Covid-19 treatments

NB: Figures for numbers needed to treat (NNT) have been calculated within this document. This is intended to provide context to the expected benefits, and a very approximate estimate of how many patients would need to be treated to see a benefit. It is not appropriate to use these figures to compare the efficacy of each treatment. Each NNT figure is wholly reliant on the study it is derived from, and the studies are not directly comparable.

Casirivimab and Imdevimab (Ronapreve) and Molnupiravir

Casirivimab and imdevimab (Ronapreve) is an IV infusion of two neutralising antibodies. The product has been available in the UK since September. Uptake has been slow, for a number of reasons.

Until recently, Ronapreve candidates needed to hospitalised with Covid-related symptoms, aged over 50 (unless immunocompromised, in which case all adults are candidates), and found to be negative for anti-S antibodies. This is a monoclonal antibody and preparation is complex.

Many restrictions have now been lifted, and from the 16th December Ronapreve may be used in symptomatic Covid positive patients in high risk groups in Primary Care. Should we wish to use it in this way, some consideration is required as to how Manx Care would be able to deliver this therapy. The best option would be to use IV trained district nursing staff rather than transport a symptomatic covid positive patient to a hub. Patient numbers are difficult to predict, and capacity of nursing staff would need to be considered.

Supplies are available to us free of charge, but we would be allocated a quota in line with UK healthcare settings. Supplies are short-dated and until now there seemed to be no appetite to use it locally. We have ordered and received a small supply within Acute, but only to be prepared should there be a request to use it within Acute at short notice. The product has not yet been used on the Isle of Man. There are risks with its use, as follows:

- **The expiry date needs to be amended**. We have procedures to overlabel the box within Pharmacy, but the original expiry will still be present on the vials themselves.
- **The packaging is confusing**, describing the product as 120mg/mL, and 6mL vials. In fact each vial only contains 2.5mL of medication, but has a 6mL capacity.
- **The packaging is unbranded**; the name 'Ronapreve' does not appear.

Efficacy

The SPC describes a trial evaluating Ronapreve in symptomatic outpatients with Covid-19 who were not hospitalised [Weinreich, attached]. 3% of those on placebo were admitted to hospital or died (any cause) within 29 days of treatment while 1% of those who received Ronapreve were admitted to hospital or died (any cause) within 29 days of treatment.

Looking at the data, this would mean 44 patients would need to be treated with Ronapreve to avoid one incident of hospitalisation or death [calculation in Appendix].

In symptomatic patients, the median time to symptom resolution was 10 days in the active group and 14 days in the placebo group.

UK guidance is available at https://www.england.nhs.uk/coronavirus/wp-content/uploads/sites/52/2021/09/C1421-interim-cc-policy-casirivimab-imdevimab-hospitalised-patients.pdf , and the SPC is available at https://www.medicines.org.uk/emc/product/12863/smpc

Molnupiravir (brand: Lagevrio) is an oral antiviral given twice a day for a 5 day course. Suitable candidates are Covid positive adults in high risk groups who present within 5 days of onset of their symptoms. As an oral therapy, this avoids the need for patients to come to Noble's for administration. It is being positioned as an alternative to Ronapreve in Primary Care where Ronapreve itself is not suitable or impractical.

Molnupiravir has demonstrated reproductive toxicity in animals. It should be avoided during pregnancy, and patients should use contraception during treatment and for 4 days after the last dose. There is no pregnancy prevention programme in place as such, so no requirement for a pregnancy test prior to use, but careful counselling is required to avoid risk.

Molnupiravir will also be available free of charge. We have been allocated 190 courses of treatment initially, and we expect to receive this imminently. Further supplies will be available into 2022.

Efficacy

The SPC describes a trial in which symptomatic adult patients with one or more risk factors were treated with molnupiravir or placebo. 7.3% of the active group experienced all-cause hospitalisation or death, while 14.1% of the placebo group experienced all-cause hospitalisation or death within 29 days.

We don't have access to a published paper, but relying on these figures from the SPC, this would mean 15 patients would need to be treated with molnupiravir in order to avoid one incident of hospitalisation or death [Calculation in Appendix]

Guidance for Primary Care which covers both Ronapreve and molnupiravir is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103184

The SPC for molnupiravir is available at https://www.medicines.org.uk/emc/product/13044

There is a draft SOP which is circulated separately for comment.

Decisions required - Ronapreve	
Do we pursue a policy for use within Acute?	Yes/No
If YES, comments on the attached SOP please.	
Do we pursue a policy for use in Primary Care?	Yes/No
If YES, delivery would be contingent on further discussion regarding capacity to deliver.	

Decisions required – Molnupiravir	
Do we pursue a policy for use in Primary Care?	Yes/No
If YES, how would supplies be managed?	

Sarilumab

This is an alternative to tocilizumab. Tocilizumab is commonly used in Covid inpatients but it is in short supply globally, and hospitals in the UK have been encouraged to switch to the similar agent sarilumab where possible as the supply of sarilumab was felt to be more reliable. However, sarilumab is now also in short supply.

Sarilumab is an unfamiliar product, presented in a plain white carton with no information leaflet, so there are risks in its use. We have never used it on the Isle of Man. Sarilumab costs £145.72 for 2 prefilled syringes. Both syringes would be required for a single dose.

Both sarilumab and tocilizumab are used in Rheumatology as well as in Covid. We use tocilizumab but we have no experience with sarilumab.
If we use sarilumab a guideline would need to be approved, but this might offer some resilience in the event that tocilizumab becomes unavailable.

UK Guidance is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAttachment.aspx?Attachment_id=103774 , and the SPC is at https://www.medicines.org.uk/emc/product/8144/smpc .

Decisions required – Sarilumab	
Do we pursue this as a treatment option?	Yes/No

Sotrovimab

Sotrovimab (Xevudy) is a monoclonal antibody given as an IV infusion over 30 minutes.

We have been allocated and received 19 x 500mg doses of sotrovimab. Initially, it would be expected to be used for high risk patients in Primary Care with active mild to moderate Covid symptoms, although it is also likely to find a place within the inpatient population. Similarly to the use of Ronapreve, this is a complex IV therapy and would require nursing support to allow it to be delivered. As with Ronapreve, this would present practical challenges.

Efficacy

The key paper described in the SPC is only available in a pre-published format (not peer reviewed). This is attached.

528 patients were randomised to receive sotrovimab. 6 (1%) were hospitalised for >24 hours for any reason or died from any cause within 29 days.

529 patients were randomised to receive placebo. 30 (6%) were hospitalised for >24 hours for any reason or died from any cause within 29 days.

This means that 22 patients would need to be treated with sotrovimab to avoid one incident of hospitalisation or death [calculation in Appendix].

UK Guidance is available at https://www.cas.mhra.gov.uk/ViewandAcknowledgment/ViewAlert.aspx?AlertID=103186 . The SPC is available at https://www.medicines.org.uk/emc/product/13097.

Decisions required - Sotrovimab	
Do we consider pursuing a policy for use in Primary Care (Primary Care administration)?	Yes/No
If YES, delivery would be contingent on further discussion regarding capacity to deliver.	
Do we consider pursuing a policy for use in Acute (bringing patients to Nobles for administration)?	Yes/No
If YES, comments on the attached SOP please. This is intended for Paediatrics, but the niche for adults is identical and it could easily be expanded to include the Adult Service.	

Appendix – Calculations

Ronapreve

From Weinreich paper, the Ronapreve 1200mg population consisted of 748 patients, and there were 7 primary outcome events (0.951% risk).
The placebo population consisted of 748 patients, and there were 24 primary outcomes (3.21% risk).

Absolute risk reduction = 0.0321 – 0.00951 = 0.0226
Number needed to treat = 1/0.0226 = 44 (rounded to nearest whole number)

Molnupiravir

From SPC:
There were 385 patients in the active group, and there were 28 primary events (7.3% risk).
There were 377 placebo patients, and 53 primary events in this group (14.1%).

Absolute risk reduction = 0.1406 – 0.0728 = 0.0679
Number needed to treat = 1/0.0679 = 15 (rounded to nearest whole number)

Sotrovimab

From SPC:
There were 528 patients in the active group, and there were 6 primary events (1.136% risk)
There were 529 placebo patients, and 30 primary events in this group (5.671% risk)

Absolute risk reduction = 0.05671 – 0.01136 = 0.04535
Number needed to treat = 1/0.04535 = 22 (rounded to nearest whole number).