Interim Recommendation on Clinical Management of Adult Cases with Coronavirus Disease 2019 (COVID-19)

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1. Purpose

1.1. To provide guidance on clinical management of patients with Coronavirus Disease 2019 (COVID-19)

2. Scope

2.1. For all healthcare workers at Hospital Authority

3. Introduction

3.1. A new strain of coronavirus (SARS-CoV-2) which has not been previously identified in human, was reported in Wuhan, China in December 2019. It belongs to a clade of betacoronavirus distinct from those associated with human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). Coronavirus Disease 2019 (COVID-19) causes acute respiratory infection and pneumonia. Symptoms include fever, malaise, dry cough, shortness of breath, anosmia and ageusia. Some patients may have respiratory symptoms without fever and some patients may also have diarrhea. People of older age or having underlying chronic disease are at a higher risk of deterioration into serious condition.

4. Surveillance and reporting criteria

4.1. Please report suspected cases fulfilling the reporting criteria of Coronavirus Disease 2019 (COVID-19) to the Central Notification Office (CENO) of CHP via fax (2477 2770), phone (2477 2772) or CENO On-line (https://cdis.chp.gov.hk/CDIS_CENO_ONLINE/ceno.html). The case definition is available on the above website of CENO On-line. Both reporting criteria and case definition are subject to change upon availability of further epidemiological, clinical and virological data.

5. Clinical Management

5.1. Isolate the patient(s) in airborne infection isolation room (AIIR) with standard, contact, droplet and airborne precautions

5.2. Notify via NDORS/ eNID, and update the confirmed patient data when necessary

5.3. Patient clinical severity

Category	Description
Satisfactory	Progressing well and likely to be discharged soon
Stable	With mild influenza-like illness symptoms
Serious	Require oxygen supplement of 3 to 6 L/min
Critical	Require intubation, ECMO, in shock, high flow oxygen with flow rate > 6 L/min

5.4. Diagnosis:

- Diagnosis can be established by either Rapid Antigen Test (RAT) or RT-PCR of SARS-CoV-2.
- For RAT, please follow manufacturer's instructions to perform the test and interpret the result.
- Specimens for RT-PCR of SARS-CoV-2
  - Lower respiratory tract (always preferred): sputum or tracheal aspirate (TA) if intubated or bronchoalveolar lavage (BAL) (if bronchoscopy)

  OR
  - Upper respiratory tract: Nasopharyngeal Flocked swab (NPFS) or Nasopharyngeal Aspirate (NPA) [Pooled with throat swab in viral transport medium] or Deep throat saliva (DTS)
  - Stool: For patient fulfilling reporting criteria with diarrhea, stool can be sent to PHLSB for RT-PCR for SARS-CoV-2 testing
- Repeated testing may be necessary to exclude the diagnosis. Please consult the clinical microbiologists or infectious disease physicians for advice
- If patient has any stool sample being tested positive for SARS-CoV-2 previously, contact precaution should be maintained until negative result from stool has been obtained
- Microbiological workup as appropriate, e.g.
  - Sputum, urine and blood culture
  - NPA +/- Tracheal aspirate for flu A/B and other respiratory viruses
  - NPA +/- Tracheal aspirate for atypical pneumonia PCR
  - Urine for legionella and pneumococcal antigen
- Other investigations e.g. CBP with D/C, L/RFT, CaPO4, glucose, ESR,

CRP, procalcitonin, CXR and ECG, etc.

5.5. Monitor vital signs and organ functions, and recognize complication(s) early

5.6. Liaise with ICU early for intensive care if anticipate clinical deterioration

5.7. Provide supportive treatments

- Monitor for any concomitant bacterial infections and start empirical antibiotics if necessary
- β lactam/β-lactamase inhibitor combination or 3rd generation cephalosporin +/- macrolide/doxycycline can be considered
- Oxygen
- IV fluid (conservative fluid management for severe respiratory failure)
- Hemodynamic support
- High-flow nasal oxygen (HFNO) may be considered in selected patients with hypoxemic respiratory failure. These patients should be closed monitored for clinical deterioration.
- Mechanical ventilation with protective lung ventilation +/- consider ECMO for refractory respiratory failure
- Renal replacement therapy (renal failure)
- Consider proton pump inhibitors (PPI) for stress ulcer prophylaxis for prevention of GI bleeding per clinical judgment of ID physician/ Intensivist for moderate to severe cases

5.8. Anticoagulation

- In patients hospitalized with COVID-19, use pharmacological prophylaxis, such as low molecular weight heparin (such as enoxaparin 40mg Q24H subcutaneous, according to local and international standards, to prevent venous thromboembolism, when not contraindicated. For those with contraindications, consider mechanical prophylaxis (intermittent pneumatic compression devices)

6. <u>Use of Specific anti-COVID-19 treatments</u>

6.1. Unlicensed treatment should be given under ethically-approved clinical trials

as far as possible. In the absence of appropriate clinical trials, the following treatment regimens may be considered early, particularly in patients having following conditions with increased risk of severe disease

- Diabetes mellitus
- Obesity (body mass index [BMI of 30kg/m^2 or higher])
- Age ≥60 years (unless otherwise specified)
- Immunocompromised state
- Underlying chronic illnesses
- Incomplete COVID-19 vaccination #

6.2. The following table summarizes different available treatment regimens. These regimens are determined based on evidence extrapolated from research performed for other coronaviruses, expert opinion, non-randomized placebo controlled trials, case series and limited randomized placebo controlled trials on treatment of COVID19, as well as the availability of therapeutics in Hong Kong. This serves as an interim guidance and will be updated according to the availability of new evidence or drug availability.

Proposed Therapeutic management of adults with COVID-19 based on disease severity

Mild symptoms, but at risk of disease progression

- ***For patients who are at risk of progressing to severe COVID-19 and at early onset of disease (within 5 days):***
- Paxlovid (preferred if not contraindicated) or Molnupiravir
- Amubarvimab/romlusevimab (within 10 days)
- +/- can consider Interferon Beta-1b sc

Moderate symptoms and requiries supplemental oxygen (SaO2 <94% RA)

- ***Use one of the following options:***
- Remdesivir (3-5 days) + dexamethasone; or
- Dexamethasone;
- +/- Interferon Beta-1b sc

- *Use of remdesivir depending on the disease stage, guided by symptom onset and CT value*

Moderate to severe symptoms and requiring oxygen through a high-flow device or NIV

- ***Use one of the following options:***
- Remdesivir (3-5 days) + dexamethasone; or
- Dexamethasone;

- *Use of remdesivir depending on the disease stage, guided by symptom onset and CT value*
- ***For patients with rapidly increasing oxygen needs and systemic inflammation***, consider add either **baricitinib** or **IV tocilizumab** to 1 of the 2 options above

Critical disease and requires mechanical ventilation or ECMO

- Dexamethasone

- ***For patients who are within 24 hours of admission to ICU:***
- Dexamethasone + IV tocilizumab

6.3. Paxlovid (nirmatrelvir/ritonavir)

- Paxlovid is a combination of nirmatrelvir, a SARS-CoV-2 main protease inhibitor that prevents viral replication, and ritonavir, an HIV-1 protease inhibitor and CYP3A inhibitor that is not active against SARS-CoV-2 but inhibits the metabolism of nirmatrelvir resulting in increased plasma concentration of nirmatrelvir.
- Dosage and administration: 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet), with all three tablets taken together twice daily for 5 days.
- Pregnancy consideration: There are no available human data on the use of nirmatrelvir during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Published observational studies on ritonavir use in pregnant women have not identified an increase in the risk of major birth defects. Published studies with ritonavir are insufficient to identify a drug-associated risk of miscarriage. There are maternal and fetal risks associated with untreated COVID-19 in pregnancy. The use of nirmatrelvir and ritonavir should not be withheld from pregnant patients when the potential benefits outweigh the possible risks (NIH 2022)
- Females and Males of Reproductive Potential: use of ritonavir may reduce the efficacy of combined hormonal contraceptives. Advise patients using combined hormonal contraceptives to use an effective alternative contraceptive method or an additional barrier method of contraception
- Breastfeeding consideration: Ritonavir is present in breast milk; excretion of nirmatrelvir is unknown. Lactation is not a contraindication for use (ACOG 2022; FDA 2021). According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother (FDA 2021)
- Warnings and precautions:
  - The concomitant use of Paxlovid and certain other drugs may result in potentially significant drug interactions. Consult the full prescribing information prior to and during treatment for potential drug interactions. (Annex A)

- Allergic Reactions/Hypersensitivity: Hypersensitivity reactions have been reported with Paxlovid. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue Paxlovid and initiate appropriate medications and/or supportive care.
- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients receiving ritonavir.
- HIV-1 Drug Resistance: Paxlovid use may lead to a risk of HIV-1 developing resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection

➢ Adverse reactions
- Dysgeusia, diarrhea, hypertension, and myalgia.

➢ Renal impairment: dose reduction for moderate renal impairment (eGFR ≥30 to <60 mL/min): 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet), with both tablets taken together twice daily for 5 days. Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 mL/min)
- From operational perspectives, the most recent eGFR result within 1 year can be used as reference. For patients without recent eGFR result available and without known renal impairment, it is reasonable to prescribe normal dose given the relatively high safety margin of the drug.

➢ Hepatic impairment: Paxlovid is not recommend in patients with severe hepatic impairment (Child-Pugh Class C).

➢ Paxlovid may be used in paediatric patients (12 years of age and older weighing at least 40 kg). Please refer to paediatric guidelines for dosage.

➢ Criteria for use
- Age ≥ 60 years (regardless of vaccination status), OR
- Age < 60 years with high risk factors (Annex B) AND incomplete vaccination [#], OR
- Severely immunocompromised individuals [@] (regardless of vaccination status)

➢ Clinical consideration
- Within 5 days of symptom onset, AND
- Test positive (RAT/PCR), AND

- SpO2 > 94% (room air)

➢ Exclusion criteria

- Patients less than 12 years of age or weighing below 40 kg (for 12-17 years of age)

6.4. Molnupiravir

➢ Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis.

➢ Dosage and administration: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.

➢ Pregnancy consideration: Based on findings from animal reproduction studies, molnupiravir may cause fetal harm when administered to pregnant individuals. The use of molnupiravir is NOT recommended during pregnancy. Advise individuals of childbearing potential to use effective contraception correctly and consistently, as applicable, for the duration of treatment and for 4 days after the last dose of molnupiravir.

➢ For sexually active males with partners of childbearing potential, they are advised to use a reliable method of contraception correctly and consistently during treatment and for at least 3 months after the last dose of molnupiravir (the risk beyond three months after the last dose of molnupiravir is currently unknown).

➢ Breastfeeding consideration: The use of molnupiravir is NOT recommended for breastfeeding women.

➢ Warnings and precautions:

- Embryo-fetal toxicity
- Hypersensitivity, anaphylaxis, angioedema, erythema, rash, and urticaria adverse reactions have been identified during post-authorization use of molnupiravir.
- Bone and cartilage toxicity: Molnupiravir should not be used in patients less than 18 years of age because it may affect bone and cartilage growth.

➢ Adverse reactions

- Diarrhea, dizziness, headache, skin itchiness, skin rash, nausea, vomiting.
- Laboratory abnormalities in chemistry (ALT, AST, creatinine, and

lipase) and hematology (haemoglobin, platelets, and leukocytes)

- Renal impairment: No dosage adjustment in patients with any degree of renal impairment is recommended. The pharmacokinetics of molnupiravir and its metabolite NHC has not been evaluated in patients with eGFR less than 30 mL/min/1.73m^2 or on dialysis.
- Hepatic impairment: No dosage adjustment in patients with hepatic impairment is recommended. The pharmacokinetics of molnupiravir and its metabolite NHC has not been evaluated in patients with moderate and severe hepatic impairment.
- Molnupiravir has not been studied in paediatric patients.
- Criteria for use
  - Age ≥ 60 years (regardless of vaccination status), OR
  - Age < 60 years with high risk factors (Annex B) AND incomplete vaccination [#], OR
  - Severely immunocompromised individuals [@] (regardless of vaccination status)
- Clinical consideration
  - Within 5 days of symptom onset, AND
  - Test positive (RAT/PCR), AND
  - SpO2 > 94% (room air)
- Exclusion criteria
  - Pregnancy
  - Breastfeeding
  - Patients less than 18 years of age

6.5. Remdesivir

- Remdesivir is an antiviral and inhibits SARS-CoV-2 RNA polymerase which perturbs viral replication. Remdesivir is given intravenously, once daily after an initial loading dose.
- 3-5-day course for moderate to severe cases

  (i) Eligibility criteria:

- Hospitalized with coronavirus disease 2019 (COVID-19) AND
- Adults, and adolescents >=12 years of age and >= 40kg AND
- eGFR based on Cockcroft-Gault equation >= 30ml/min AND
- ALT below 5 times the upper limit normal at baseline

With

- pneumonia and SaO2 <94% on room air requiring supplemental oxygen
  AND
- Clinical deterioration with impending respiratory failure
- DTS or NPS+TS or sputum RT-PCR CTv <25

(ii) Dosage: 200mg IV loading dose following by 100mg IV daily as maintenance. The total duration of treatment should be 3-5 days

(iii) Remdesivir should be sensibly used in cases with better recovery potential and quality of life after recovery, in view of limited drug supply

(iv) Pregnancy: Remdesivir should be avoided in pregnancy unless clinicians believe the benefits of treatment outweigh the risks to the individual

(v) Obtain consent for treatment. Major side effects: Phlebitis, Nausea, vomiting, ALT elevations, hyperglycemia, hyperbilirubinemia, hypersensitivity reactions, bradycardia

(vi) Coadministration of remdesivir and interferon beta-1b may be considered in the discretion of ID physicians, particularly in severe patients with early onset of disease

(vii) Stopping criteria:
Remdesivir should be discontinued in patients who develop any of the following:

- ALT >= 5 times ULN during treatment with remdesivir
- ALT elevation accompanied by signs and symptoms of liver inflammation or increasing conjugated bilirubin, alkaline

phosphates, or INR

(viii) For patients with eGFR< 30ml/min: the benefit of using remdesivir may outweigh the risk in selected patients. In such scenario, the use of remdesivir is left to the discretion of Infectious Diseases Physician in charge.

(ix) Remdesivir is considered if meeting the above criteria and if available. Some data suggest remdesivir may reduce time to recovery and risk of mechanical ventilation. IDSA and the NIH recommend remdesivir but WHO conditionally recommend against remdesivir because a definitive mortality benefit has not been shown.

6.6. Interferon-based regimen

➢ May consider the following regimen in confirmed patients who are at risk of disease progression

Interferon beta-1b 0.25mg (8-16 MIU) subcutaneous daily* (3 doses)

➢ Pre-treatment workup

- Check blood x CBP, LRFT, RG, LDH, CK, HBsAg, anti-HCV,
- + blood x TFT, ANA (for starting interferon)
- CXR
- ECG (if preexisting cardiac abnormalities or disease or clinically indicated). For patients with underlying pre-existing cardiac problems, follow-up monitoring of the cardiac condition is suggested.
- Pregnancy test for females with reproductive potential (Before starting interferon or molnupiravir)
- Avoid pregnancy in female patients and female partners of male patients during and after molnupiravir therapy
- Check any drug interactions with concomitant medications (in particular, with ritonavir)
- Obtain consent for treatment
  (i) Unlicensed indication and treatment is experimental

(ii) Side effects of treatment

(iii) Contraindications:

- Interferon beta-1b: history of hypersensitivity to interferon beta, albumin; decompensated liver disease, current severe depression and/or suicidal ideation
- Molnupiravir: pregnancy, breastfeeding

(iv) For pregnant women, detailed explanation on the benefits and potential risks should be provided before the commencement of interferon beta-1b

(v) For mentally incapacitated patients, may communicate with next of kin and attain consent from them with proper documentation.

*Dosing and frequency of interferon beta 1b can be adjusted at the discretion of the Infectious Diseases Physician in charge

6.7. Amubarvimab/romlusevimab (BRII-196/198)

- Amubarvimab/romlusevimab is a human immunoglobulin G-1 (IgG1-λ) monoclonal antibody cocktail that target the RBD of Spike protein of SARS-CoV-2 with neutralizing action.
- Dosage and administration
  - For adults and adolescents (12-17 years old, body weight ≥40kg) dose of amubarvimab/romlusevimab is 1000mg respectively.
  - Each must be diluted with 100ml normal saline, before infusion by intravenous route, at a rate of not more than 4ml/min
  - Administer amubarvimab first, followed immediately by romlusevimab. In case romlusevimab is given first, amubarvimab can be immediately given afterwards.
- Pregnancy consideration
  - There are no available human data on the use of this drug during pregnancy to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Amubarvimab/romlusevimab should be used only when clinicians believe the benefits of treatment outweighs the risk to the individual
- Breastfeeding consideration

- No data on presence or excretion of amubarvimab/romlusevimab in human or animal breast milk. According to manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and the benefits of treatment to the mother.

➢ Contraindication

- History of clinically significant hypersensitivity reactions to the active ingredients (amubarvimab/romlusevimab) or any other components

➢ Warnings and Precautions

- For the target group of adolescents at 12-17 years of age and body weight ≥40kg, the approval of use is conditional as no clinical data on efficacy and safety is available for confirmation at this stage
- Allergic reactions
  - ➢ Hypersensitivity reactions have been reported with amubarvimab/romlusevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue amubarvimab/romlusevimab and initiate appropriate medical and/or supportive care.
- Infusion-related reactions
  - ➢ During infusion and within 24 hours post-infusion, observe for infusion-related reactions that may be severe or potentially life-threatening, including:
    - Pyrexia, dyspnea, desaturation, chills, fatigue, arrhythmia, chest pain, change in mental status, nausea, headache, bronchospasm, hypotension, hypertension, vasogenic edema, rash, pruritis, myalgia, vasovagal reactions, dizziness, profuse sweating.
  - ➢ If infusion-related reactions occur, consider slowing down or stop the infusion, and initiate appropriate medical and/or supportive care.
- There have been reports of post monoclonal antibody treatment of COVID-19 clinical deterioration, including fever, desaturation,

dyspnea, arrhythmia, malaise, change in mental status, etc. Some of them have led to hospitalization for treatment. It is not known if these events are related to the use of monoclonal antibody or due to natural progression of COVID-19 infection.

- Adverse reactions
  - Treatment-emergent adverse events occurring in ≥1% of participants in the ACTIV-2 Study through day 28 include:
    - Diarrhea, nausea, vomiting, fatigue, pyrexia, chills, COVID-19 pneumonia, bronchitis, infusion-related reactions, blood pressure increase, myalgia, headache, insomnia, oropharyngeal pain, cough, dyspnea, rhinorrhea and hypertension.
- Renal impairment:
  - The effect of renal impairment on amubarvimab/romlusevimab pharmacokinetics is still unknown
- Hepatic impairment
  - The effect of hepatic impairment on amubarvimab/romlusevimab pharmacokinetics is still unknown
- Paediatric patients
  - Amubarvimab/romlusevimab is not yet approved for <12 years of age or body weight <40kg. Amubarvimab/romlusevimab is conditionally approved for adolescents of 12-17 years of age and body weight ≥40kg without clinical trial data. Safety and efficacy in paediatric patients have not been evaluated yet.
- Geriatric patients
  - It is not known if the pharmacokinetics of amubarvimab/romlusevimab differ between geriatric and younger adult patients.
- Drug-drug interaction is unlikely given that amubarvimab/romlusevimab is not expected to be renally excreted nor metabolized by the Cytochrome P450 system
- Criteria for use
  - The use of amubarvimab/romlusevimab can be considered in patients with confirmed COVID-19 infection (by RAT or PCR) at mild to moderate severity with risk factors for progression to severe

disease and within 10 days of symptom onset.

- The risk factors for progression to severe disease include the following medical conditions according to manufacturer:
  - Age ≥60
  - Smoker
  - Immunosuppressed
  - Cirrhosis
  - Cancer
  - Obesity (defined as BMI>30kg/m2 for adults)
  - Pregnancy
  - Chronic kidney disease
  - Diabetes mellitus
  - Cardiovascular disease or hypertension
  - Chronic lung disease
  - Sickle cell disease
  - Neurodevelopmental disorder, inherited metabolic diseases
  - Patients on medical support e.g. tracheostomy, positive pressure ventilation unrelated to COVID-19
  - Other illnesses or conditions on an individual risk-benefit assessment basis
- Monoclonal antibody should be used at the discretion of ID physicians.

6.8. Corticosteroids

- Consider dexamethasone 6mg daily PO/IV up to 10 days in patients with pneumonia, and requiring oxygen supplement or invasive mechanical ventilation, Prolonged duration or higher dose of dexamethasone may be considered according to individual clinical condition
- Equivalent total daily doses of alternative glucocorticoids are methylprednisolone 32mg and prednisolone 40mg
- Dexamethasone may cause hyperglycemia, viral rebound of SARS-CoV-2 and increased risk of bacterial, fungal and parasitic infections
- Use of short-period, stress dose steroids (hydrocortisone 200mg max daily) for refractory septic shock or other clinical indications on

physician discretion

6.9. Tocilizumab

- Monoclonal antibody to IL6 receptor
- There are data from clinical trials suggesting use of tocilizumab in combination with dexamethasone in certain hospitalized patients who are exhibiting rapid respiratory decompensation due to COVID-19, including:
  - Recently hospitalized patients (i.e. within first 3 days of admission) who have been admitted to intensive care unit (ICU) within the prior 24 hours and who require invasive mechanical ventilation, noninvasive ventilation, or high-flow nasal cannula (HFNC) oxygen (>0.4 FiO2/ 30L/min of oxygen flow) or
  - Recently hospitalized patients (i.e. within first 3 days of admission) not admitted to the ICU who have rapidly increasing oxygen needs and require noninvasive ventilation or HFNC oxygen and who have significantly increased markers of inflammation (CRP >=75mg/L)
- Dose: 8mg/kg (Max: 800mg/dose), one dose
- Use at the discretion of Infectious Disease (ID) Physician and intensivist for severe patients with evidence of cytokines release syndrome (Supported by elevated inflammatory markers like CRP, d-dimer, ferritin, etc)
- Major side effects: hypertension, increased ALT, injection site infections, risk of opportunistic infections particularly bacterial, anaemia; serious side effects: gastrointestinal perforation, neutropenia
- Live vaccines should be avoided for at least 3 months, after commencement of tocilizumab.

6.10. Baricitinib

- An orally administered, selective inhibitor of Janus Kinase (JAK) 1 and 2. Baricitinib inhibits the intracellular signaling pathway of cytokines known to be elevated in severe COVID-19.
- Among hospitalized adults with severe COVID-19 having elevated inflammatory markers but not on invasive mechanical ventilation,

concomitant use of baricitinib with remdesivir can be considered. Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high flow oxygen or non-invasive ventilation at baseline. The benefits for persons on mechanical ventilation are uncertain.

- Dosing: oral 4mg once daily for up to 14 days of treatment or until hospital discharge, whichever is first. Longer duration can be considered at the discretion of ID physician/ ICU intensivist.
- Renal adjustment: oral 2mg daily (30 to <60 ml/min), 1mg daily (15 to <30 ml/min)
- Use in combination with remdesivir. Limited information on the use of baricitinib in combination with systemic corticosteroids. Consider use at ID physician's discretion
- Potential side effects: Infection (particularly upper respiratory tract infection, herpes zoster), nausea, raised ALT, neutropenia, arterial thrombosis, malignant lymphoma (<1%), malignant neoplasm (<1%)
- Not recommended for patients on dialysis, having eGFR <15ml/min, having acute kidney injury, or having known active tuberculosis
- Pregnancy: Should be used during pregnancy only if potential benefit justifies the potential risk for the mother and the fetus
- Avoid use of live vaccines with baricitinib
- Monitoring: CBP, LRFT (Consider interruption if ALC <0.2 or ANC <0.5)

6.11. Casirivimab and imdevimab

- Anti-SARS-CoV-2 monoclonal antibody products currently have Emergency Use Authorizations (EUAs) from the Food and Drug Administration (FDA) for the treatment of mild to moderate COVID-19 patients who are at risk of progressing to severe disease and/or hospitalization.
- Casirivimab and imdevimab: These are recombinant human monoclonal antibodies that bind to nonoverlapping epitopes of the spike protein RBD of SARS-CoV-2.
- Dosing: Casirivimab 600mg plus imdevimab 600mg intravenous infusions for one dose. If intravenous route is not feasible, administration by four subcutaneous injections (2.5ml per injection) can be used as an alternative.

- The use of casirivimab and imdevimab can be considered in patients with mild to moderate severity, at risk of progression to severe COVID-19 infection and with a confirmed delta variant strain
- Medical conditions or other factors that were represented in clinical trials that evaluated anti-SARS-CoV-2 monoclonal antibodies
  - Age >=65
  - Obesity (BMI >30)
  - Diabetes
  - Cardiovascular disease (including congenital heart disease) or hypertension
  - Chronic lung disease (e.g. COPD, moderate to severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- Monoclonal antibodies should be used at discretion of ID physicians, particularly for other conditions or factors at risk of progressing into severe disease.
- Side effects: Uncommon (up to 1 %): allergic reactions or reactions following infusions: fever, chills, headache, difficulty breathing, hypotension, facial swelling, itching, myalgia
- Pregnancy: The safety for use in pregnancy is inadequate. Use if potential benefits of treatment outweigh the potential risks to the mother and fetus.

6.12. Monitoring during treatment

- Blood x CBP, LRFT, LDH, CRP
- Repeat DTS (or other respiratory specimens) x SARS-CoV-2 twice, 24 hours apart before isolation release
- Repeat Stool x SARS-CoV-2 if there are previous positive results before isolation release
- Monitor for any concomitant bacterial or fungal infections
- Observe for any side effects

7. Release from Isolation

Please refer to updated criteria for releasing confirmed COVID-19 patients from isolation by CHP and HA

8. Follow-up arrangement

8.1. Follow-up arrangement should be subject to parent team's decision. In general, patients who developed pneumonia or complications during hospitalization should be monitored for any long term sequelae from COVID-19 infection

8.2. Consider refer regional specialist clinic follow-up for patients who

- are still symptomatic on discharge OR
- had abnormal radiological changes for further review OR
- had grossly abnormal biochemical parameters on date of discharge

8.3. Subject to patient's need, referral may be sent to clinical psychologist, medical social worker, physiotherapist, occupational therapist, traditional Chinese medicine practitioner or District Health Centre

8.4. Monitoring during follow-up

- Blood tests (e.g. CBP, LRFT, CRP) +/- 2 clotted blood for SARS-CoV2 antibody if not taken previously
- CXR
- Consider lung function tests for moderate to severe cases
- Consider HRCT for cases with residual lung changes

Individuals aged 18 years or above, including pregnant and breastfeeding women, are recommended to receive three doses of COVID-19 vaccine (i.e. Comirnaty vaccine or CoronaVac vaccine). (Source: Consensus Interim Recommendations on the Use of COVID-19 Vaccines in Hong Kong (As of 6 April 2022). Available at https://www.chp.gov.hk/files/pdf/consensus_interim_recommendations_on_the_use_of_covid19_vaccines_in_hong_kong_6_apr.pdf

@ Medical conditions or treatments that may result in severe immunocompromise include but are not limited to:

- Active treatment for solid tumor and hematologic malignancies
- Receipt of solid-organ transplant and taking immunosuppressive therapy
- Receipt of chimeric antigen receptor (CAR)-T-cell or hematopoietic stem cell transplant (within 2 years of transplantation or taking immunosuppression therapy)
- Moderate or severe primary immunodeficiency (e.g., DiGeorge syndrome, Wiskott-Aldrich syndrome)

- Advanced or untreated HIV infection (people with HIV and CD4 cell counts <200/mm3, history of an AIDS-defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV)
- Active treatment with high-dose corticosteroids (i.e., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, transplant-related immunosuppressive drugs, cancer chemotherapeutic agents classified as severely immunosuppressive, tumor-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents) (Source: https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/immuno.html (accessed 20/3/2022)

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Annex A. Important Drug Interactions with Paxlovid (nirmatrelvir/ritonavir)^

Paxlovid is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life-threatening reactions:

- Alpha1-adrenoreceptor antagonist: alfuzosin
- Analgesics: pethidine, propoxyphene
- Antianginal: ranolazine
- Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
- Anti-gout: colchicine
- Antipsychotics: lurasidone, pimozide, clozapine
- Ergot derivatives: dihydroergotamine, ergotamine, methylergonovine
- HMG-CoA reductase inhibitors: lovastatin, simvastatin
- PDE5 inhibitor: sildenafil (Revatio®) when used for pulmonary arterial hypertension (PAH)
- Sedative/hypnotics: triazolam, oral midazolam

Paxlovid is contraindicated with drugs that are potent CYP3A inducers where significantly reduced nirmatrelvir or ritonavir plasma concentrations may be associated with the potential for loss of virologic response and possible resistance. Paxlovid cannot be started immediately after discontinuation of any of the following medications due to the delayed offset of the recently discontinued CYP3A inducer:

- Anticancer drugs: apalutamide
- Anticonvulsant: carbamazepine, phenobarbital, phenytoin
- Antimycobacterials: rifampin
- Herbal products: St. John's Wort (*hypericum perforatum*)

^Please refer to Fact Sheet for Healthcare Providers: Emergency Use Authorization for Paxlovid (Table 1) for listing of clinically significant drug interactions (Available at: https://www.fda.gov/media/155050/download)

Annex B. Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19

1. **Higher risk** for severe COVID-19 outcomes:
    - Cancer
    - Cerebrovascular disease
    - Chronic kidney disease*
    - Chronic lung diseases limited to:
        - Interstitial lung disease
        - Pulmonary embolism
        - Pulmonary hypertension
        - Bronchiectasis
        - COPD (chronic obstructive pulmonary disease)
    - Chronic liver diseases limited to:
        - Cirrhosis
        - Non-alcoholic fatty liver disease
        - Alcoholic liver disease
        - Autoimmune hepatitis
    - Cystic fibrosis
    - Diabetes mellitus, type 1 and type 2*
    - Disabilities
        - Attention-Deficit/Hyperactivity Disorder (ADHD)
        - Cerebral Palsy
        - Congenital Malformations (Birth Defects)
        - Limitations with self-care or activities of daily living
        - Intellectual and Developmental Disabilities
        - Learning Disabilities
        - Spinal Cord Injuries
    - Heart conditions (such as heart failure, coronary artery disease, or cardiomyopathies)
    - HIV (human immunodeficiency virus)
    - Mental health disorders limited to:
        - Mood disorders, including depression
        - Schizophrenia spectrum disorders
    - Neurologic conditions limited to dementia

- Obesity (BMI ≥30 kg/m^2)*
- Primary Immunodeficiencies
- Pregnancy and recent pregnancy
- Physical inactivity
- Smoking, current and former
- Solid organ or hematopoietic cell transplantation
- Tuberculosis
- Use of corticosteroids or other immunosuppressive medications

2. **Suggestive higher risk** for severe COVID-19 outcomes:
   - Children with certain underlying conditions
   - Overweight (BMI ≥25 kg/m^2, but <30 kg/m^2)
   - Sickle cell disease
   - Substance use disorders
   - Thalassemia

3. **Mixed evidence:**
   - Alpha 1 antitrypsin deficiency
   - Asthma
   - Bronchopulmonary dysplasia
   - Hepatitis B
   - Hepatitis C
   - Hypertension*

Footnote: * indicates underlying conditions for which there is evidence for pregnant and non-pregnant people

(Source: Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19: Information for Healthcare Professionals. US CDC. Updated Feb. 15, 2022. Available at https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html)

Annex C. Information and Consent form for experimental treatment of COVID-19

醫院管理局 HOSPITAL AUTHORITY

Information and Consent form for experimental treatment of COVID-19

(14 April 2022 version)

Up till now, there is no consensus on international recommendation of using specific antiviral agents for treatment of COVID-19. However, there have been evidences (including in vitro studies, animal models, case studies, observational studies, as well as some randomized controlled trials (RCT) suggesting possible clinical benefits for the following agents:

- Interferon β-1b (subcutaneous injection)
- Casirivimab and imdevimab (intravenous or subcutaneous injection)
- Amubarvimab/romlusevimab (intravenous infusion)

Interferon β-1b is registered medication in Hong Kong. It has been used to manage multiple sclerosis. The unlicensed use of this drug to treat COVID-19 is experimental, **not standard treatment.** Casirivimab and imdevimab, mubarvimab/romlusevimab are unregistered drugs in Hong Kong.

The above listed drugs have potential side effects (see table below), but their side effects will be closely monitored. If the risk of the drugs is considered to outweigh their benefits, the drugs will be stopped immediately. Moreover, the treatment regimen is subject to change according to the latest evidence from studies and updates in overseas guidelines. For enquiries, please contact our health care staff for assistance.

Potential side effects of the drugs listed below include but not limited :	
Interferon β-1b	Flu-like symptom complex (fever, chills, arthralgia, malaise, sweating, headache, or myalgia), neutropenia, decreased blood glucose, depression, anxiety, headache, dizziness, insomnia, etc.
Casirivimab and imdevimab	Allergic reactions or reactions following infusions: fever, chills, headache, difficulty breathing, hypotension, facial swelling, itching, myalgia
Amubarvimab/romlusevimab	Allergic reactions, hypersensitivity reactions, infusion-related reactions including pyrexia, dyspnea, desaturation, chills, fatigue, arrhythmia, chest pain, diarrhoea, nausea, vomiting, change in mental status, nausea, headache, bronchospasm, hypotension, hypertension, vasogenic edema, rash, pruritus, myalgia, vasovagal reactions, dizziness,

	profuse sweating; possible COVID-19 clinical deterioration; No available human data on the use of this drug during pregnancy and breastfeeding; If you have any question and for details, please refer to drug product insert and consult your attending doctor.

Consent

I understand the limitations and potential side effects of the above medications under the condition of unlicensed use, and I do freely give my consent to accept the treatment below:

☐ Interferon β-1b

- ☐ (Female) Pregnancy test negative
- ☐ (Female) Pregnancy test positive. Explained benefits and potential risks in details

☐ Casirivimab and imdevimab

☐ Amubarvimab/romlusevimab

☐ Other treatment _____

Patient's signature _____ Date _____

Patient's name _____

Witness's signature _____ Date _____

Witness's name _____

Doctor's signature _____ Date _____

Doctor's name _____

醫院管理局 HOSPITAL AUTHORITY

關於 2019 年新型冠狀病毒感染 （COVID-19） 試驗性質藥物治療的資料及同意書

（2022 年 04 月 14 日版本）

迄今為止，尚未有國際準則關於抗病毒藥物在新型冠狀病毒感染（**COVID-19**）有明確的臨床效果。但根據其他有限證據（包括體外研究、動物模型、案例研究、內地及本地專家的意見、一些隨機對照試驗（Randomized controlled trial））， 病者可以考慮接受以下藥物治療。

- 干擾素 β-1b（interferon β-1b）（皮下注射）
- 抗體療法 （casirivimab and imdevimab）（靜脈或皮下注射）
- 安巴韋單抗/羅米司韋單抗單抗（amubarvimab / romlusevimab）（靜脈注射）

干擾素 β-1b 是在香港註冊的藥物，用於治療多發性硬化症。但在未經許可情況下使用藥物（unlicensed use）治療 2019 年新型冠狀病毒感染（COVID-19）屬於試驗性質，並**不是**對 COVID-19 的**標準治療**。抗體療法（casirivimab and imdevimab）和安巴韋單抗/羅米司韋單抗單抗（amubarvimab / romlusevimab）在香港是未經註冊的藥物。

以上藥物有機會出現潛在副作用（見下表），但藥物的副作用將受到密切監測，如果發現風險大於益處，醫生會即時終止治療。另外，治療方案亦可能隨着最新的研究數據和各地指引的更新而有所調整，希望能令病者得到最理想的治療效果。

如有查詢，請聯絡我們的醫護人員尋求協助。

以下藥物的潛在副作用包括但不限於:	
干擾素 β-1b	流感樣症狀 （發燒，發冷，關節痛，出汗，頭痛或肌痛），注射部位反應 （發紅，腫脹，變色，發炎，疼痛），白細胞下降，血糖下降，抑鬱，焦慮，頭痛，頭暈，失眠等等
抗體療法	過敏反應，注射部位反應， 發燒，發冷，頭痛，呼吸困難，低血壓，面部腫脹，發癢，肌痛
安巴韋單抗/羅米司韋單抗	過敏反應、超敏反應、輸液相關反應包括發熱、呼吸困難、去飽和、寒顫、疲勞、心律失常、胸痛、精神狀態改變、噁心、頭痛、支氣管痙攣、低血壓、高血壓、血管源性水腫、皮疹、瘙癢、肌痛、血管迷走神經反應、頭暈、大量出汗; COVID-19 臨床病情惡化；至目前為止，沒有數據關於人類在懷孕期間使用安巴韋單抗/羅米司韋單抗，會否導致胚胎或胎兒受損或出現缺陷、流產或母體受損或不良反應。至目前為止，沒有數據關於人類或動物母乳中存在或排泄安巴韋單抗/羅米司韋單抗。如有任何問題，詳情請參閱藥品說明書並諮詢您的主治醫生

同意書

本人明白在未經許可的情況下使用以下藥物（unlicensed use）的局限性及潛在的副作用，並同意接受以下治療。

☐ 干擾素 β-1b （interferon β-1b）

- ☐ （女性）驗孕結果陰性
- ☐ （女性）驗孕結果陽性 ： 使用藥物前已經向病人詳細解釋干擾素 β-1b 的益處、潛在風險和副作用

☐ 抗體療法（casirivimab and imdevimab）

☐ 安巴韋單抗/羅米司韋單抗單抗（amubarvimab + romlusevimab）

☐ 其他: _____

病人簽署 _____ 日期 _____

病人姓名 _____

見證人簽署 _____ 日期 _____

見證人姓名 _____

醫生簽署 _____ 日期 _____

醫生姓名 _____

Annex D. Fact sheet on the use of nirmatrelvir/ritonavir (Paxlovid™)

Use of nirmatrelvir/ritonavir in COVID-19 patients

(Version 1, 21 March 2022)

Paxlovid™ is nirmatrelvir tablets co-packaged with ritonavir tablets. Nirmatrelvir is a SARS-CoV-2 main protease (Mpro) inhibitor, and ritonavir is an HIV-1 protease inhibitor and CYP3A inhibitor. The product is conditionally approved with limited safety, efficacy, and quality data for public health emergency to satisfy local unmet medical need in Hong Kong.

Contraindications

- Patients less than 12 years of age or weighing below 40kg
- History of clinically significant hypersensitivity reactions to the ingredients or components of the product

Warnings and precautions

- Hepatotoxicity: Hepatic transaminase elevations, clinical hepatitis, and jaundice
- Risk of developing drug resistance to HIV protease inhibitors in individuals with uncontrolled or undiagnosed HIV-1 infection
- Examples of significant/potentially significant drug interactions [consult full prescribing information if needed]
    - Alpha1-adrenoreceptor antagonist: alfuzosin
    - Analgesics: pethidine, propoxyphene
    - Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine
    - Antimycobacterial: rifampicin
    - Anticancer drug: apalutamide
    - Anticoagulants: warfarin, rivaroxaban
    - Anticonvulsant: carbamazepine, phenobarbital, phenytoin
    - Anti-gout: colchicine
    - Antipsychotics: lurasidone, pimozide, clozapine
    - Cardiac glycosides: digoxin
    - HMG-CoA reductase inhibitors: atorvastatin, lovastatin, rosuvastatin, simvastatin
    - Hormonal contraceptive: ethinyl estradiol
    - PDE5 inhibitor: sildenafil when used for pulmonary arterial hypertension

- Sedative/hypnotics: triazolam, oral midazolam

Adverse reactions

- Dysgeusia (altered sense of taste), diarrhoea, hypertension (high blood pressure), myalgia (muscle aches)

Dosage and administration

- 300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir (one 100 mg tablet) taken orally every 12 hours for 5 days, with or without food
  - Moderate renal impairment *(eGFR ≥30 to <60 mL/min)*: 150 mg nirmatrelvir (one 150 mg tablet) with 100 mg ritonavir (one 100 mg tablet) taken orally every 12 hours for 5 days, with or without food
  - Severe renal impairment *(eGFR <30 mL/min)*: NOT recommended
  - Severe hepatic impairment *(Child-Pugh Class C)*: NOT recommended

新冠肺炎口服抗病毒治療藥物
奈瑪特韋(nirmatrelvir) / 利托那韋(ritonavir)須知
（第 1 版，2022 年 3 月 21 日）

帕克斯洛維德(Paxlovid™)包裝內含有兩種藥物，奈瑪特韋(nirmatrelvir)和利托那韋(ritonavir)。Nirmatrelvir是一種SARS-CoV-2主要蛋白酶(Mpro)的擬肽抑制劑，而ritonavir是一種 HIV-1 蛋白酶抑制劑。雖然只有有限的安全性、效能及素質的資料，在公共衞生緊急事態以及本地的醫療需要下，帕克斯洛維德在本港已獲得有條件批准註冊。

以下人士<u>不可使用</u>帕克斯洛維德 (Paxlovid™)

- 12 歲以下或體重少於 40 公斤的病人
- 曾對帕克斯洛維德中的任何成分有嚴重過敏史

警告和注意事項

- 肝臟毒性 ： 出現肝轉氨酶升高、臨床肝炎和黃疸
- 對 HIV 藥物的抗藥性 ： 在未受控制或未經治療的 HIV 感染情況下，帕克斯洛維德可能會影響某些 HIV 藥物在未來發揮作用
- 以下藥物相互作用例子可能會導致嚴重副作用或影響帕克斯洛維德的藥效（如有需要，請查閱詳細藥物資料）
  - α1 -腎上腺素能受體拮抗劑：alfuzosin
  - 止痛藥：pethidine, propoxyphene
  - 抗心律不正藥：amiodarone, dronedarone, flecainide, propafenone, quinidine
  - 抗結核病藥：rifampicin
  - 抗癌藥物：apalutamide
  - 抗凝血藥：warfarin, rivaroxaban
  - 抗腦癇藥：carbamazepine, phenobarbital, phenytoin
  - 抗痛風藥：colchicine
  - 抗精神病藥：lurasidone, pimozide, clozapine
  - 洋地黃類藥：digoxin
  - HMG-CoA 還原酶抑制劑 (他汀類)：atorvastatin, lovastatin, rosuvastatin, simvastatin
  - 荷爾蒙避孕藥 ：ethinyl estradiol
  - PDE5 抑制劑：sildenafil (用於治療肺動脈高壓)
  - 鎮靜/安眠藥：triazolam, oral midazolam

副作用

- 味覺改變、腹瀉、高血壓、肌肉疼痛

劑量

- 每 12 小時一次，每次 300 毫克 nirmatrelvir (兩粒 150 毫克藥丸) **和** 100 毫克 ritonavir (一粒 100 毫克藥丸)，空肚或飽肚服用均可，整個療程為期五天。
  - 中度腎功能不全病人(eGFR 30 to <60 mL/min): 每 12 小時一次，每次 150 毫克 nirmatrelvir (一粒 150 毫克藥丸) **和** 100 毫克 ritonavir (一粒 100 毫克藥丸)，空肚或飽肚服用均可，整個療程為期五天。
  - 嚴重腎功能不全病人(eGFR <30 mL/min): 不建議使用
  - 嚴重肝功能不全病人(Child-Pugh Class C): 不建議使用

Annex E. Fact sheet on the use of molnupiravir

Use of molnupiravir in COVID-19 patients

(Version 2, 21 March 2022)

Molnupiravir is a nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis. The United States Food and Drug Administration has granted emergency use authorization (EUA) to molnupiravir.

Contraindications

- Pregnancy
- Breastfeeding
- Patients less than 18 years of age

Warnings and precautions:

- Embryo-fetal toxicity
- Allergic reactions: stop if it occurs.
- Bone and cartilage toxicity: molnupiravir should not be used in patients less than 18 years of age because it may affect bone and cartilage growth.

Adverse reactions

- Diarrhea, dizziness, headache, skin itchiness, skin rash, nausea, vomiting.
- Laboratory abnormalities in kidney and liver functions tests and haematology (haemoglobin, platelets, and leukocytes)

Dosage and administration: 800 mg (four 200 mg capsules) taken orally every 12 hours for 5 days, with or without food.

- Renal impairment: No dosage adjustment.
- Hepatic impairment: No dosage adjustment.

醫院管理局
新冠肺炎口服抗病毒治療藥物莫納皮拉韋（Molnupiravir）須知
（第 2 版，2022 年 3 月 21 日）

莫納皮拉韋（Molnupiravir）是一種有醫學實證能夠治療新冠肺炎的口服抗病毒藥物，用於輕度及中度病情有高風險未接種疫苗的新冠肺炎患者，能有效減低入院率及死亡率。莫納皮拉韋已獲得美國食品和藥物管理局授權緊急使用（EUA），但在香港並未註冊。如要在香港臨床上使用，必須先徵求病人或家屬的同意。

以下人士<u>不可使用莫納皮拉韋</u>

- 懷孕女性（莫納皮拉韋對胚胎或胎兒有害）
- 哺乳女性（莫納皮拉韋對胚胎或胎兒有害）
- 十八歲以下人士（莫納皮拉韋可能會影響骨和軟骨的生長）

警告和注意事項

- 莫納皮拉韋治療對胚胎及胎兒毒性
  - 建議有生育能力的女性，在莫納皮拉韋治療期間，和在服用最後一劑莫納皮拉韋後的 4 天內，正確和一致地使用有效的避孕方法
  - 建議有生育能力的男性，在莫納皮拉韋治療期間，和在服用最後一劑莫納皮拉韋後的 3 個月內，正確和一致地使用有效的避孕方法（註：直到目前為止，醫學界尚未清楚男性在服用最後一劑莫納皮拉韋 3 個月後，莫納皮拉韋會否對他們的子女產生胚胎或胎兒異常、傷害或毒性風險）
- 過敏、嚴重過敏反應、血管性水腫、紅斑、皮疹和蕁麻疹、化學（ALT、AST、肌酐和脂肪酶）和血液學（血紅蛋白、血小板和白細胞）的化驗報告異常等

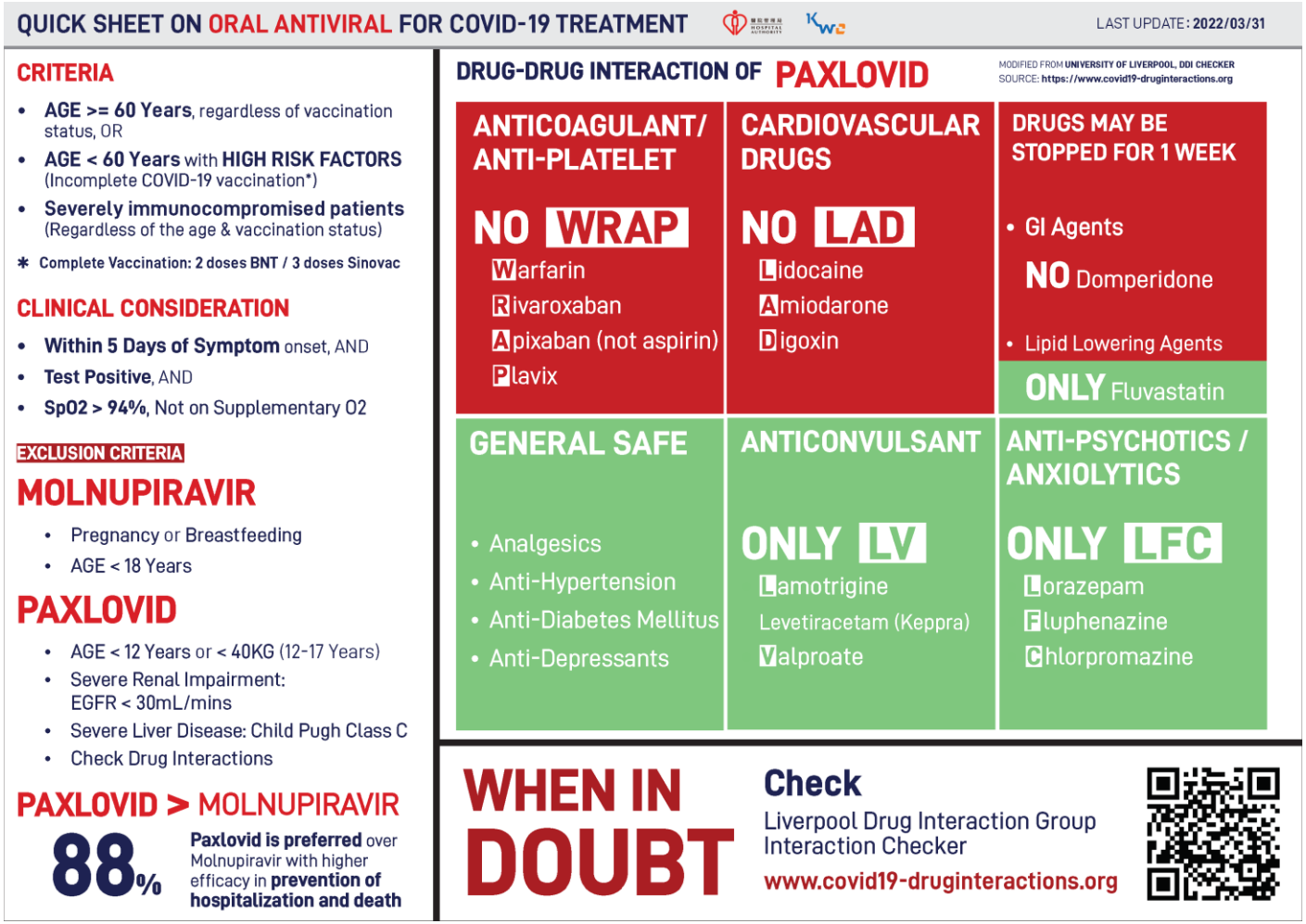
副作用

- 在醫學臨床研究中其副作用與安慰劑相約
- 較為可預見（<2%）的副作用包括：過敏反應、頭暈、嘔心、腹瀉等

劑量

- 每 12 小時一次，每次 800 毫克（四粒膠囊），一個療程為期五天

Annex F. Quick sheet on oral antiviral for COVID-19 treatment



Annex G. Principles of prescription of Paxlovid (oral antiviral) for treatment of early COVID-19 infection