required. | n/a | Hyperglycaemia |
| **Arm 5 - Hydroxychloroquine** | 800mg at 0 + 6 hours, then 400mg at 12 and 24 hours. Then 400mg 12 hourly thereafter. | No dose adjustment needed for body weight.  Tablets may be crushed and dispersed in water to give via NG or in swallowing difficulties.  Doses are much higher than those seen in the BNF and SmPC but are in line with doses used by the WHO.  Protocol states can be used in pregnancy. | Contraindicated in prolonged QT interval.  Caution with other drugs that prolong QT interval (macrolides, quinolones) – consider ECG to check QT interval.  SmPC states contraindicated in pregnancy however protocol states prophylaxis of choice as anti-malarial. | Trial states clinicians may reduce maintenance dose (do standard loading dose for first 24 hours) if eGFR < 30ml/min – including patients on dialysis. | Digoxin (increased levels), anti-diabetics (hypoglycaemia), antacids (reduce absorption), ciclosporin, tamoxifen. | Dyspepsia, nausea, vomiting (occasionally), visual disturbances, headache, urticaria.  Hypoglycaemia, rash, dizziness (uncommon), anorexia. (See SmPC for more) |

* Information in red is taken from the SmPC and not the trial protocol – see references below.
* Trial Protocol & Pharmacy Information is available at <https://www.recoverytrial.net/>
* For information on use in pregnancy see <https://www.recoverytrial.net/files/recovery-information-for-pregnant-patients-v1-0-final-080420.pdf>

References

Bristol Laboratories Ltd, 2017. Quinoric 200mg Film Coated Tablets. Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/product/477/smpc> [Accessed 03.04.20]

Abbvie Ltd, 2020. Kaletra 200mg / 50mg film coated tablets. Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/product/221/smpc> [Accessed 03.04.20]

Sandoz Limited, 2019. Azithromycin 500mg tablets. Summary of Product Characteristics. Available at: <https://www.medicines.org.uk/emc/product/6541/smpc> [Accessed 14.04.20]

The University of Oxford. Recovery Trial, Randomised Evaluation of COVID-19 Therapy. Protocol V3 (07.04.20). Available at: https://www.recoverytrial.net/files/recovery-protocol-v3-0-2020-04-07.pdf [Accessed 09.04.20]

The University of Oxford. Recovery Trial, Randomised Evaluation of COVID-19 Therapy. Recovery Clinical Trial Pharmacy Briefing Document – 07-04-20. Available at: https://www.recoverytrial.net/files/recovery-pharmacy-faqs-v3-0-final-2020-04-07.pdf [Accessed 09.04.20]

The University of Oxford. Recovery Trial, Randomised Evaluation of COVID-19 Therapy. Randomisation Intervention Sheet Lopinavir 400mg – Ritonavir 100mg. Available at: <https://www.recoverytrial.net/files/professional-downloads/recovery-intervention-sheet-lopinavir-ritonavir-v1-0.pdf> [Accessed 03.04.20]

The University of Oxford. Recovery Trial, Randomised Evaluation of COVID-19 Therapy. Randomisation Intervention Sheet Hydroxychloroquine. Available at: <https://www.recoverytrial.net/files/recovery-intervention-sheet-hydroxychloroquine-v2-0.pdf> [Accessed 03.04.20]

The University of Oxford. Recovery Trial, Randomised Evaluation of COVID-19 Therapy. Randomisation Intervention Sheet Dexamethasone. Available at: <https://www.recoverytrial.net/files/professional-downloads/recovery-intervention-sheet-dexamethasone-v2-0.pdf> [Accessed 03.04.20]

The University of Oxford. Recovery Trial. Randomised Evaluation of COVID-19 Therapy. Information for Managing Patients with Chronic Kidney Disease. Available at: <https://www.recoverytrial.net/files/recovery-ckd-v1-0-final080420.pdf> [Accessed 14.04.20]

The University of Oxford. Recovery Trial. Randomised Evaluation of COVID-19 Therapy. For Pregnant and Post-Partum Women. Available at: https://www.recoverytrial.net/files/recovery-information-for-pregnant-patients-v1-0-final-080420.pdf [Accessed 14.04.20]