Treatment Guidelines for COVID-19

(Version 12, dated 11 September 2023)

ABSTRACT

Background

In December 2019, a cluster of pneumonia cases caused by a novel coronavirus "SARS-CoV-2" were reported in Wuhan, China. Despite imposition by the China authorities of an unprecedented lockdown in Wuhan and other cities in Hubei province on 23 January 2020, within and outside China the outbreak continued to spread. On 11th March 2020, the World Health Organisation officially declared the outbreak of Coronavirus Disease 2019 (COVID-19) a pandemic. The availability of highly effective vaccines in 2021 appeared to herald the beginning of the end of the pandemic. However, since 2022 the pandemic has been reshaped by the emergence of the Omicron variant of concern and successive waves of outbreaks by immune evasive sub-variants. This guideline provides updated evidence-based recommendations for the therapeutic management of patients with COVID-19 in Singapore, from our initial guidance issued on 2 April 2020.

Methods

Published clinical trials, selected pre-print data, and where relevant in-vitro susceptibility data, and society and professional guidelines related to the treatment of COVID-19 till 1st May 2023 were reviewed. In previous iterations of this guidance, each recommendation was discussed and arrived at via consensus by the guideline committee, with the evidence behind each recommendation reviewed, and screened for conflicts of interest. Since version 10, a modified Delphi method was used to achieve consensus for the updates. The committee first met to discuss and frame statements for the update, and in round one members individually provided their level of agreement with the statements using a 7-option Likert scale [Strongly agree, agree, somewhat agree, neither agree nor disagree, somewhat disagree, disagree, strongly disagree], and were encouraged to provide additional comments. Consensus was set at 80% agreement [Strongly agree, agree, somewhat agree]. Results from round 1 were provided to members and statements not reaching consensus were then re-framed and shared with the panel in an iterative fashion till consensus was achieved.

Summary of recommendations

Mild-moderate COVID-19

1. For patients within the first 5-7 days from symptom onset, with mild-moderate COVID-19 and at significant risk of progression to severe disease, treatment with an antiviral should be considered.

2. The decision for treatment and choice of antiviral may be guided by whether a person is up to date with COVID-19 vaccinations, their expected immune response to vaccination, treatment site and availability of therapies, and patient factors such as age, co-morbid conditions and drug-drug interactions. If suitable, the oral antiviral nirmatrelvir/ritonavir is preferred, with intravenous remdesivir an alternative.

Severe COVID-19

3. Remdesivir may be considered for hospitalised patients who have severe COVID-19 (i.e. SpO2 <94% on room air, requiring supplemental oxygen) in combination with steroids.

4. Dexamethasone (or equivalent steroid) is recommended for patients with severe COVID-19 (receipt of supplemental oxygen or mechanical ventilation).

5. Combination immune modulation with a JAK kinase inhibitor (e.g. baricitinib) or IL-6 antagonist (e.g. tocilizumab) should be considered in patients with severe COVID-19 with progressively worsening disease. Baricitinib may also be considered as an alternative to steroids and used in conjunction with remdesivir. Tocilizumab may be considered in patients who require high-flow or more intensive respiratory support and have features of hyperinflammation due to COVID-19.

Anticoagulation

6. Given the propensity for thromboembolic disease with COVID-19, pharmacologic prophylaxis should be considered in patients with severe or critical disease, or those who are elevated risk of thromboembolic disease (e.g. as stratified by a risk score such as the PADUA score), who do not have contraindications.

Other therapies

7. We do not currently recommend any of the monoclonal antibodies currently authorised/approved in Singapore (casirivimab/imdevimab; sotrovimab; tixagevimab-cilgavimab) as treatment or post-exposure prophylaxis for COVID-19. This is due to the emergence and predominance of Omicron sub-variants which evade neutralisation by these antibodies.

8. Outside of a clinical trial we do not recommend the following as treatment or prophylaxis for COVID-19: favipiravir, fluvoxamine, hydroxychloroquine, inhaled budesonide, interferon preparations, ivermectin, lopinavir/ritonavir, donor lymphocyte or mesenchymal stem cell infusions, non-steroid anti-inflammatories (NSAIDs) including aspirin, convalescent plasma.

CONTENTS

Versions (issue date)

12.0 (11 Sep 2023)

11.0 (5 Dec 2022); 10.0 (27 August 2022) (addendum, 10.1 issued 29 August 2022); 9.0 (28 April 2022); 8.0 (23 March 2022); 7.0 (28 July 2021); 6.0 (14 June 2021); 5.0 (4 Jan 2021); 4.0 (31 Aug 2020); 3.0 (6 July 2020); 2.0 (15 June 2020); 1.0 (2 April 2020)

# 1.	Overview

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA beta-coronavirus which causes COVID-Similar to SARS-CoV and MERS-CoV, SARS-CoV-2 infection may lead to severe respiratory disease.

Most patients with COVID-19 who are fully vaccinated against SARS-CoV-2 (i.e. up-to-date with vaccination as defined by the National Vaccination Programme) do not require specific treatment, and may be adequately managed with supportive care. The probability of progression to severe illness strongly correlates with age and vaccination status. In Singapore, approximately 1.4% of unvaccinated patients with COVID-19 progressed to severe pneumonia, ICU care or death but only 0.24% of fully vaccinated patients (MOH data from 1 May 2021 to 30 Sept 2022). Among adults aged 80 years or older, this proportion was 26% of unvaccinated patients and 3.7% of fully vaccinated.

For patients during early illness who are at significant risk, antivirals reduce progression to severe disease. For patients who develop a severe infection, SARS-CoV-2 antivirals and/or immunomodulatory agents can be beneficial. Early supportive care and monitoring—including oxygen supplementation, organ support and prevention of complications—remain as cornerstones of the clinical management of severe COVID-19.

The COVID-19 treatment guideline outlines pharmacologic treatment guidance for patients with COVID- 19 in Singapore, and is a living document which is updated with evolving data. Key changes from our last update are enumerated in Box 1. Key studies informing our recommendations are detailed in Box 2.

Box 1. Key changes since last interim guidance (version 11 dated 5 Dec 2022)

- Key Drug Summary Table and Update to Annex C: Algorithm for consideration of oral antivirals: Nirmatrelvir and ritonavir tablets (Paxlovid) may be crushed for administration. Molnupiravir capsules may be open for administration via naso/orogastric tubes 12 Fr or greater in size. Nirmatrelvir/ritonavir may be considered for those between 50-60 years of age, after a physician-patient discussion on benefits/risks.
- Addition of section regarding long COVID.
- Updates on new/emerging therapies: Ensitrevir and Pegylated-lamda
- Non-recommended therapies moved to Annex E.

Box 2. Key studies informing these therapeutic guidelines

Treatments for COVID-19

Dexamethasone and other steroids

RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with COVID-19. N Engl J Med 2021 Feb 25;384(8):693-704.

WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Oct 6;324(13):1330-1341. doi: 10.1001/jama.2020.17023. PMID: 32876694; PMCID: PMC7489434.

Remdesivir

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med. 2020 Nov 5;383(19):1813-1826. doi: 10.1056/NEJMoa2007764. Epub 2020 Oct 8. PMID: 32445440; PMCID: PMC7262788.

Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med. 2020 Nov 5;383(19):1827-1837.

Garibaldi BT, Wang K, Robinson ML, et al. Comparison of Time to Clinical Improvement with vs without Remdesivir Treatment in Hospitalized Patients with COVID-19. JAMA Netw Open 2021; 4:1–14.

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395:1569-1578.

WHO Solidarity Trial Consortium, Pan H, Peto R, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2021 Feb 11;384(6):497-511.

Ader, F., Bouscambert-Duchamp, M., Hites, M., et al, & DisCoVeRy Study Group (2022). Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. The Lancet. Infectious diseases, 22(2), 209–221. https://doi.org/10.1016/S1473-3099(21)00485-0 Gottlieb RL, Vaca CE, Paredes R, et al; GS-US-540-9012 (PINETREE) Investigators. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. N Engl J Med. 2021 Dec 22

Nirmatrelvir/Ritonavir

Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R, Rusnak JM; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542. Epub ahead of print. PMID: 35172054.

Arbel R, Wolff Sagy Y, Hoshen M, et al. Nirmatrelvir Use and Severe Covid-19 Outcomes during the Omicron Surge. N Engl J Med. 2022 Aug 24. doi: 10.1056/NEJMoa2204919.

Najjar-Debbiny R, Gronich N, et al. Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients. Clin Infect Dis. 2022 Jun 2:ciac443. doi: 10.1093/cid/ciac443. Epub ahead of print. PMID: 35653428; PMCID: PMC9214014.

Molnupiravir

Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. MOVe-OUT Study Group. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2021 Dec 16:NEJMoa2116044. doi: 10.1056/NEJMoa2116044. Epub ahead of print. PMID: 34914868; PMCID: PMC8693688.

Wong CKH, Au ICH, Lau KTK, et al. Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study. Lancet Infect Dis. 2022 Dec;22(12):1681-1693.

Baracitinib

Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med 2021 Mar 4;384(9):795-807.

Marconi VC, Ramanan AV, de Bono S, et al; COV-BARRIER Study Group. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. Lancet Respir Med. 2021 Dec;9(12):1407-1418.

Wesley EW, Ramanan AV, Kartman CE, et al; COV-BARRIER Study Group. Efficacy and safety of baricitinib plus standard of care for the treatment of critically ill hospitalised adults with COVID-19 on invasive mechanical ventilation or extracorporeal membrane oxygenation: an exploratory, randomised, placebo-controlled trial. Lancet Respir Med. 2022. Published online: February 03, 2022. DOI:https://doi.org/10.1016/S2213-2600(22)00006-6

Tofacitinib

Guimarães PO, Quirk D, Furtado RH, et al; STOP-COVID Trial Investigators. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021 Jun 16. doi: 10.1056/NEJMoa2101643. PMID: 34133856.

Tocilizumab

Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021 Mar 18;3:CD013881. doi: 10.1002/14651858.CD013881. PMID: 33734435.

RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206; PMCID: PMC8084355

REMAP-CAP Investigators,Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. N Engl J Med 2021 Apr 22;384(16):1491-1502.

Stone JH, Frigault MJ, Serling-Boyd NJ, et al; BACC Bay Tocilizumab Trial Investigators. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med. 2020 Dec 10;383(24):2333-2344. doi: 10.1056/NEJMoa2028836. Epub 2020 Oct 21. PMID: 33085857; PMCID: PMC7646626.

Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021; 384(1): 20-30.

2.   Clinical severity and staging of COVID-19

COVID-19 severity		
Asymptomatic / Presymptomatic		Test positive for SARS-CoV-2 with a virologic test but have no symptoms consistent with COVID-19
Mild	Upper respiratory tract infection (URTI)	Any signs/symptoms of COVID-19 (e.g. fever, cough, sore throat, malaise, headache, myalgia, nausea, vomiting, diarrhoea, loss of taste/smell) but who do not have shortness of breath or clinical signs of pneumonia or abnormal chest imaging
Moderate	Pneumonia	Shows evidence of lower respiratory tract disease during clinical assessment or imaging and who have a SpO2 of $\geq$ 94% on room air.
Severe	Pneumonia with hypoxia	Individuals who have a SpO2 of <94% on room air, or P/F ratio of <300 mmHg, respiratory rate of >30 breaths/minute or lung infiltrates occupying >50% of lung fields
Critical illness		Individuals with respiratory failure, septic shock, and/or multiple organ dysfunction

The staging proposed by Siddiqi et al is a conceptual framework for patients with COVID-19. The natural history of COVID-19 will vary, particularly based on prior immunity, and most patients will not develop severe pneumonia or critical illness.
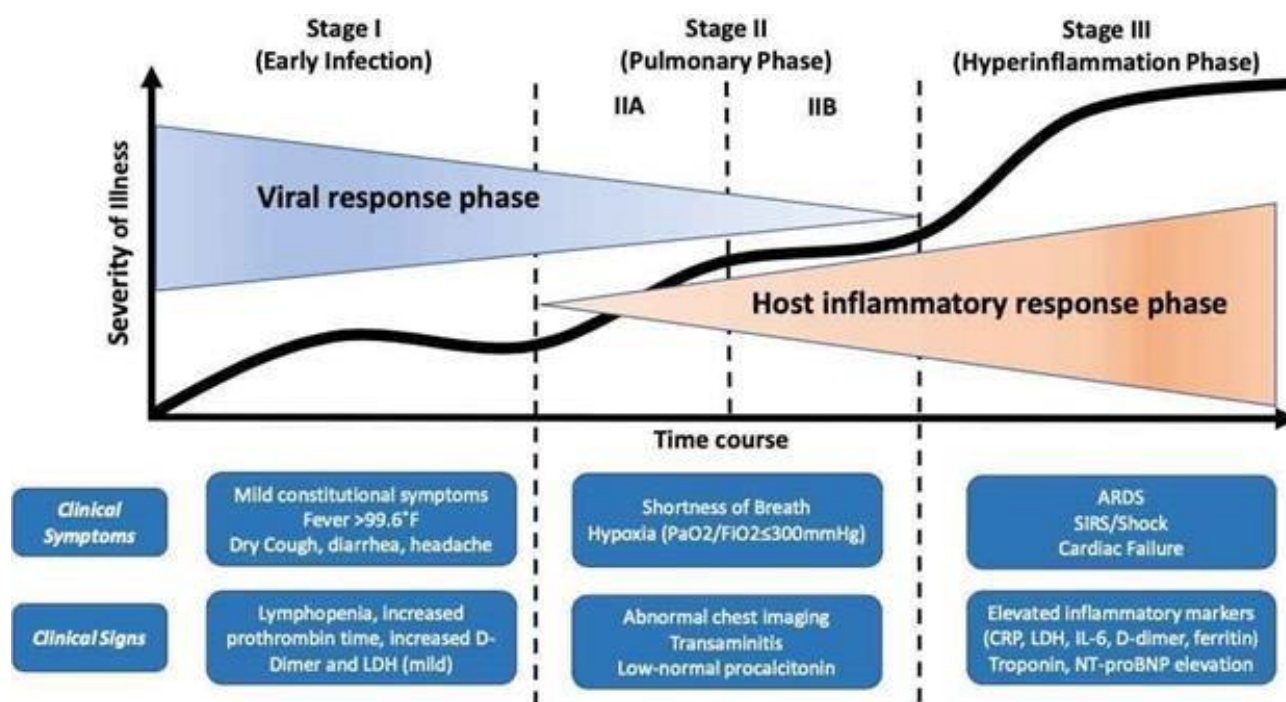
Framework proposed by Siddiqi et al, "COVID-19 Illness in Native and Immunosuppressed States", J Heart and Lung Transplantation, 2020.

3.   Therapeutic Recommendations for COVID-19
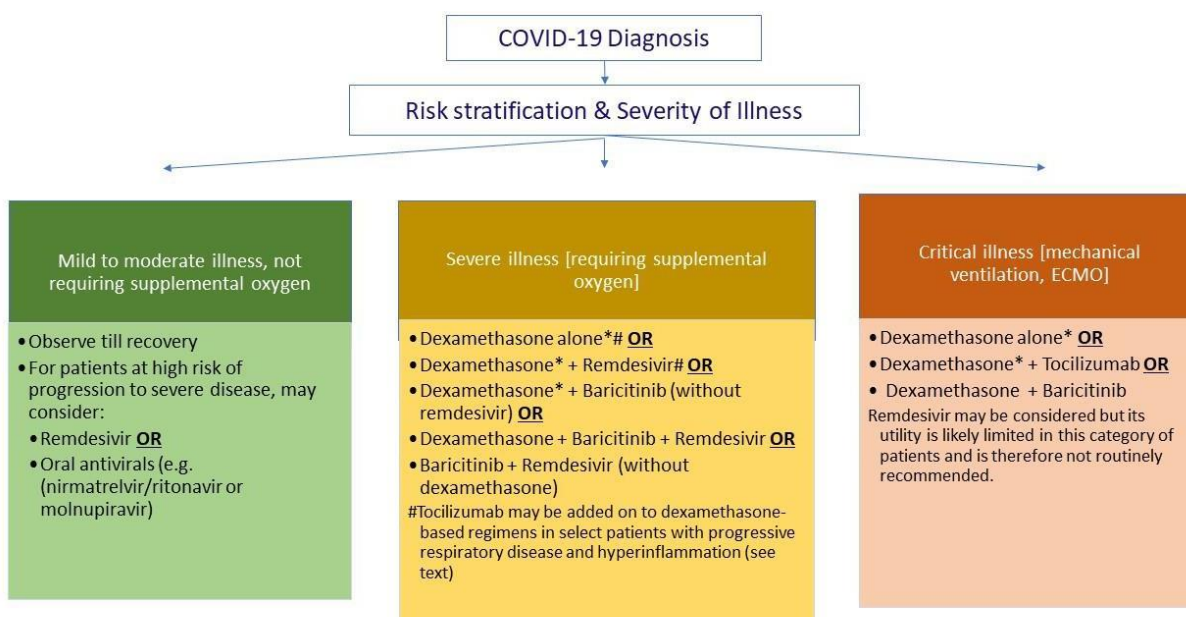
I)   Levels of Evidence and Recommendations

The levels of evidence and recommendations are adapted from the Oxford Centre for Evidence-Based Medicine.

Category	Definition
Levels of evidence	
I	Systematic reviews, meta-analyses, well-designed randomized controlled trials (Phase 3)
II	Two groups, non-randomized studies (e.g. cohort, case-control) or early phase (e.g. Phase 2, or which lack sufficient power) or Phase 3 randomized controlled trials which may be limited by generalisability or biases
III	One-group, non-randomized studies (e.g. before and after, pre-test and post-test)
IV	Descriptive studies that include analysis of outcomes (single-subject design, case series), randomized controlled trials which are not peer reviewed
V	Case reports and expert opinion that include narrative literature, reviews and consensus statements
Grades of evidence	
A	Consistent level I studies
B	Consistent level II or III studies or extrapolations from level I studies or pending replication of results from further level I studies
C	Level IV studies or extrapolations from level II or III studies
D	Level V evidence or troublingly inconsistent or inconclusive studies at any level
Strength of recommendations*	
Strong	Evidence from studies at low risk of bias
Moderate	Evidence from studies at moderate risk of bias
Weak	Evidence from studies at high risk of bias

* Recommendations may also be labelled as "conditional", where the workgroup considers that there are sufficient evidence for desirable effect of adherence to a recommendation probably outweigh the undesirable effects, but is not confident about these trade-off, or full peer-review of data is awaited.

II)   Summary Treatment Algorithm for COVID-19

COVID-19 Diagnosis

Risk stratification & Severity of Illness

Mild to moderate illness, not requiring supplemental oxygen
- Observe till recovery
- For patients at high risk of progression to severe disease, may consider:
- Remdesivir **OR**
- Oral antivirals (e.g. (nirmatrelvir/ritonavir or molnupiravir)

Severe illness [requiring supplemental oxygen]
- Dexamethasone alone*# **OR**
- Dexamethasone* + Remdesivir# **OR**
- Dexamethasone* + Baricitinib (without remdesivir) **OR**
- Dexamethasone + Baricitinib + Remdesivir **OR**
- Baricitinib + Remdesivir (without dexamethasone)

#Tocilizumab may be added on to dexamethasone-based regimens in select patients with progressive respiratory disease and hyperinflammation (see text)

Critical illness [mechanical ventilation, ECMO]
- Dexamethasone alone* **OR**
- Dexamethasone* + Tocilizumab **OR**
- Dexamethasone + Baricitinib

Remdesivir may be considered but its utility is likely limited in this category of patients and is therefore not routinely recommended.

*Or equivalent steroid. All patients: Risk stratify risk for venous thromboembolism with the PADUA score and risk for bleeding VTE bleeding risk score. Patients with severe COVID-19 or a PADUA score $\geq$ 4, and without contraindications should be started on pharmacologic thromboprophylaxis, till discharge from acute or community care facility. If there are contraindications to pharmacologic thromboprophylaxis, mechanical thromboprophylaxis should be considered (e.g. pneumatic calf pumps)

Note: For oral antivirals: Nirmatrelvir/ritonavir (Paxlovid) is preferred over molnupiravir if there are no contraindications

III)   Recommendations

RECOMMENDED THERAPEUTIC MANAGEMENT BASED ON DISEASE SEVERITY

> *A. Mild to moderate illness (not requiring supplemental oxygen)*
> 1. Most patients with COVID-19 **do not** require specific antiviral treatment, beyond supportive care.
> 2. For selected patients who are at high risk of disease progression, we recommend either
>   a. Oral antivirals (nirmatrelvir/ritonavir preferred if no contraindications; molnupiravir or ensitrelvir are alternatives if available)
>   b. Intravenous remdesivir
> 3. Currently available monoclonal antibodies are not routinely recommended as treatment for COVID-19.
> 4. Clinicians may consider using tools such as the ISARIC 4C Mortality Score for COVID-19 (https://www.mdcalc.com/4c-mortality-score-covid-19) to risk stratify patients.

1.   RATIONALE FOR ORAL ANTIVIRALS
(Level 1, Grade A, Strong, nirmatrelvir/ritonavir, Level 1, Grade A, Moderate, molnupiravir)

Two oral antivirals are available in Singapore – nirmatrelvir/ritonavir (Paxlovid) and molnupiravir.

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Nirmatrelvir/ritonavir was granted interim authorisation by HSA on 3 February 2022, and molnupiravir on 19 April 2022, via the Pandemic Special Access Route (PSAR).

- Nirmatrelvir/ritonavir (Paxlovid): The Phase 2/3 EPIC-HR study was a randomized, double-blind 1:1 study of non-hospitalized adult patients with COVID-19, who were deemed to be at high risk of progressing to severe illness[1]. Subjects were > 18 years with at least 1 risk factor for progression to severe disease. Subjects with COVID-19 symptom onset of <5 days were included in the study. Individuals with a history of COVID-19 vaccination or previous infection were excluded. The final analysis showed an 89% relative risk reduction in risk of COVID-19-related hospitalization or death from any cause compared to placebo. In patients treated within three days of symptom onset (primary endpoint); 0.7% of patients who received nirmatrelvir/ritonavir were hospitalized through Day 28 following randomization (5/697 hospitalized with no deaths), compared to 6.5% of patients who received placebo and were hospitalized or died (44/682 hospitalized with 9 subsequent deaths) (p<0.0001). Real world observational data from Singapore in a study population of ~140,000 adults aged ≥60 years, and in which 95% had received ≥3 doses of mRNA vaccines reported that nirmatrelvir/ritonavir treatment was associated with lower odds of hospitalization (adjusted odds ratio [aOR] = 0.65, 95% CI = 0.05-0.65)[2]. Similar real world data from Israel among patients with previous immunity to SARS-CoV-2 (induced by vaccination, infection or both) has also found that hospitalization and death due to COVID-19 were lower in older adults (>=65 years) for those who received nirmatrelvir/ritonavir versus those who did not (adjusted hazard ratio, aHR 0.27 95% CI 0.15-0.49), with no evidence of such benefit in younger adults[3]

- Molnupiravir: In the phase 3 MOVe-OUT trial comprising a total of 1433 subjects, 716 were assigned to receive molnupiravir and 717 to receive placebo[4]. Participants had symptomatic COVID-19 with onset within 5 days and laboratory-confirmed disease, and at least 1 risk factor for severe disease. The percentage of participants who were hospitalized or died through day 29 was lower in the molnupiravir group than in the placebo group (6.8% [48 of 709] vs. 9.7% [68 of 699]; difference, −3.0 percentage points; 95% confidence interval, −5.9 to −0.1). The rate of hospitalization or death through day 29 was approximately 31% lower with molnupiravir than with placebo (hazard ratio, 0.69; 95% CI, 0.48 to 1.01). This trial enrolled laboratory-confirmed COVID-19 patients who had not been vaccinated against SARS-CoV-2 and had symptom onset within 5 days.

Further real-world data from large cohorts in Hong Kong and Israel have demonstrated benefits of both nirmatrelvir/ritonavir and molnupiravir in decreasing severe COVID-19 and mortality in high risk patients. One Hong Kong study on hospitalised COVID-19 patients not on oxygen (n=40,776) found a lower risk of all-cause mortality and composite disease progression outcome with molnupiravir (HR 0.48, 95% CI 0.40-0.59 and HR 0.60, 95% CI 0.52-0.69, respectively) and nirmatrelvir/ritonavir (HR 0.34, 95% CI 0.23-0.50 and HR 0.73, 95% CI 0.54-0.97, respectively)[5].

One other Hong Kong study of 93,883 patients did not find a reduced risk of hospitalization with molnupiravir but did so for nirmatrelvir/ritonavir (HR 0.79, 95% CI 0.65-0.95)[6]. Of the Israeli studies, one found reduced rates of severe COVID-19 and mortality (HR 0.54, 95% CI 0.39-0.75)[7] and another

comprising 109,254 patients found reduced hospitalization (HR 0.27, 95% CI 0.15- 0.49) and mortality (HR 0.21, 95% CI 0.05- 0.82)[3]. A meta-analysis which pooled data from patients of varied vaccination and risk status, showed a significant difference between the Paxlovid and non-Paxlovid groups in both mortality rate (OR 0.25, 95% CI 0.14-0.45) and hospitalization or death rate (OR 0.17, 95% CI 0.06-0.46). However, no significant difference was observed between the two groups in terms of COVID-19 rebound (OR 0.84, 95% CI 0.67-1.04)[8].

Based on the above trials and real world data, oral antivirals should be considered for patients for whom there is concern for progressive disease who are within 5 days of symptom onset, **AND** who have lab confirmed COVID (positive PCR/nucleic acid amplification test (NAAT), or a positive antigen test) who have one or more risk factors for progression to severe disease (Annex C).

Risk factors for severe disease include:
- Not being up-to-date with COVID-19 vaccinations
- Age $\geq$ 60 years,
- Active cancer,
- Chronic kidney disease,
- Chronic lung disease including asthma and chronic obstructive pulmonary disease (COPD)
- Obesity,Heart conditions (e.g. heart failure, coronary artery disease (CAD), and/or cardiomyopathies),
- Diabetes mellitus (DM) with or without complications
- Immunosuppressive disease/treatment.

If treatment with oral antivirals are indicated, and being considered, we **recommend prioritising nirmatrelvir/ritonavir over molnupiravir**, given the greater relative risk reduction anticipated in severe outcomes / mortality, although there are no head-to-head randomized clinical trials. Molnupiravir may be considered when there are contraindications to nirmatrelvir/ritonavir (e.g. due to drug-drug interactions, a GFR of <30 ml/min or severe hepatic impairment [Child-Pugh Score C]).

Cautions with nirmatrelvir/ritonavir (Paxlovid)

Nirmatrelvir/ritonavir (Paxlovid) is a potent CYP3A inhibitor. Concomitant administration of medications that inhibit or induce CYP3A may increase or decrease concentrations of nirmatrelvir/ritonavir (Paxlovid), respectively**. Serious and/or life-threatening reactions may occur due to these interactions**, and prescribers should carefully evaluate for such concomitant drug interactions when prescribing nirmatrelvir/ritonavir (Paxlovid). In patients on chronic medications which may interact with nirmatrelvir/ritonavir, a drug database (e.g. the University of Liverpool COVID-19 drug interaction checker, https://www.covid19-druginteractions.org) should be consulted, and clinicians should consider consultation with the patient's primary doctor managing their chronic medical condition and/or Infectious Diseases, if in any doubt.

Nirmatrelvir/ritonavir 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. Commonly prescribed medications include the Alpha1-adrenoreceptor antagonist alfuzosin; the

Antiarrhythmic amiodarone; Anticoagulant rivaroxaban; Anti-gout colchicine; HMG-CoA reductase inhibitors lovastatin, simvastatin; Immunosuppressants cyclosporine, tacrolimus, sirolimus.

Nirmatrelvir/ritonavir 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*)

The above interactions are **not exhaustive**. **Clinicians are advised to review drug interactions with a drug reference or interaction checker (e.g. https://www.covid19-druginteractions.org by the Liverpool Drug Interaction Group), and consult a pharmacist if needed**. **Common drug-drug interactions and possible actions are listed in Annex D.** Management of drug interactions may be complex, and options may include using an alternate COVID-19 therapeutic, temporarily pausing or dose-adjusting concurrent medications (for a further 3-5 days *after* the completion of the 5-day course of nirmatrelvir/ritonavir, i.e. a total of 8-10 days)

Cautions with molnupiravir
Molnupiravir is not authorized for use in patients younger than 18 years of age because it may affect bone and cartilage growth. It should not be prescribed to pregnant women or those who are breastfeeding because of theoretical concerns of mutagenesis. **Females** of childbearing potential should use a reliable method of contraception correctly and consistently, as applicable, for the duration of treatment and for **four days after the last dose of molnupiravir**. **Males** of reproductive potential who are sexually active with females of childbearing potential should use a reliable method of contraception correctly and consistently during treatment and **for at least three months after the last dose**.

Symptom and Viral rebound
A phenomenon known as "symptom" or "viral rebound" has been described, where patients may report developing acute respiratory infection symptoms associated with COVID-19 again, and antigen tests may become positive again. Symptom rebound has been described in approximately [9]0.8% -8% of patients treated with paxlovid or molnupiravir[9,10]. In untreated patients symptom and viral rebound have been described in up to 26 and 31% of patients, respectively [11]. In one study looking at rebound in those treated with paxlovid these were generally mild, occurred at a median of 9 days after treatment, and all resolved without any further COVID-19 directed therapy. As these are usually mild and follow a benign course, re-treatment with OAVs is not typically necessary. In terms of the isolation period for patients with "viral rebound", patients may need to clinically reviewed and be provided with an extension if still symptomatic, as per the initial assessment of patients with COVID-19,.

Ensitrelvir
Ensitrelvir is a new oral antiviral drug for COVID-19. It is a 3CL protease inhibitor. It suppresses the replication of SARS-COV-2 by selectively inhibiting 3CL protease. Results from the Phase 3 part of the

SCORPIO-SR trial (Phase 2/3 study) demonstrated that in patients with mild/moderate COVID-19 (more than 90% were vaccinated) who received ensitrelvir within five days of symptom onset regardless of risk factors, the time to resolution of five symptoms of COVID-19 (runny/stuffy nose, sore throat, cough, feeling hot or feverish, and low energy/tiredness) was shorter (difference of median time of 24.3 hours) in the treatment arm compared to placebo (p=0.0407). The study also showed a statistically significant reduction (p<0.0001) in the time to negative infectious viral titer[12]. Ensitrelvir, where available, may be considered for use in patients with mild to moderate COVID-19 illness within 5 days of symptom onset, although it should be noted that it is not currently HSA-approved nor routinely available in Singapore as of August 2023. Of note, drug-drug interactions exists as ensitrelvir is considered to be a strong inhibitor of CYP3A4 and is also metabolized by multiple CYP enzymes with the major contributions being from CYP3A4/5. Ensitrelvir should be not coadministered with strong inducers of CYP3A4 as this may result in a marked decrease in ensitrelvir concentrations and the loss of virologic response and possible resistance.

2.   RATIONALE FOR REMDESIVIR (Level I, Grade A, Strong)

The phase 3 PINETREE study consisting of 562 high risk patients (aged ≥12 years with risk factors or ≥60 years) with confirmed COVID-19 (within 4 days of diagnosis, symptoms for ≤7 days) who were not hospitalised were randomised 1:1 to received 3 days of remdesivir or placebo, found a 87% reduction in the risk of a composite of COVID-19 related hospitalisation or all-cause death with remdesivir vs placebo [0.7% vs 5.3%; p=0.008] at day 28. The risk of COVID-19-related medically attended visits or all-cause death by day 28 was also reduced by 81% with remdesivir compared with placebo (1.6% vs 8.3%; p=0.002)[13]. It should be noted there were no deaths in either arm of the PINETREE trial and only unvaccinated subjects were included. The trial was also conducted prior to the emergence of the Delta and Omicron variants.

Prior to the PINETREE study, an open-label randomised controlled trial in patients with moderate COVID-19 pneumonia (i.e. not on oxygen at enrolment) found a better clinical status distribution in persons randomised to a 5 day course of remdesivir than those who received standard of care and suggested a modest clinical benefit, but did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment[14].

A recent systematic review and individual patient data meta-analysis of randomised controlled trials (RCTs) showed that remdesivir reduced progression to mechanical ventilation or death (15.5% vs 19%; aOR 0.78 [0.69-0.87]) as well as 28-day all-cause mortality (9.2% vs 11.2%; aOR 0.80 [0.70-0.93]) in patients hospitalised with COVID-19 who required no oxygen or low-flow oxygen[15].

3.   RATIONALE FOR NOT RECOMMENDING MONOCLONAL ANTIBODIES AS TREATMENT FOR COVID-19 (casirivimab/imdevimab; sotrovimab; tixagevimab-cilgavimab, ungraded)

Three monoclonal antiboides (MAbs) – casirivimab/imdevimab (REGEN-COV), sotrovimab and tixagevimab-cilgavimab (Evusheld) – have been authorised/approved in Singapore for the management of COVID-19. Casirivimab/imdevimab and sotrovimab were approved by HSA via the PSAR

(pandemic special access route) and also received US FDA emergency use authorization (EUA) for the treatment of mild-moderate COVID-19 in adults who are at high risk for progression. Tixagevimab-cilgavimab was approved by HSA via PSAR and the US FDA for **pre-exposure prophylaxis** for COVID-19, it has not received HSA or US FDA approvals for treatment but has been used off-label for this purpose. The trials supporting the use of the monoclonals were performed prior to the emergence of the Omicron variant. There are no head-to-head clinical trials to determine whether there are differences in clinical efficacy or safety between these therapies.

Successive waves of Omicron variant infections have been characterised by increasing immune evasion. *In vitro* studies using a variety of methodologies (including surrogate virus, pseudovirus and live virus neutralisation) have reported the capacity of available MAbs to neutralising these variants.

• Casirivimab/imdevimab does not have activity against BA.1 and while imdevimab has some in-vitro activity against BA.2, BA.4/5, data has been inconsistent in different studies[16–18].

• Sotrivimab retained some neutralising activity against Omicron variants BA.1 and BA.1.1, but has poorer in vitro neuralization for BA.2 and BA.4/5. In observational (non-randomised) cohort studies with the OpenSAFELY platform done when different subvariants of Omicron were dominant, treatment with Paxlovid was associated with a similar risk of hospitalisation or death from COVID-19 as treatment with sotrovimab (HR=1.14, 95% CI: 0.62 to 2.08; P=0.673). In contrast, treatment with sotrovimab was associated with a substantially lower risk of hospitalisation or death from COVID-19 compared to treatment with molnupiravir (HR 0.54, 95% CI 0.33 to 0.88, P=0.01), even when restricted to people who were fully vaccinated (HR 0.53, 95% CI 0.31 to 0.90, P=0.02)[19]. Specifically, among patients on kidney replacement therapy, sotrovimab was associated with substantially lower risk of 28-day COVID-19 related hospitalisation/death than treatment with molnupiravir (HR=0.35, 95% CI: 0.17 to 0.71; P=0.004)[20].

• Tixagevimab-cilgavimab retained some activity against BA.2 and BA.4/5, but not against more recent Omicron subvariants including BA.2.75.2, BA.4.6, BQ.1.1 and XBB.

Since October 2022 XBB and subsequently its subvariants became the predominant circulating variant in Singapore. *In vitro* pseudovirus neutralisation data indicates this virus is not as effectively neutralised by any of the above MAbs. While it is uncertain which variants may come to dominate in the future, other newly emerging Omicron variants have also demonstrated evasion from neutralising MAbs. Given this data **we recommend against using monoclonal antibodies for treatment of COVID-19 in favour of antivirals.** On a **case-by-case** basis, for patients with a complicated course (e.g. immunocompromised hosts with persistent infection despite optimizing non-humoral therapies), therapy with MAbs may be considered and viral genotyping can be performed to guide therapy. This recommendation will continue to be reviewed periodically depending on circulating VOCs and their susceptibility to the MAbs.

Useful sites to refer to for the activity of the various MAbs and antivirals against specific SARS- CoV-2 variants include:

1)   NIH COVID-19 Therapeutic Activity Explorer: https://opendata.ncats.nih.gov/variant/activity

2)   Stanford   University   Coronavirus   Antiviral   &   Resistance   Database:

https://covdb.stanford.edu/page/susceptibility-data/

4.   THE ISARIC 4C SEVERITY OR MORTALITY SCORE AND ANTIBODY TITRES

The ISARIC 4C Severity or Mortality scores may be used to risk stratify patients. One study found that the 4C mortality score still performed reasonably in the Omicron era (if score > 10, sensitivity 76.2% and specificity 62.67% for mortality). It should be noted that the mortality rates reported in the original studies was higher than with the Omicron variant[21]. High risk patients in particular those who are not up-to-date with COVID-19 vaccination/not fully vaccinated may be considered for antiviral therapy. We do not recommend checking Anti-S or neutralising antibody titres to guide therapy decisions, and clinicians should not delay antiviral treatment while awaiting results of antibody titres, if these are checked. There is, as yet, no generally defined Anti-S antibody or neutralising antibody titre that correlates with protection from severe COVID-19. With a surrogate virus neutralisation test (Cpass®, GenScript) a result of inhibition <30% indicates a sample which is negative for neutralizing antibodies, per the manufacturer[22].

B. Severe illness (requiring supplemental oxygen but not invasive ventilation or ECMO)

For patients will severe illness requiring supplemental oxygen but not invasive ventilation or ECMO, we recommend either

- i.   Dexamethasone (or equivalent steroid)
- ii.   Dexamethasone (or equivalent steroid) + Remdesivir
- iii.   Remdesivir + Baricitinib
- iv.   Dexamethasone (or equivalent steroid) + Baricitinib
- v.   Dexamethasone (or equivalent steroid) + Remdesivir + Baricitinib

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5.   RATIONALE FOR DEXAMETHASONE (Level I, Grade A, Strong, ==with caveats in the elderly== $\geq$ 70 years)

Prior to results released by the RECOVERY trial, steroids were not conclusively shown to have specific benefits in COVID-19 infection, and the evidence had been somewhat conflicting[23]. Studies with reported benefits have been uncontrolled, and confounded by concurrent treatments, and steroids have been known to cause deleterious effects (e.g. bacterial/fungal superinfection) from SARS (2003) data. Steroid bursts (≤ 14 days) have also been found to be associated with a significant increase in incidence of gastrointestinal bleeding, sepsis, and heart failure within the first month after initiation of steroid therapy[24].

The RECOVERY trial results reported on 2104 patients who were randomised (unblinded) to received dexamethasone and 4321 patients to standard of care[25]. It should be noted that <0.1% of patients in the RECOVERY trial received concomitant remdesivir. Patients were eligible if they were hospitalised, and had clinically suspected or laboratory confirmed COVID-19. Dexamethasone was given orally or intravenous at a dose of 6mg once daily for up to 10 days (or until hospital discharge if sooner) (median duration, 7 days). The trial found that significantly lower mortality in patients allocated to dexamethasone (overall 22.9% vs 25.7%, *p*<0.001; if on mechanical ventilation 29.3% vs 41.4%, 95% CI 0.51 to 0.81); if receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; 95% CI 0.72 to 0.94). There was no statistically significant benefit if patients were not receiving any respiratory support (17.8% vs. 14.0%, 95% CI 0.91 to 1.55).

A RCT (n=86 hospitalised patients) which compared methylprednisolone (2 mg/kg/day; intervention group) versus dexamethasone (6 mg/ day; control group) found that methylprednisolone demonstrated better clinical status compared to the control group at day 5 (4.02 vs. 5.21, p = 0.002) and day 10 (2.90 vs. 4.71, p = 0.001) of admission, a significant difference in the overall mean score (3.909 vs. 4.873, p = 0.004), a shorter mean length of hospital stay (7.43 ± 3.64 vs. 10.52 ± 5.47 days, p = 0.015), and a lower need for a ventilator (18.2% vs 38.1%, p = 0.040)[26]. Further studies are needed to assess the comparative performance and optimal dosing of various steroid preparations.

A prospective meta-analysis of 7 randomised trials (DEXA-COVID 19, CoDEX, RECOVERY, CAPE COVID, COVID STEROID, REMAP-CAP, Steroids-SARI) consisting of 1703 patients had also found that treatment with corticosteroids (dexamethasone, hydrocortisone, methylprednisolone) was associated with a lower 28-day all-cause mortality for critically ill patients with COVID-19, compared with usual care or placebo. There were 222 deaths among 678 patients randomised to corticosteroids, and 425 deaths among 1025 patients randomised to usual care or placebo (summary OR 0.66; 95% CI: 0.53 to 0.82; *P*<0.001)[27].

The COVID STEROID 2 Trial Group randomized adults with confirmed COVID-19 requiring at least 10L/min of oxygen or mechanical ventilation comparing intravenous dexamethasone 12mg/day vs. 6mg/day for up to 10 days. The median number of days alive without life support (22.0 days vs 20.5 days; p=0.07) and mortality at 28 days [27.1% vs 32.3%; adjusted relative risk, 0.86 (99% CI 0.68-1.08)] was not significantly different between the groups[28]. The HIGHLOWDEXA trial was a randomized, controlled clinical trial evaluating high dose dexamethasone (20 mg once daily for 5 days, followed by 10 mg once daily for 5 days) vs low dose dexamethasone (6 mg once daily for 10 days) in patients hospitalized with COVID-19 pneumonia requiring oxygen therapy[29]. They found that while that 31.4% of patients in the low dose group and 16.3% of those in the high dose group exhibited clinical worsening within 11 days of randomization (rate ratio, 0.427; 95% CI, 0.216-0.842; P =.014), there was no significant difference in the 28-day mortality (5.9% in the low dose group and 6.1% in the high dose group, P = 0.844), time to recovery or in the 7-point ordinal scale at day 5, 11, 14 and 28. The results in this trial were confounded because 32 (31.4%) of the 102 patients in the low dose dexamethasone group subsequently received high dose dexamethasone due to clinical worsening, which was allowed per the clinical protocol, and this potentially biased results.

In summary, oral or intravenous dexamethasone 6 mg daily (equivalent to oral prednisolone 40 mg daily, intravenous methylprednisolone 32 mg daily or intravenous hydrocortisone 50mg q8 hours) for up to 10 days is recommended in patients with severe COVID-19 requiring supplemental oxygen or mechanical ventilation and who do not have contraindications to such treatment. Caution however, with steroid use should be exercised in the elderly, which is discussed in the following section.

Steroids in the elderly (> 70 years)

Data from the RECOVERY trial showing a benefit of dexamethasone in the elderly were largely driven by those <70 years old, and sub-analyses did not demonstrate a mortality benefit in those > 70 years.[25] One study among patients aged 80 years or older who required oxygen ≥3L/min and with an inflammatory syndrome (C-reactive protein ≥40mg/L), receipt of steroids (at least 0.4mg/kg/day

equivalent prednisone) was associated with a significant increase in the overall survival, albeit this was studied at the day 14 mark (weighted hazard ratio 0.67, 95% CI 0.46-0.99). Also, ahigher proportion (16.8% vs 6.4%) of patients receiving steroids developed adverse events, which included hyperglycemia, heart failure, confusion and infection[30]. Additionally, the COVIP Study (Coronavirus Disease in Very Elderly Intensive Care Patients) which had a median age of 75 in those studied showed a 53% mortality in those receiving corticosteroids and 42% in the non-steroid receiving group, with a secondary analysis finding steroid use associated with higher mortality in those who were critically ill(aOR 1.6; 95% CI 1.26-2.04; p<0.001)[31]. Given the heterogeneity in severity of disease and end-points in these studies, we advise caution with corticosteroid *monotherapy* in severe COVID-19 in the elderly (e.g. $\geq$ 70 years), and that steroids are utilized they be used for the shortest duration practicable, with careful monitoring of adverse effects and other therapy adjuncts be considered (e.g. JAK inhibitors or remdesivir)[32,33].

6. RATIONALE FOR DEXAMETHASONE + REMDESIVIR (Level 2, Grade B, Weak)

Remdesivir plus dexamethasone has not been directly compared to dexamethasone alone in large randomized clinical trials. One retrospective, multicentre study (n=2483) comprising a subset of 184 patients receiving remdesivir plus corticosteroids with 158 patients receiving remdesivir alone found that adding dexamethasone to remdesivir compared to remdesivir alone did not show a significant reduction in the hazard of death for patients who received remdesivir and corticosteroids compared with remdesivir alone (aHR, 1.94; 95%CI, 0.67-5.57)[34]. Another prospective controlled nonrandomised study of 151 patients found that remdesivir- dexamethasone was associated with significant reduction in mortality (1.3% vs 16% p <0.005), length of hospitalization (p <0.0001), and faster SARS-CoV-2 clearance, compared to dexamethasone alone[35]. Remedesivir in one study in very old patients ($\geq$ 80 years) was associated with a lower mortality rate than those not treated with remdesivir (adjusted OR 0.40, 95% CI 0.22-0.61), even after adjustment for steroid use (90% vs 79.1% use in remdesivir and non-remdesivir group, respectively), high-flow nasal canula oxygen support and other factors potentially associated with mortality[32].

One large RCT, ACTT-1, on 1062 patients (541 remdesivir, 521 placebo) showed a shortened time to recovery in hospitalised patients with COVID-19 (10 days vs 15 days, *P* <0.001) based on an eight-point ordinal scale, although no significant mortality difference was noted (6.7% with remdesivir and 11.9% with placebo by day 15, and 11.4% with remdesivir and 15.2% with placebo by day 29; hazard ratio 0.73; 95% CI 0.52 to 1.03; p=0.07)[36]. Specifically, the largest difference observed in HR for mortality was 0.30 (95% CI 0.14-0.64) for patients in category 5 (hospitalized, requiring any supplemental oxygen, but not non-invasive or invasive ventilation, or ECMO). In this study, remdesivir was more effective when given to patients who were not as severely ill, and in subgroup analyses the time to recovery was significant for the group on supplemental oxygen (but not for those with more severe disease on ECMO, invasive mechanical ventilation or high flow nasal oxygen), or milder disease (not on oxygen)[36]. The benefit of remdesivir for reducing time to recovery was most evident in the subgroup of patients who required supplemental oxygen (baseline ordinal score of 5; recovery rate ratio 1.45 (95% CI 1.18 to 1.79). This is hypothesized to be related to the mechanism of action of remdesivir as an antiviral which is usually best given during the viral replicative phase in early illness in COVID-19, prior

to clinical worsening (e.g. need for mechanical ventilation). ACTT-1 also showed that remdesivir reduced progression to high flow oxygen or non-invasive ventilation, or progression to mechanical ventilation.

Another study did not find a difference in clinical improvement between a 5-day vs 10-day course of remdesivir for hospitalised patients with COVID-19[37], although this study was limited in terms of not having a control group, and was thus unable to measure the magnitude of benefit. It should be noted that those receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening were excluded, as were those who had signs of multi-organ failure. A third study with 237 patients in COVID-19 in China did not find a statistically significant different time to clinical improvement, although this trial was felt to be underpowered as it was terminated earlier due to improvement in the COVID-19 situation in Hubei, China and inability to recruit further[38].

A randomised open-label adaptive trial sponsored by the World Health Organisation evaluating remdesivir, hydroxychloroquine, lopinavir/ritonavir, interferon-beta versus standard of care (SOLIDARITY trial) consisting of a total of 14, 304 patients in its final enrolment[39]. SOLIDARITY's data did not separate low-flow and high-flow oxygen, and ventilation (invasive or not) was considered together. In this trial, of those on oxygen but not ventilated, 14·6% given remdesivir died versus 16·3% of controls (RR 0·87 [0·76–0·99], p=0·03), and combining all those not ventilated initially (i.e. not on oxygen, or on oxygen but not ventilated), 11·9% in the remdesivir group died versus 13·5% of controls (RR 0·86 [0·76–0·98], p=0·02) and 14·1% versus 15·7% progressed to ventilation (RR 0·88 [0·77–1·00], p=0·04). The non-prespecified composite outcome of death/progression to ventilation occurred in 19·6% in the remdesivir group versus 22·5% in controls (RR 0·84 [0·75–0·93], p=0·001). Overall the trial found that in non-ventilated patients but hospitalised patients, remdesivir reduced the risk death or progression to ventilation (or both) by 16%.

Methodological differences between SOLIDARITY and ACTT-1 should be noted, despite both being RCTs, including study size and different primary end-points, and the former being a pragmatic open label trial (remdesivir versus standard of care) whereas the latter a placebo- controlled double blinded trial.

The Health Sciences Authority (HSA) conditionally approved remdesivir for treatment of COVID- 19 in Singapore on 10 June 2020, for adult patients with SpO2 $\leq$ 94% (room air), or those requiring oxygen supplementation, mechanical ventilation or ECMO, for treatment up to 10 days. Based on the data by Beigel et al [36]and the other studies discussed above, we recommend an initial treatment duration of 5 days in early, severe COVID-19. This might be extended for up to 10 days in patients with more severe illness. If remdesivir is considered in patients with severe COVID-19, combination therapy (e.g. with steroids or JAK inhibitor) should be strongly considered unless there is a contraindication. In a very select group of patients with early severe disease on low flow oxygen (i.e., ≤4L/min), remdesivir alone, with close observation, may be a reasonable initial option, with a view of add on steroid treatment if there is worsening. One retrospective study found that remdesivir-only patients (n=985) on low-flow oxygen were also significantly more likely to clinically improve with a median time to improvement of 5 days (IQR, 4,8) compared to 8 days (IQR, 5,19) in controls (aHR 1.66 [95% CI, 1.35-2.04][34].

7. RATIONALE FOR REMDESIVIR + BARICITINIB (Level I, Grade B, Moderate)

Baricitinib is an oral JAK inhibitor used in the treatment of rheumatoid arthritis. Its antiviral activity lies in its affinity for adaptor-associated kinase-1 (AAK1) which is a regulator of viral endocytosis, thereby preventing SARS-CoV-2 from entering and infecting pulmonary cells. It also blunts the downstream inflammatory cascade by the inhibition of JAK1/JAK2 kinase and IL-6-induced STAT3 phosphorylation.

On 19 November 2020, the FDA released an Emergency Use Authorisation (EUA) for remdesivir combined with baricitinib. The data supporting this EUA are based on a double-blind, placebo-controlled RCT (ACTT-2) which included 1,033 patients with moderate or severe COVID-19 (515 patients with remdesivir plus baricitinib versus 518 patients with remdesivir plus placebo)[40]. The median time to recovery was 7 days for baricitinib plus remdesivir, versus 8 days for remdesivir plus placebo (rate ratio for recovery, 1.16; 95% CI 1.01 to 1.32, p=0.03). Patients who showed the greatest benefit were those with a baseline ordinal score of 6 (i.e. on non-invasive ventilation or high-flow nasal oxygen). These patients had a time to recovery of 10 days in the baricitinib plus remdesivir group versus 18 days in the control group (rate of recovery, 1.51; 95% CI 1.10 to 2.08), and were most likely to have clinical improvement at day 15 (odds ratio 2.2; 95% CI 1.4 to 3.6). The incidence of progression to death or non-invasive ventilation was lower in the combination group than in the control group (22.5% vs 28.4%; rate ratio 0.77, 95% CI 0.60-0.98), as was the incidence of progression to death or invasive ventilation (12.2% vs 17.2%; rate ratio 0.69; 95% CI 0.50 to 0.95). The overall 28-day mortality was 5.1% for the remdesivir plus baricitinib group versus 7.8% for the remdesivir plus placebo group (hazard ratio for death 0.65; 95% CI 0.39 to 1.09).

The ACTT-4 trial which aimed to examine the efficacy of remdesivir plus baricitinib versus remdesivir plus dexamethasone in preventing progression to intubation or death in patients with severe COVID-19, comprised of 516 subjects in the remdesivir plus baricitinib and 494 subjects in the remdesivir plus dexamethasone arm. The ventilation-free survival was 87.0% in the remdesivir plus baricitinib group and 87.6% in the remdesivir plus dexamethasone group [risk difference (RD) 0.6%; 95%CI 3.6% to 4.8%; P=0.91]. The clinical status at day 15 was comparable [odds ratio 1.01; 95% CI 0.80 to 1.27]. Adverse events were seen in 29.6% of those treated with remdesivir plus baricitinib group versus 37.1% of those treated with remdesivir plus dexamethasone [RD 7.5%; 95%CI 1.6% to 13.3%; P=0.01], treatment related-adverse events were 4.2% vs. 10.2% [RD 6.0%; 95%CI 2.8% to 9.3%; P=0.0004], and severe or life-threatening adverse events were 28.4% vs. 36.1% [RD 7.7%; 95%CI 1.8% to 13.4%; P=0.01], all respectively higher in the remdesivir plus dexamethasone arm compared to remdesivir plus baricitinib[41].

8. RATIONALE FOR DEXAMETHASONE + BARICITINIB (Level I, Grade B, Moderate)

COV-BARRIER was a phase 3 RCT evaluating baricitinib 4 mg once daily for up to 14 days plus standard of care (n=764) (SoC)(which included 79% receiving corticosteroids and 19% receiving remdesivir, with some receiving both) versus placebo plus SoC (n=761)[42]. The trial did not meet statistical significance on the primary endpoint, which was defined as a difference in the proportion of participants progressing to the first occurrence of non-invasive ventilation including high flow oxygen or invasive mechanical ventilation or death by Day 28 (27.8% vs 30.5%; p=0.18). However, the 28-day all-cause mortality was 8.1% for baricitinib and 13.1% for placebo, corresponding to a 38.25% reduction in

mortality (hazard ratio 0.57, 95% CI 0.41 to 0.78; nominal p=0.002). A numerical reduction in mortality was observed for all baseline severity subgroups of baricitinib-treated patients and was most pronounced for patients receiving non-invasive mechanical ventilation at baseline (17.5% versus 29.4% for baricitinib plus SoC versus SoC; hazard ratio [HR]: 0.52; 95% CI: 0.33, 0.80; nominal p-value=0.0065).

An RCT (STOP-COVID) comprising 289 patients in Brazil found the decreased cumulative incidence of death or respiratory failure through day 28 with tofacitinib vs placebo (18.1% vs 29%, risk ratio 0.63, 95% CI 0.41-0.97, p = 0.04)[43] The trial included patients 18 years or older with laboratory confirmed COVID-19 infection with pneumonia, who had been hospitalised for <72 hours. Tofacitinib was dosed at 10 mg BD up to 14 days and dose adjusted with renal and hepatic function on those on concurrent medications which were CYP3A4/CYP2C19 inhibitors. Patients on non- invasive or invasive mechanical ventilation and ECMO, and a history of thrombosis or current thrombosis, known immunosuppression, and active cancer on treatment were excluded. In this trial tofacitinib was dosed for a median of 5 days in the intervention group and 89.3% of patients overall received glucocorticoids, and none received remdesivir. Based on these results, , JAK inhibitors may be considered in combination with corticosteroids in patients with severe COVID-19.

9. RATIONALE FOR DEXAMETHASONE + REMDESIVIR + BARICITINIB (Ungraded)
Please refer to discussion in the above section under *Severe Illness (requiring supplemental oxygen but not invasive ventilation or ECMO)—RATIONALE FOR DEXAMETHASONE + BARICITINIB.*

> ### C. Critical illness (requiring mechanical ventilation or ECMO)
> For patients will critical illness requiring mechanical ventilation or ECMO, we recommend either
> - i. Dexamethasone (or equivalent steroid)
> - ii. Dexamethasone (or equivalent steroid) + Tocilizumab
> - iii. Dexamethasone (or equivalent steroid) + Baricitinib

10. RATIONALE FOR DEXAMETHASONE (Level I, Grade A, Strong)
Please refer to discussion in the above section under *Severe Illness (requiring supplemental oxygen but not invasive ventilation or ECMO), and section on 'Steroids in the elderly'.*

11. RATIONALE FOR DEXAMETHASONE + TOCILIZUMAB (Level I, Grade B, Moderate)
Meta-analyses conducted by the WHO Rapid Evidence Appraisal Working Group (REACT)[44] and Cochrane collaboration[45] concluded there was likely to be a mortality benefit with IL-6 antagonists in severe COVID-19 (all-cause mortality at Day 28: OR, 0.86 [95% CI, 0.79-0.95] and RR 0.89, [95 CI 0.82-0.97] respectively).

The two largest clinical trials completed to date (RECOVERY [46] and REMAP-CAP [47]) reported clinical benefits from IL-6 antagonists, however, the next largest trial REMDACTA trial did not [35]. The meta-analysis conducted by REACT included data from all three of these trials:

RECOVERY is an open-label randomised trial conducted in >4000 patients with oxygen saturation <92% on room air, or oxygen supplementation, and a CRP ≥75 mg/L[46]. Study participants were

treated with one or two weight adjusted doses of tocilizumab along with standard of care, e.g. steroids (82% receipt). The median CRP at randomisation was 143 (107-203) mg/L. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0.85; 95% CI 0·76–0·94). Consistent results were seen in all pre-specified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% vs 50%; rate ratio 1.22; 1.12–1.33). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the composite endpoint of invasive mechanical ventilation or death (35% vs 42%; risk ratio 0.84; 95% CI 0.77–0.92).

In the REMAP-CAP trial of 804 adult patients critically ill with COVID-19, were randomized within 24 hours after starting organ support in the intensive care unit to receive open-label tocilizumab or sarilumab or usual care alone[47]. Respiratory organ support was defined as invasive or non- invasive mechanical ventilation, including through high-flow nasal cannulae. In this trial, >80% also received concomitant steroids and 33%, remdesivir. The median (IQR) CRP for patients enrolled in the tocilizumab arm was 150 (85-221) mg/L. Compared to usual care, the use of tocilizumab reduced in-hospital mortality (28% vs. 36%) and increased the number of days free of respiratory and cardiovascular organ support (10 days vs. 0 days; OR 1.64; 95% CI, 1.25–2.14)

In REMDACTA 434 patients were randomised to tocilizumab plus remdesivir and 215 to placebo plus remdesivir[48]. Overall, 566 patients (88.2%) received corticosteroids during the trial to day 28. Median time from randomization to hospital discharge or "ready for discharge" (study primary endpoint) was 14 (95% CI 12–15) days with tocilizumab plus remdesivir and 14 (95% CI 11–16) days with placebo plus remdesivir; 78 (18.2%) and 42 (19.7%) patients, respectively, died by day 28.

Other individual trials have not shown a consistently beneficial effect of an IL-6 antagonist on clinical outcomes such as mortality or clinical progression (CORIMUNO-TOCI[49], COVACTA[50], EMPACTA[51], Salvarani et al[52], BACC Bay Tocilizumab Trial[53], TOCIBRAS[54], COVINTOC[55]). These studies may have had varied results as they either recruited smaller populations, were heterogenous in their inclusion criterion and importantly, many were conducted before remdesivir and corticosteroids were standard of care.

We recommend a JAK inhibitor **or** IL-6 antagonist in addition to systemic corticosteroids for selected patients. No data is currently available to determine which should be used in preference. We suggest choosing an IL-6 antagonist for patients with hyperinflammation (e.g. as evidenced by elevated inflammatory markers such as a CRP ≥75 mg/L and rising) and who are at high risk or are exhibiting rapid respiratory decompensation due to COVID-19. Treating physicians should be aware of the risk of opportunistic infection(s) and lower intestinal perforation, in particular in patients with underlying gastrointestinal disease. Use of IL-6 antagonists should be guided by Infectious Diseases or an intensivist. Consultation with rheumatologists-allergist- immunologists (RAI) may be needed for complex cases. Currently, we do not recommend the use of tocilizumab in patients who are receiving JAK inhibitors (e.g. baricitinib) due to the lack of efficacy and safety data.

12. RATIONALE FOR DEXAMETHASONE + BARICITINIB (Level II, Grade B, Moderate)

In an addendum trial to the COV-BARRIER trial, baricitinib was studied in patients on baseline invasive mechanical ventilation/ECMO in a 1:1 randomisation to baricitinib 4-mg (n=51) or placebo (n=50) for up to 14 days in combination with standard of care, which included systemic corticosteroids in 86% of participants[56]. Treatment with baricitinib reduced 28-day all-cause mortality compared to placebo (39.2% vs 58.0%; hazard ratio [HR]=0.54 [95%CI 0.1– 0.96]; p=0.030), and also 60-day mortality (45.1% vs 62.0%; HR=0.56 [95%CI 0.33–0.97]; p=0.027). While a large effect size was noted, consistent with results in the main COV-BARRIER trial, this was a small trial. Taken together however, we recommend that baricitinib may be considered in patients on mechanical ventilation or ECMO, and when used, should be in combination with corticosteroids (if there are no contraindications), with or without remdesivir, for the treatment of patients COVID-19 critical illness on mechanical ventilation.

D. Prophylaxis for COVID-19

i.   Active immunity via an effective SARS-CoV-2 primary vaccine series and boosters as recommended by the National Vaccination Programme is preferable.

ii.   We do not currently recommend monoclonal antibodies as pre- (or postexposure prophylaxis of COVID-19 due to predominance of immune evasive variants, rendering the currently available monoclonal antibodies ineffective.

iii.   The oral antivirals are not currently indicated for pre- or post-exposure prophylaxis of COVID-19.

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13. PRE- AND POST-EXPOSURE PROPHYLAXIS

Given the advent of the Omicron variant and lack of activity of we no longer recommend the use of tixagevimab/cilgavimab for pre- (or post-) exposure prophylaxis.

14. LONG COVID-19

Several studies confirmed the presence of persistent symptoms after acute COVID-19, a condition known as "long COVID", "post-COVID-19 condition", or "long-haul COVID-19". WHO defines post-COVID-19 condition as occuring in individuals with "a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis." The National Institute for Health and Care Excellence (NICE) defined post-COVID-19 syndrome as "signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis". A meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety, and depression as primary clinical symptoms of 'long COVID'. Although several guidelines on long COVID management have been released, there remains a large practice gap and specific treatments have yet to be robustly reviewed. Post-COVID-19 syndrome is prevented by vaccination[57]. Emerging data indicate that nirmatrelvir/ritonavir and metformin may also prevent post-COVID-19 syndrome[58,59]. It should be noted that the COVID-OUT study which examined

metformin was performed before widespread COVID-19 vaccination and the point estimate for the vaccinated subgroup showed a weaker effect and its 95% CI crossed 1·00, and thus further studies are needed to determine benefits of metformin in those vaccinated/boosted and also those who have had prior infection[59]. Nirmatrelvir/ritonavir in a veteran's study comprising mostly older males was associated with reduced risk of post-COVID condition (RR, 0.74; 95% CI, 0.72-0.77; ARR, 4.51%; 95% CI, 4.01-4.99), including reduced risk of 10 of 13 post–acute sequelae in the cardiovascular system (dysrhythmia and ischemic heart disease), coagulation and haematologic disorders (pulmonary embolism and deep vein thrombosis), fatigue and malaise, acute kidney disease, muscle pain, neurologic system (neurocognitive impairment and dysautonomia), and shortness of breath[58].

THROMBOPROPHYLAXIS AND THERAPEUTIC ANTICOAGULATION

15. THROMBOPROPHYLAXIS

We recommend the use of pharmacological venous thromboembolism (VTE) prophylaxis for patients with critical or severe COVID-19. We recommend patient risk stratification with the PADUA risk score for patients with mild/moderate COVID-19, in determining whether pharmacological thromboprophylaxis is warranted. If pharmacological prophylaxis is contra- indicated, mechanical prophylaxis is recommended (Level 1, Grade A, Strong).

This recommendation represents good clinical practice in the intensive care setting, and is in keeping with international guidelines[60,61] based on RCTs which in absolute and relative terms, have demonstrated that pharmacological prophylaxis reduces mortality, pulmonary embolism, and deep vein thrombosis. COVID-19 is associated with thromboembolic disease as a result of various factors, including endothelitis associated with COVID-19, an increase in circulating prothrombotic factors, and immobility in critical illness[60,61]. D-dimer should not be used as a screening tool for VTE; instead, it should be used as a diagnostic tool of exclusion. Higher rates of thrombosis are seen in ICU COVID-19 patients, in studies that systematically evaluate for them[62–66].

All COVID-19 patients should have thrombotic and bleeding risk assessments such as PADUA score (https://www.mdcalc.com/padua-prediction-score-risk-vte) and VTE bleed score (https://practical-haemostasis.com/Clinical%20Prediction%20Scores/Formulae%20code%20and%20formulae/Formulae/VTED_bleedng/vte_bleed_score.html), or any Risk Assessment Model that the hospital uses, upon diagnosis and as part of the admission process for COVID-19 patients in both acute hospitals and also at out-of-hospital isolation facilities (e.g. Community Care Facilities). In the absence of a locally validated scoring system, we propose adaopting the PADUA risk stratification, acknowledging that it has not been extensively validated in the Asian/Singaporean population. Persons at high risk of VTE (such as PADUA score ≥4 points) should be assessed for thromboprophylaxis with an appropriate agent and duration at an acute hospital. In patients with severe COVID-19 infection, we recommend pharmacological thromboprophylaxis unless contraindicated as they are at higher risk of thrombotic events[67]. In patients with mild/moderate COVID-19 infection, we recommend risk stratification of patients, such as with the PADUA risk score, to determine whether pharmacological thromboprophylaxis is warranted. In patients with contraindications to pharmacological

thromboprophylaxis, the use of pneumatic calf pumps is recommended.

As a general guidance, persons with high risk of VTE (such as PADUA score ≥4 points) be administered thromboprophylaxis with SC enoxaparin 40mg once daily (or renal adjusted dose of 20mg once daily) or other low molecular weight heparin (LMWH), until discharge (i.e. from acute hospital or the out-of-hospital facility if transferred from an acute hospital, whichever is later). If patients are discharged to an out-of-hospital facility, where they have to self-administer LMWH, they should receive the appropriate training and education prior to transfer.

Patients should be educated on general measures to prevent thromboembolism or seek urgent consultation for symptoms of thromboembolism. Patients should be encouraged to maintain hydration and to avoid immobility, so as to reduce the risk of thromboembolism.

We recommend that treating clinicians have a high index of suspicion and low threshold for imaging in situations where VTEs are suspected, such as when heart rate ≥100 beats/min, oxygen saturation <94% on room air, or desaturations on exercise). For lower limb DVT or PE provoked by COVID-19, the recommended length of treatment is 3 months.

Due to the lack of positive data, we do not recommend thromboprophylaxis (including extended thromboprophylaxis) with the direct oral anticoagulants (DOACs) in COVID-19. Routine antiplatelet treatment for all COVID-19 recovered patients is not recommended – the RECOVERY trial found no benefit on 28-day mortality or in the risk of progressing to invasive mechanical ventilation or death with aspirin dosed at 150 mg per day till discharge vs placebo[68].

16. THERAPEUTIC ANTICOAGULATION

Several trials (REMAP-CAP/ATTACC/ATIV-4A[69], INSPIRATION[70]) found no benefit of therapeutic anticoagulation doses of heparin, or doses higher than for prophylaxis, in critically ill patients with COVID-19, but benefit in hospitalised non-ICU patients (REMAP-CAP/ATTACC/ATIV- 4A[69], RAPID[71] , HEP-COVID[72]). This benefit in the REMAP-CAP/ATTACC/ATIV-4A trial was a primary outcome was a composite of 21-day "organ-support–free" days, defined as the number of hospital days not requiring high-flow nasal oxygen, invasive or non-invasive mechanical ventilation, vasopressor therapy, extracorporeal membrane oxygenation (ECMO) support together with in-hospital mortality, for the RAPID trial was a composite of death, invasive mechanical ventilation, non-invasive mechanical ventilation, or admission to an intensive care unit, assessed up to 28 days, and for the HEP-COVID trial was venous thromboembolism (VTE), arterial thromboembolism (ATE), or death from any cause, at 30 ± 2 days.

Although benefit of therapeutic heparin was shown in the three RCTs in hospitalised non-ICU patients (REMAP-CAP/ATTACC/ATIV-4A, RAPID, HEP-COVID), and some guidance (e.g. IDSA/NIH/ASH guidelines) have recommended the consideration of therapeutic doses of heparin- anticoagulation in this group), the interpretation and wide-spread applicability of the results are complicated by [73]:
- Different trial inclusion criteria
- Different definitions of positive outcomes

- Differences in control group anticoagulant intensity across trials
- Significant proportions of patients receiving anticoagulant doses higher or lower than the assigned treatment and thus complicating interpretation of results, for e.g. in the largest trial (REMAP-CAP/ATTACC/ATIV-4A), 28.2 percent assigned to the standard care arm received higher than prophylactic dose heparin and 20.3 percent assigned to therapeutic dose heparin received a lower dose.
- Unclear risk/benefits in different or real-life populations. The largest trial (REMAP-CAP/ATTACC/ATIV-4A) found an absolute risk difference for progression to organ support or death at 21 days at only 4 percent, with a 1 percent major bleeding rate, diminishing possible risk/benefits. The trial also was not able to specify the most common reasons for exclusion (e.g. bleeding risk).

o The improved clinical outcome in these trials were contributed mainly by reduced thrombotic events brought about by therapeutic dose of heparins

o The decrease in mortality in the (REMAP-CAP/ATTACC/ATIV-4A) trial is likely to have been contributed significantly by reduced venous or arterial thrombotic complications.

o In the HEP-COVID trial, the better composite outcome is **mainly** driven by the reduction of venous and arterial thrombotic events, with no difference in mortality rates between the study and control groups.

o Patients in Singapore are documented to have much lower thrombotic rates as compared to Caucasian patients, and thus these results may not be applicable to local Asian populations[74–77]. Indeed, in the RAPID trial, subgroup analysis based on race and ethnicity showed no difference in composite outcome seen in the Asians receiving therapeutic doses of LMWH.

o The time period of these studies was prior to the emergence of the Omicron VOC and many instances prior to the Delta VOC, which may have quite different clinical characteristics

o Patients enrolled were mostly non-vaccinated (or enrolled in the period prior to widespread vaccination)

Given the above, these guidelines and the COVID-19 Thrombosis Workgroup do not recommend routine therapeutic anticoagulation for patients with mild-moderate COVID-19 infection, but prophylactic anticoagulation for patients assessed to be at higher risk of developing venous thrombosis.

SPECIAL POPULATIONS: PAEDIATRIC PATIENTS, PREGNANT WOMEN, IMMUNOCOMPROMISED HOSTS

17. PAEDIATRIC PATIENTS

Remdesivir: Remdesivir may be considered for children with COVID-19 weighing $\geq$ 3 kg who have risk factors for severe disease, have an increasing need for supplemental oxygen, have a SpO2 of <94% on room air, or who have severe or critical illness. There is currently a lack of data for neonates and very young infants. The FDA in April 2022 approved a supplemental new drug application (sNDA) for remdesivir for the treatment of paediatric patients who are older than 28 days and weighing $\geq$ 3 kg, who are either hospitalized with COVID-19 or have mild-to-moderate COVID-19 and are considered high risk for progression to severe COVID-19, including hospitalization or death. This was supported by data from the CARAVAN trial (NCT 004431453)[78].

Remdesivir dosing for children weight ≥3 kg to <40kg: Loading dose: IV 5mg/kg/dose Q24H on Day 1, followed by maintenance dose of IV 2.5mg/kg/dose Q24H from Day 2 onwards. Refer to adult dosing for ≥40kg.

Dexamethasone: Children with clinically significant or worsening COVID-19 pulmonary or systemic disease should be given oxygen and/or supportive treatment, Dexamethasone 0.15 mg/kg IV or orally once daily (maximum dose 6 mg) (or equivalent steroid) can be considered in children who require oxygen (e.g. high-flow oxygen, non-invasive, invasive mechanical ventilation), or on a case-by-case basis otherwise.

Nirmatrelvir-ritonavir: May be considered for children who are at high risk for severe disease who are ≥ 12 years and ≥ 40 kg.

Molnupiravir should not be used in patients <18 years.

MAbs: As per adult guidance, MAbs are not recommended for treatment currently due to non-susceptibility of circulating variants. On a case-by-case basis, for patients ≥ 12 years and ≥ 40 kg with a complicated course (e.g. immunocompromised hosts with persistent infection despite optimizing non-humoral therapies), therapy with MAbs may be considered if viral genotyping can be performed to guide therapy. This recommendation will continue to be reviewed periodically depending on circulating VOCs and their susceptibility to the MAbs.

Other immunomodulators (Baricitinib and Tocilizumab): There is very limited paediatric data and insufficient evidence to make a formal recommendation. Tocilizumab if used should be used in combination with a glucocorticoid.

COVID-19 associated Multisystem Inflammatory Syndrome in Children (MIS-C): Should be managed by experienced paediatricians and a multi-disciplinary team with relevant expertise[79]. IVIG plus methylprednisolone is recommended. In refractory MIS-C, high-dose anakinra, higher dose glucocorticoids, tocilizumab or infliximab may be considered. Low dose aspirin should be initiated for all patients without risk for bleeding. For children with coronary artery aneurysms, moderate to severe left ventricular dysfunction, therapeutic anticoagulation should be considered. Otherwise, anticoagulation at prophylactic doses should be considered in the presence of specific risk factors.

Treating physicians should refer to Paediatric Infectious Disease specialists and their respective institutional guidelines[80].

18. PREGNANT WOMEN

The specific therapies for COVID-19 in pregnant patients should follow that of nonpregnant patients. Treatment for COVID-19 should not be withheld from pregnant or lactating individuals because of theoretical safety concerns. Treatment decisions and decisions to breast-feed while on therapy or temporarily pause (in post-partum individuals) should be a joint-decision making process with the patient and primary/specialty care-providers.

Remdesivir: Remdesivir was not studied specifically in the trials that led to its approval, however data from 86 pregnant and postpartum hospitalised patients with severe COVID-19 treated with remdesivir on a compassionate use programme found that it was well tolerated with minimal serious adverse events (16%, mostly grade 1/2 laboratory abnormalities)[81]. At Day 28 of follow- up, among pregnant women (n=67), and among postpartum women (n=19, all immediate postpartum, median duration post-delivery, 1 day), respectively, 93% and 89% of those on mechanical ventilation were extubated, 93% and 89% recovered, and 90% and 84% were discharged.

Nirmatrelvir/ritonavir: Pregnancy is a risk factor for severe COVID-19, and nirmatrelvir/ritonavir may be considered in pregnancy or recently pregnant patients especially if they have one or more additional risk factors (e.g. obesity, cardiovascular disease, diabetes mellitus etc) per the COVID-19 OAV prescribing checklist in Annex C 'Algorithm for consideration of oral antivirals'. As with other patients, evaluate for potential drug interactions prior to prescribing. Limited real-world data in a cohort of 47 pregnant patients of which 63.8% had an additional risk factor besides pregnancy for severe disease found that it was generally tolerated[82].

Molnupiravir: Molnupiravir is **CONTRAINDICATED** in pregnancy. Breast-feeding is not recommended during therapy and for 4 days after the last molnupiravir dose.

Steroids: Dexamethasone has a history of use to decrease neonatal complications in premature delivery and used for foetal lung maturity have not been associated with ill-effects. There is however some concern of potential adverse foetal effects (e.g. small head circumference, growth restriction, and neonatal hypoglycaemia) with repeated doses of antenatal glucocorticoids. Further there is less data of corticosteroids for pregnant women with COVID-19 (e.g. only 6 pregnant women were enrolled in the RECOVERY trial). However, given the benefits, we recommend the use of steroids for pregnant women with severe or critical COVID-19.

Prednisolone, methylprednisolone and hydrocortisone are metabolised by the placenta and have limited foetal transfer. Dexamethasone (and betamethasone) cross the placenta and have substantial foetal transfer. Methylprednisolone and dexamethasone have the most data for benefit in acute lung injury. As such, we recommend the algorithm suggested by Saad et al, with the choice and duration of steroids in a pregnant patient with COVID-19 will depending on whether glucocorticoids are indicated for foetal lung maturity.

Pregnant patient with severe or critical COVID-19, requiring oxygen therapy and/or mechanical ventilation:

Glucocorticoids indicated for foetal lung maturity?	Steroid regimen
Yes (24 weeks to 33 weeks of gestation)	Dexamethasone 6 mg IM q12hourly for 4 doses, then switch to methylprednisolone 32 mg daily (oral or IV) to complete a total of 10 days or until recovery/discharge (whichever comes first)

No (outside 24 to 33 weeks of gestation, or post- partum and breastfeeding)	Methylprednisolone 32 mg daily (oral or IV) to complete a total of 10 days or until recovery/discharge (whichever comes first)

General comments on the management of pregnant women:

Maternal SpO2 should be kept at least 95% and above, PaO2 above 70 mmHg to maintain sufficient oxygen diffusion gradient across the placenta to the foetus. Hypoxia in adults is defined as $\leq$94%.

Prone positioning may be difficult in pregnant patient in later trimesters due to aortocaval compression. Left lateral position may be an alternative if proning not feasible for pregnant woman with COVID-19 related ARDS.

VTE prophylaxis in pregnant women with COVID-19 is an individualized decision and should be considered for those with severe COVID-19. Unfractionated heparin may be preferred for those closer to delivery as it is more readily reversed.

19. IMMUNOCOMPROMISED HOSTS

In select patients (e.g. immunocompromised hosts), anti-virals and other therapeutics may be deployed beyond the usual durations studied in trials, but this should be a shared-decision between infectious diseases physician and the primary specialist managing the immunocompromised patient[83–86].

Please note that the recommendations above are based on current data, and that updates will be made to this guidance as more evidence becomes available. **Clinical evidence summaries for various therapeutics for COVID-19 are also available from the Ministry of Health-Agency for Care Effectiveness at https://www.ace-hta.gov.sg/resources/archives/covid-19-resources and US- NIH https://www.covid19treatmentguidelines.nih.gov/.**

4. Key Drug Summary Table (Note: Therapy should be guided by an Infectious Diseases Physician or by established institutional protocols in consultation with Infectious Diseases)

Medication	Class	Adult Dose with normal renal/hepatic function	Notes (Please see full product information leaflet/drug use guide)
Antivirals			
Remdesivir	RNA-dependent RNA polymerase inhibitor	200 mg IV loading dose, followed by 100 mg IV daily for 5 to 10 days	Timing of antiviral initiation may be important, as administration with high viral loads seen after peak viral titre has been found to fail in reducing lung damage despite reducing viral loads. Early therapy may be more beneficial compared to later therapy. May cause LFT abnormalities/hepatitis. Monitor LFTs prior to initiation and regularly while on remdesivir.
Nirmatrelvir/ritonavir	Protease inhibitors	Nirmatrelvir 300 mg / Ritonavir 100 mg BD for 5 days	**If GFR 30-60 ml/min: DOSE REDUCE to** Nirmatrelvir 150 mg/ Ritonavir 100 mg BD **If GFR <30 ml/min: Use is CONTRAINDICATED** **Not recommended for use in severe hepatic impairment (Child-Pugh Class C)** Numerous interactions with drugs which depend on CYP3A for clearance or which induce CYP3A4 **Please consult a drug-interaction database (e.g. Liverpool COVID-19 drug interaction site : https://www.covid19-druginteractions.org/checker)** Nirmatrelvir and ritonavir tablets may be split or crushed for administration via a feeding tube or mixed with food or liquid.
Molnupiravir	Mutagenesis - induced Inhibition of replication by RNA-dependent RNA polymerase inhibitor	800 mg every 12 hours for 5 days	Do not use in women of childbearing age who cannot avoid pregnancy or who are pregnant or breast feeding. Avoid pregnancy for 4 days after the last dose of molnupiravir (for females) and for at least 3 months after last dose of molnupiravir (for males). Do not use in patients < 18 years of age due to effect on bone/cartilage growth. Capsules may be opened for administration via a feeding tube. Special access route as drug is currently not HSA-registered.
Immunomodulators			
Dexamethasone	Steroid	6 mg PO or IV for up to 10 days	If dexamethasone is unavailable, may consider substitution with equivalent daily doses of another corticosteroid (e.g. oral prednisolone 40 mg daily, IV methylprednisolone 32 mg daily or IV hydrocortisone 50mg q8 hours) Dexamethasone is not recommended for patients without hypoxemia, or not requiring oxygen. Caution in patients with concurrent infections. Monitor for hyperglycaemia, psychiatric effects, gastrointestinal bleeding, sepsis and heart failure. Please see also **Special populations: Paediatric patients and pregnant women** for recommendations in paediatric and pregnancy.
Baricitinib	JAK inhibitor	4mg PO once daily, for up to 14 days	Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed. Prophylaxis for VTE is recommended unless contraindicated. Monitor LFTs and FBC prior to initiation and regularly while on baricitinib.

			Not recommended for patients with known active tuberculosis infections, who are on dialysis, have end-stage renal disease, or have acute kidney injury.
Tofacitinib	JAK inhibitor	10 mg twice daily for up to 14 days	Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed. Prophylaxis for VTE is recommended unless contraindicated. Dose reduce to 5 mg twice daily in moderate to severe renal or hepatic impairment Patients receiving tofacitinib are at higher risk of serious infections which may result in fatality. Not recommended in patients with other concurrent chronic or recurrent infections, lymphoma and other active malignancies requiring treatment.
Tocilizumab	IL-6 inhibitor	8 mg/kg IV ONCE (up to maximum of 800mg per dose). A repeat dose may be given after 12-24 hours.	Consider discussion with Rheumatology-Allergy-Immunology/Intensive Care Physicians for complex cases. Tocilizumab, in particular in combination with corticosteroids, may increase the risk of opportunistic infections or reactivation and lower intestinal perforation. Some experts recommend prophylactic treatment with ivermectin for patients who are from areas where strongyloidiasis is endemic.

*LFT=Liver function tests, VTE = Venous thromboembolism

Annex A: Data on various Monoclonal Antibodies (Mab) and activity against SARS-CoV-2

Table 1. Stanford Database - https://covdb.stanford.edu/susceptibility-data/table-mab-susc/: Virus variants and spike mutations vs monoclonal antibodies: Fold reduced neutralizing susceptibility to monoclonal antibodies under Emergency Use Authorization (EUA) [c.a.a. 5 June 2023]

The color scheme indicates the fold-reduction in neutralization: <u>absence of color</u> – <5-fold reduced susceptibility; light blue – 5 to 24.9-fold reduced susceptibility; dark blue – ≥25-fold reduced susceptibility. The fold reduction in susceptibility is the median value of results, the subscript is the number of samples. "-" indicates absence of susceptibility data.

Test\mAb	BAM	ETE	BAM/ETE	CAS	IMD	CAS/IMD	CIL	TIX	CIL/TIX	SOT	BEB	ADI
Alpha	1_{23}	13_{20}	1.3_9	1_{32}	0.6_{33}	0.9_{14}	0.6_{15}	1.5_{14}	0.8_{14}	1.8_{30}	0.9_6	1.3_6
Beta	$>1000_{29}$	516_{25}	990_{12}	91_{38}	0.6_{38}	1.6_{19}	1.1_{16}	5.8_{17}	1.7_{16}	1_{31}	1_8	2.8_6
Gamma	$>1000_{16}$	348_{16}	404_4	124_{24}	0.4_{24}	1_9	0.5_{12}	3.7_{11}	0.9_{10}	1_{23}	1_5	2.2_6
Delta	$>1000_{25}$	0.4_{25}	1_9	0.7_{33}	1.5_{34}	1.3_{14}	2.4_{15}	1.0_{16}	1_{17}	1.1_{31}	1_{12}	1.5_8
Omicron/BA.1	$>1000_{42}$	459_{42}	980_{17}	$>1000_{50}$	$>1000_{51}$	$>1000_{23}$	263_{48}	264_{50}	63_{35}	3.8_{64}	1_{27}	108_{20}
Omicron/BA.2	$>1000_{24}$	515_{24}	744_{15}	$>1000_{34}$	219_{33}	387_{23}	1.8_{39}	928_{38}	8_{35}	21_{52}	1_{33}	$>1000_{15}$
Omicron/BA.2.12.1	$>1000_{12}$	515_{12}	794_8	$>1000_{13}$	125_{13}	250_9	2.8_{15}	410_{15}	9.1_{10}	20_{18}	1_{13}	968_6
Omicron/BA.2.75	$>1000_9$	383_9	554_5	477_{11}	$>1000_{11}$	$>1000_7$	14_{15}	29_{15}	24_{11}	12_{15}	3.1_{15}	437_7
Omicron/BA.2.75.2	556_2	489_2	$>1000_1$	589_4	588_4	$>1000_3$	$>1000_7$	$>1000_7$	$>1000_7$	8_9	2.8_7	509_2
Omicron/XBB	$>1000_1$	$>1000_1$	-	589_2	588_2	200_1	$>1000_3$	$>1000_3$	738_2	14_4	$>1000_4$	$>1000_1$
Omicron/XBB.1	$>1000_1$	$>1000_1$	$>1000_1$	880_3	$>1000_3$	887_3	$>1000_6$	$>1000_6$	$>1000_6$	15_8	900_6	-
Omicron/XBB.1.5	-	-	-	650_2	572_2	751_2	433_3	$>1000_3$	867_3	18_5	475_4	-
Omicron/XBB.1.16	-	-	-	420_1	143_1	615_1	127_1	448_1	488_1	5.3_1	149_1	-
Omicron/BA.4/5	$>1000_{19}$	504_{19}	588_{11}	$>1000_{26}$	143_{26}	387_{17}	8.1_{33}	$>1000_{33}$	25_{27}	22_{39}	1_{29}	$>1000_{13}$
Omicron/BA.4.6	556_2	489_2	$>1000_1$	589_4	173_4	738_4	527_6	819_6	738_6	44_5	1_7	509_2
Omicron/BQ.1	-	-	-	177_1	175_1	200_1	$>1000_3$	$>1000_3$	$>1000_3$	26_5	900_4	-
Omicron/BQ.1.1	$>1000_2$	972_2	$>1000_1$	$>1000_4$	$>1000_4$	$>1000_3$	$>1000_7$	$>1000_7$	$>1000_6$	118_9	$>1000_7$	$>1000_2$
Omicron/BF.7	-	-	-	$>1000_1$	383_1	878_1	$>1000_3$	$>1000_3$	$>1000_3$	48_5	1.3_4	-
Omicron/CH.1.1	-	-	-	$>1000_1$	$>1000_1$	$>1000_1$	$>1000_2$	$>1000_2$	$>1000_2$	16_3	$>1000_2$	-

Monoclonal antibody(mAb) abbreviations: **BAM**: Bamlanivimab/LY-CoV555/LY3819253, **ETE**: Etesevimab/LY-CoV016/JS016/CB6, **CAS**: Casirivimab/REGN10933, **IMD**: Imdevimab/REGN10987, **CIL**: Cilgavimab/COV2-2130/AZD1061, **TIX**: Tixagevimab/COV2-2196/AZD8895, **SOT**: Sotrovimab/Vir-7831/S309, **BEB**: Bebtelovimab/LY-CoV1404/LY3853113, **REG**: Regdanivimab/CT-P59, **AMU**: Amubarvimab/BRII-196/P2C-1f11, **ROM**: Romlusevimab/BRII-198/P2B-1G5, **ADI**: Adintrevimab/ADG20/ADG-2.

Annex B: Immunocompromise Definitions – following EC19V (Expert Committee on COVID-19 Vaccination)

Immunocompromised (Follows EC19V Definition)*:

a. Transplant patients on medications that suppress the immune system, including solid organ and allogenic stem cell transplants
b. Cancer patients on active treatment with chemotherapy or on other therapies that suppress the immune system
c. Haematological cancers
d. Non-cancer conditions that suppress the immune system#
e. End-stage kidney disease *(i.e. on haemodialysis or peritoneal dialysis)*
f. Advanced or untreated HIV

Less likely to mount an immune response to vaccination and more likely to have poor outcome from severe COVID-19

 # Including patients on treatments which suppress the immune system (e.g. Active treatment with high-dose corticosteroids (e.g., ≥20 mg prednisone or equivalent per day when administered for ≥2 weeks), alkylating agents, antimetabolites, tumour-necrosis (TNF) blockers, and other biologic agents that are immunosuppressive or immunomodulatory (e.g., B-cell depleting agents)) or those with moderate or severe primary immunodeficiencies.

Annex C: Algorithm for consideration of oral antivirals

Ver 10/ 17July2023/ 11:00 – MOH PCC (PHPC)

SIMPLIFIED CHECKLIST FOR PRESCRIBING ORAL ANTIVIRALS (OAV) PAXLOVID & MOLNUPIRAVIR: ACUTE & COMM HOSP, ED, PRIMARY CARE, NURSING HOMES, CTF, & HRP

Patient must fulfil **ALL** the following BASE ELIGIBILITY criteria:
- ☐ Within 5 days of onset of symptoms (must be symptomatic)
- ☐ Test-confirmed COVID-19 (PCR or Antigen Test Positive)
- ☐ ≥18 years old [Adult patient] OR ≥12 years old AND weight 40 kg or more [Paediatric patient]
- ☐ Does not have severe disease (e.g., hypoxic, SpO2 < 94%)

NB: OAVs should be considered regardless of vaccination status although the option of careful observation/reassessment without OAV therapy may be reasonable if patient is clinically well and with minimum protection[1] for vaccination status, immunocompetent, with no concern for pneumonia and CRP <20 mg/L (if available).

Please note that Paxlovid MAY be crushed for administration if necessary[2], and molnupiravir may be opened for administration through an NG (nasogastric) or OG (orogastric) feeding tube size 12 French or larger[3].

[1] Persons who have completed a primary series and at least one booster dose, such as having received at least three doses of mRNA or Novavax/Nuvaxovid vaccines, or four doses of Sinovac-CoronaVac.
[2] Nirmatrelvir and ritonavir tablets may be split or crushed for administration via a feeding tube or mixed with food or liquid, based on available data that suggests that crushing Paxlovid (nirmatrelvir/ritonavir) does not alter the ritonavir boosting effect and results in comparable nirmatrelvir exposure. Due to lack of information on stability after crushing, it is recommended that any suspension or preparation made with crushed Paxlovid (nirmatrelvir/ritonavir) be consumed/administered immediately. Please see : www.covid19-druginteractions.org/prescribing_resources/paxlovid-crushing-tablets for further details
[3] Please refer to "Fact Sheet for Patients And Caregivers Emergency Use Authorization (EUA) Of LAGEVRIO™ (molnupiravir) capsules For Coronavirus Disease 2019 (COVID-19)" at https://www.fda.gov/media/155055/download and FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR LAGEVRIO™ (molnupiravir) CAPSULES at https://www.fda.gov/media/155054/download for details and instructions.

YES & treatment being considered

Patient must have **1 or more of the following RISK FACTORS** for severe COVID*:
- ☐ Age (≥60 regardless of vaccine status)
- ☐ Age (≥ 50-59 regardless of vaccine status, Paxlovid may be considered)**
- ☐ Active cancer
- ☐ BMI ≥25 kg/m^2 (no minimum protection)
- ☐ BMI ≥30 kg/m^2 (minimum protection)
- ☐ Chronic Kidney Disease (CKD)
- ☐ Chronic obstructive lung disease (including asthma)
- ☐ Serious heart conditions (e.g., heart failure, coronary artery disease, cardiomyopathies)
- ☐ Diabetes mellitus
- ☐ Ongoing immunosuppressive condition/ treatment

* Patients with 1 or more of the above risk factors and who have clinical or radiographic evidence of pneumonia (if available) or a CRP ≥ 50 mg/L (if available) should be prioritised for treatment.

** Paxlovid initiation can be considered, based on patient-doctor discussion

YES

Does the patient have **any of the following CONTRAINDICATIONS** to Paxlovid?
- ☐ Significant drug-drug interactions that cannot be adjusted for
- ☐ GFR < 30mL/ min (no need Renal Function Test if patient has no known renal impairment)
  [Pls refer to next page on drug interactions with Paxlovid/ creatinine clearance]
- ☐ Severe hepatic impairment (Child-Pugh Class C)(Not recommended, insufficient data)

NO contraindications to Paxlovid | **YES** there are contraindications to Paxlovid

PAXLOVID should be considered as the 1st line (default) OAV treatment

Please remember to submit OAV Prescription for each patient prescribed on Patient Risk Profile Portal (PRPP) (applicable for PHPCs only): www.patientprofile.gov.sg

MOLNUPIRAVIR may be considered

NB: Patient must **not** be pregnant or breastfeeding, and must be ≥ 18 years old. Molnupiravir is **not** recommended routinely for patients aged between ≥ 50-59 who are without any other risk factors.

This guidance does not replace sound clinical judgement & professional practice standards. Patient allergy & contraindications must be considered when prescribing these medications. Please refer to drug information sheets, consult patient's primary doctor, pharmacist, or drug interaction database for detailed prescribing guidance

Annex D: Managing Common Drug-Drug Interactions with Nirmatrelvir/Ritonavir (Paxlovid)

*Please note list is not exhaustive. Please consult a drug-interaction database (e.g. www.covid19-druginteractions.org) or pharmacist if required.

Class	Drugs	Recommendations
Antimicrobials		
Antibiotics	Rifampicin	Coadministration is **contraindicated**; may cause large decreases in paxlovid concentrations and significantly decrease its therapeutic effect. Due to the persisting inducing effect upon discontinuation of a strong inducer, **consider an alternative COVID-19 treatment.**
	Rifabutin	Coadministration may increase exposure of rifabutin. It is recommended to give rifabutin 150 mg every day in presence of paxlovid; can return to usual dose 3 days after completion of paxlovid
Anti-retrovirals	Protease inhibitors	No dose adjustments necessary (even if on ritonavir/cobicistat boosted regimen) monitor for protease inhibitor adverse effects. Patients should be informed about the potential occurrence of gastrointestinal side effects (e.g. diarrhoea) due to the higher dose of ritonavir
Central nervous system drugs		
Anticonvulsants	Carbamazepine	Strong CYP inducers - **coadministration is contraindicated**. Decreased plasma concentrations of paxlovid may lead to loss of virologic response and possible resistance. Cannot be started immediately after discontinuation of anticonvulsant due to the delayed offset of the recently discontinued CYP3A inducer.
	Phenobarbital	
	Phenytoin	
Antipsychotic	Aripiprazole	Paxlovid could potentially increase aripiprazole concentrations. **Monitor adverse effects and decrease aripiprazole dosage if needed.** The decision to modify the dosage should be done in consultation with a specialist in mental health medicine. After stopping paxlovid, can resume previous dose after 3 days.
	Clozapine	Coadministration may increase clozapine concentrations. **Co-administration contraindicated** due to serious and/or life-threatening reactions (i.e., serious haematological abnormalities)
	Quetiapine	Coadministration may increase quetiapine concentrations and is **not recommended**. If coadministration is necessary, US product label recommends to reduce quetiapine dose to one sixth the normal dose and monitor for quetiapine associated adverse reactions. Refer to the quetiapine prescribing information for detailed recommendations . To

		resume old dose/restart quetiapine 3 days after last dose of paxlovid
Benzodiazepines	Alprazolam	Consider a lower dose of alprazolam used cautiously and monitor for adverse effects. After stopping paxlovid, resume old dose 3 days after last dose
	Clonazepam	Coadministration is **contraindicated**. May increase concentrations and increase the risk of extreme sedation and respiratory depression. **Can resume 3 days after completing paxlovid.**
	Diazepam	
	Midazolam (Oral)	
	Midazolam (IV)	Coadministration of paxlovid and PARENTERAL midazolam should be done with caution and in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. **Dosage reduction for IV midazolam should be considered, especially if more than a single dose of midazolam is administered.**
	Lorazepam	**No dose adjustment is required**
Cardiac and related		
Anti-arrhythmic	Amiodarone	Coadministration is **contraindicated**. Potentially increased plasma concentrations of antiarrhythmics may result in arrhythmias or other serious adverse effects. **Consider an alternative COVID-19 treatment.**
	Flecanide	
	Propafenone	
	Quinidine	
Calcium channel blockers	Amlodipine	May increase plasma concentrations of calcium channel blockers. **A dose reduction may be considered** (but is optional), to monitor for symptoms of hypotension and to temporarily pause the antihypertensive drug if needed. To **resume dose 3 days after** completion of paxlovid
	Nifedipine	
	Diltiazem	
	Verapamil	
Alpha-1 blockers	Alfuzosin	Coadministration may increase alfuzosin concentrations which may result in severe hypotension. Given the short duration of paxlovid treatment, alfuzosin should be stopped. To resume 3 days after the last dose of paxlovid.
	Tamsulosin	Coadministration may increase tamsulosin exposure. Given tamsulosin's higher affinity for alpha-1A receptors located in

		prostatic smooth muscle and its demonstrated tolerability when combined with other CYP3A4/CYP2D6 inhibitors, coadministration can be considered. Patients should be advised to monitor for signs/symptoms of hypotension and to watch their blood pressure. Tamsulosin may be stopped for the duration of paxlovid treatment if symptomatic hypotension occurs.
	Terazosin	Coadministration may increase terazosin levels due to inhibition of CYP3A4. Given short duration of paxlovid treatment, no dose adjustment is recommended. Patients should be advised to monitor for signs/symptoms of hypotension and to watch their blood pressure. Terazosin may be stopped for the duration of paxlovid treatment if symptomatic hypotension occurs.
	Prazosin	Prazosin is metabolised primarily via demethylation and conjugation, and possibly to a lesser extent via CYP enzymes. Given short duration of paxlovid treatment, no dose adjustment is recommended.
Direct oral anticoagulants	Rivaroxaban	Potentially increased concentrations of anticoagulants which may lead to an increased bleeding risk. **Concomitant use with Paxlovid is not recommended.** The management of this interaction should also take into account the **indication of the anticoagulation** and whether or not NOACs can be stopped during the course of paxlovid treatment. If withheld, it should be **resumed 3 days after** last dose of paxlovid.
	Apixaban	
	Dabigatran	
Warfarin	-	Coadministration is expected to decrease warfarin concentrations. Closely monitor INR if coadministration with warfarin is necessary. If close INR monitoring is not possible, consider alternate COVID-19 therapy.
Antiplatelets	Clopidogrel	Coadministration with paxlovid is likely to reduce the effect of clopidogrel. The management of this interaction requires to **take into account whether or not a transient loss of clopidogrel efficacy during the short duration** of paxlovid treatment is acceptable. **Consider alternative covid-19 treatment in patients at very high-risk of thrombosis,** e.g. at least within 6 weeks of coronary stenting.
	Ticagrelor	Coadministration is **contraindicated** as it may lead to a substantial increase in exposure to ticagrelor. Prasugrel can be used with paxlovid unless the patient has a clinical condition which contraindicates its use in which case an alternative antiplatelet agent should be considered
PDE5 inhibitors	Sildenafil	Coadministration is **contraindicated** when used for the treatment of pulmonary arterial hypertension. Increased plasma concentrations of PDE5 inhibitors can potentially result in visual abnormalities, hypotension, prolonged erection and syncope.
	Tadalafil	

HMG-CoA reductase inhibitors	Lovastatin	Coadministration with potent CYP3A4 inhibitors, such as ritonavir, is **contraindicated** due to the high risk of presenting serious reactions such as risk of myopathy including rhabdomyolysis. **To stop temporarily and resume 5 days after the last dose of paxlovid**
	Simvastatin	
	Atorvastatin	Less dependent on CYP3A for metabolism. When used with paxlovid, **the lowest possible doses of statin should be administered**. Given the short duration of nirmatrelvir/ritonavir treatment, **can consider withholding these statins** as well, and to resume 5 days after completion of paxlovid. .
	Rosuvastatin	
Ivabradine	-	Co-administration contraindicated as ivabradine concentrations will increase and this is associated with the risk of bradycardia.
Cardiac glycosides	Digoxin	Co-administration may increase digoxin concentrations. Caution should be exercised when co-administering PAXLOVID with digoxin, with **appropriate monitoring of serum digoxin levels**. Refer to the digoxin product label for further information
Immunosuppressants and pulmonary		
Corticosteroids (oral/parenteral)	-	Given short duration of Paxlovid, this interaction is unlikely to be clinically significant. No dose change required.
Inhaled corticosteroids	**Budesonide**	**No specific action needed**. Co-administration may increase corticosteroid concentrations. Increased risk for Cushing's syndrome and adrenal suppression. Unlikely clinically relevant due to short treatment duration of Paxlovid (triamcinolone may present a higher risk compared to other corticosteroids due to its long half-life and high potency) – to monitor
	Fluticasone	
	Triamcinolone	
Salmeterol	-	Coadministration may increase salmeterol concentrations, which may result in increased risk of cardiovascular adverse events associated with salmeterol, including QT prolongation, palpitations, and sinus tachycardia. Therefore, **concomitant use is not recommended.**
Immunosuppressants	Cyclosporine	Increases plasma concentrations of immunosuppressants which rapidly reach toxic levels. Therapeutic concentration monitoring is recommended for immunosuppressants. **Avoid use of PAXLOVID when close monitoring of immunosuppressant serum concentrations is not feasible**. If co-administered, refer to individual product label for immunosuppressant for further information. Considering the complex management of this interaction, **an alternative COVID treatment will need to be considered.**
	Tacrolimus	
	Sirolimus	

Miscellaneous		
Colchicine	-	Co-administration **contraindicated** due to potential for serious and/or life-threatening reactions in patients with renal and/or hepatic impairment
Herbal products	St. John's Wort (*Hypericum perforatum*)	Co-administration **contraindicated** due to potential loss of virologic response and possible resistance

Annex E: Therapies that are not recommended or have insufficient evidence for recommendation

1. We do not recommend the routine use of convalescent plasma for the treatment of COVID-19. (Level I, Grade B, Moderate).

Convalescent plasma has not been definitively shown to be effective as a treatment for COVID-19 and concerns remain regarding the risk and benefits of such treatment, in the light of available therapies which have proven efficacy in COVID-19. Efficacy is also uncertain, for example, of units collected prior to the emergence of VOCs, for treatment of disease caused by new VOCs.

One RCT published (103 patients), with a primary outcome of time to clinical improvement within 28 days, defined as patient discharged alive or reduction of 2 points on a 6-point disease severity scale, but this trial was terminated early and was likely underpowered[87]. In this study, severe COVID-19 was defined as respiratory distress as indicated by ≥30 breaths/min; in resting state, oxygen saturation $\leq$ 93% on room air; or arterial partial pressure of oxygen (PaO2)/fraction of inspired oxygen (FiO2) of 300 or less. Life-threatening COVID-19 was defined as respiratory failure requiring mechanical ventilation; shock; or other organ failure (apart from lung) requiring intensive care unit (ICU) monitoring. There was no significant difference in the primary outcome in the convalescent plasma group 51.9% (27/52) vs 43.1% (22/51) in the control group (difference 8.8% [95% CI, −10.4% to 28.0%]; hazard ratio [HR], 1.40 [95% CI, 0.79-2.49]; P=0.26). In a post-hoc sub-analysis of those with severe disease, the primary outcome occurred in 91.3 % (21/23) of the convalescent plasma group vs 68.2 % (15/22) of the control group (HR, 2.15 [95% CI, 1.07-4.32]; P=0.03). No difference was found in the group with life-threatening disease, possibly because the trial was underpowered. At 24, 48 and 72 hours, the convalescent plasma group statistically significant a higher rate of viral nucleic acid negative conversion rate.

Another RCT consisting of 228 patients who received convalescent plasma versus 105 patients who received placebo found no significant difference between the groups in the distribution of clinical outcomes according to the ordinal scale at day 30 (odds ratio, 0.83; 95% CI 0.52 to 1.35; p=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of -0.46 percentage points (95% CI, -7.8 to 6.8)[88]. Similarly, another trial conducted in India (PLACID), which was an open label phase II RCT comprising 464 patients failed to find benefit with convalescent plasma for a composite outcome of progression to severe disease (PaO2/FiO2 <100 mm Hg) or all-cause mortality at 28 days post-enrolment[89].

A retrospective US national registry based study comprising 3082 patients found a 30-day mortality rate after plasma transfusion in 115 of 515 patients (22.3%) in the high-titre group, 549 of 2006 patients (27.4%) in the medium-titre group, and 166 of 561 patients (29.6%) in the low-titre group, with a sub analysis showing no mortality benefit in those on mechanical ventilation[90].

One randomized, double-blind, placebo-controlled trial (n=160) of convalescent plasma with high IgG titres against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in older adult patients within 72 hours after the onset of mild Covid-19 symptoms, however, found a reduction

in the progression of Covid-19 (severe respiratory disease) (relative risk, 0.52; 95% confidence interval [CI], 0.29 to 0.94; P = 0.03), with a relative risk reduction of 48%.

A large multicentre, double-blind, randomized, controlled trial [91] evaluated the efficacy and safety of COVID-19 convalescent plasma, as compared with control plasma in symptomatic adults (≥ 18 years of age) who had tested positive for SARS-CoV-2, regardless of their risk factors for disease progression or vaccination status. Participants were enrolled within 8 days after symptom onset and received a transfusion within 1 day after randomization. Among 1225 participants who underwent randomization, 1181 received a transfusion. The primary outcome (COVID-19-related hospitalisation within 28 days after transfusion) occurred in 17 of 592 participants (2.9%) who received convalescent plasma and 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction, 3.4 %; 95% confidence interval, 1.0 to 5.8; P = 0.005, relative risk reduction 54%). However, as all the patients in that study were recruited before the Omicron wave and were mainly unvaccinated, the results from this study may not be ==extrapolatable to vaccinated patients with infection with currently circulating variants==. Of note, in the small subgroup of fully vaccinated patients, none in either arm of the study was hospitalised. In addition, plasma infusion was associated with transfusion adverse events (5.7% in the convalescent plasma group and 9.3% in the control group.

In terms of safety there is theoretical risk of exacerbating lung injury secondary to immune-enhancement, but a large study on key safety metrics after transfusion of ABO-compatible human COVID-19 convalescent plasma in 20,000 hospitalised adults with severe or life-threatening COVID-19 as part of the US FDA Expanded Access Program for COVID-19 convalescent plasma found the incidence of all serious adverse events (SAEs) in the first four hours after transfusion to be <1%[92].

Considering the available evidence, and given the availability of other effective treatments, we do not recommend the routine use of convalescent plasma for the treatment of COVID-19. The convalescent plasma programme in Singapore has ceased prospective collection of units and was suspended in September 2021.

2. We do not recommend the use of interferon preparations (e.g. interferon beta-1a/1b, interferon alpha-2b, pegylated interferon lamda) (Level II, Grade C, Weak) or lopinavir/ritonavir (Level I, Grade B, Strong).

In a phase 2 RCT in 125 adults in Hong Kong, combination treatment (lopinavir/ritonavir and ribavirin, with interferon beta-1b if within 7 days of onset of illness, was found to have more rapid nasopharyngeal virologic clearance (7 vs. 12 days) [the study's primary end point], shorter time to symptom alleviation (4 vs. 8 days), and shorter median hospital stay (9 vs. 15 days). In a subgroup analysis, patients in the combination therapy group who did not receive interferon did not have better outcomes than the control group, suggesting that interferon may have been the backbone of this treatment. Patients had mild COVID-19 in both combination and control groups in this trial, however, as indicated by a median NEWS score of 2. One small open-label RCT comprising 81 patients found that early administration of interferon beta-1a subcutaneously at

12 million IU/ml 3 times weekly for 2 consecutive weeks (before 10 days from onset of symptoms) reduced mortality (OR 13.5, 95% CI 1.5-118), and overall 28-day mortality (19% vs 43.6, *P* = 0.015)[93]. However, the WHO-sponsored SOLIDARITY trial, comprising 11,330 adults (and 2063 to interferon beta-1a) also failed to show a mortality benefit, or reduction in ventilation or hospitalization duration in patients receiving interferon beta-1a,[24]and another multicentre randomized controlled trial involving 969 patients from 5 countries found that interferon beta-1a plus remdesivir was not superior to remdesivir alone in hospitalised patients with COVID-19 pneumonia[94].

The LOTUS trial which was a non-blinded RCT on lopinavir/ritonavir monotherapy with 199 patients with more severe COVID-19 (overall mortality 22%), showed that time to clinical improvement did not differ between the two groups (median, 16 days), and the mortality rate at 28 days was numerically lower for lopinavir/ritonavir compared with standard care (19.2% vs 25%, −5.8 percentage points; 95% CI, −17.3 to 5.7) but this did not reach statistical significance[95]. In a modified intention-to-treat analysis, which excluded three patients with early death, the between-group difference in the median time to clinical improvement (median, 15 days vs. 16 days) was significant, albeit only very modest (hazard ratio, 1.39; 95% CI, 1.00 to 1.91), and this did not clearly correlate with virologic clearance.

A randomized, controlled, adaptive platform trial involving predominantly vaccinated adults (83% vaccinated) found that the incidence of hospitalization or an emergency department visit was lower among those who received a single dose of pegylated interferon lambda compared to those who received placebo (relative risk, 0.49; 95% Bayesian credible interval, 0.30 to 0.76; posterior probability of superiority to placebo, >99.9%). Further data, however, will be needed to define and support the use of interferons for COVID-19[96].

Based on these results, as well as the results from the RECOVERY and SOLIDARITY trials, we do not recommend lopinavir/ritonavir as therapy. We do not recommend interferon therapy outside of a clinical trial.

3. **We do not recommend the use of fluvoxamine for the treatment of COVID-19 (Level II, Grade B, Weak)**

One preliminary RCT, STOP-COVID, with a small cohort (n=152) and limited follow up found a lower likelihood of deterioration over 15 days with fluvoxamine[97], and another RCT (TOGETHER, 741 randomised to fluvoxamine and 756 to placebo) found that treatment with fluvoxamine 100 mg twice daily for 10 days in high-risk outpatient with early COVID-19 reduced the need for hospitalisation (defined as retention in a COVID-19 emergency setting >6 hours or transfer to a tertiary hospital up to 28 days post-randomisation (111% vs 16%, RR 0.68, 95% CI 0.52-0.88)[98]. The significance of the TOGETHER trial's end point (> 6 hours retention in the emergency room) and its broader applicability may be limited, and a follow on trial examining the utility of fluvoxamine (STOP-COVID 2) was stopped early for futility due to low case rates and recruitment, and no differences found between fluvoxamine and placebo up to the time of trial cessation[99].

Another RCT with a 2-by-3 factorial design, COVID-OUT found no benefit of fluvoxamine, or ivermectin or metformin in preventing serious SARS-CoV-2 infection (hypoxemia, emergency room visit, hospitalization or death) in patients enrolled within 3 days of a confirmed infection and less than 7 days after onset of symptoms[100].

4. We do not recommend the use of inhaled corticosteroids (e.g. budesonide) for the treatment of COVID-19 (Level II, Grade B, Weak)

The PRINCIPLE trial was an open label RCT (n=1856) which found a decreased time to self-reported recovery with the inhaled budesonide arm (11.8 days vs 14.7 days), but no difference in 28 days mortality or hospitalisation[101]. The open label nature and the end-point of self-reported recovery limits the generalisability and significance of this trial. The STOIC trial included 146 patients and looked at an endpoint of COVID-19 related urgent care visit or hospitalisation and found a reduction in the primary outcome of 3% in budesonide arm vs 15% in usual care arm (*P*=0·009, ITT) but this was a small trial and further RCTs are needed[102].

5. We do not recommend the use of hydroxychloroquine or chloroquine for the treatment of COVID-19 (Level I, Grade A, Strong).

A small study of 20 COVID-19 patients treated with hydroxychloroquine +/- azithromycin by a French group generated interest as it showed a significant reduction of the viral carriage at D6-post inclusion compared to controls, and much lower average carrying duration than reported of untreated patients in the literature. Azithromycin added to hydroxychloroquine (in six of 20 patients) was reported to more effectively clear the virus. However numerous concerns were raised with this trial, in particular its open-label and non-randomized nature and small number of patients[103].

One large purported registry study has been retracted due to doubts over the veracity of data, several large observational trials have since shown no clear benefit and a potential for cardiac toxicity[104–107], in particular when hydroxychloroquine is combined with azithromycin. Additionally, the RECOVERY trial interim analysis of 1542 patients who were randomised to hydroxychloroquine, compared with 3132 patients randomised to usual care alone found no significant difference in the primary endpoint of 28-day mortality (25.7% hydroxychloroquine vs. 23.5% usual care; hazard ratio 1.11 [95% CI 0.98-1.26]; P =0.10), and no evidence of beneficial effects on hospital stay duration[108]. The SOLIDARITY trial also failed to show and benefit of hydroxychloroquine on mortality, need for mechanical ventilation or hospitalization duration[39,109]. We therefore do not recommend the use of hydroxychloroquine or chloroquine.

6. We do not recommend the use of favipiravir outside of a clinical trial (Level II, Grade B, Weak).

One prospective, open-label, RCT of favipiravir in Japan comprising 89 patients randomised to get favipiravir early (day 1) or late (day 6) did not find differences in times to defervescence, viral

clearance, disease progression or 28-day mortality[110]. An adaptive, multicentre, open label phase II/III RCT of favipiravir vs standard of care in hospitalised patients with moderate COVID-19 pneumonia reported interim results consisting of 60 patients enrolled in the pilot stage[111].] On day 5, the viral clearance was achieved in 25/40 (62.5%) patients on favipiravir and in 6/20 (30.0%) patients on standard of care (p=0.018). By day 10, the viral clearance was achieved in 37/40 (92.5%) patients on favipiravir and in 16/20 (80.0%) patients on standard of care. The median time to body temperature normalization was 2 days (IQR 1–3) in the favipiravir group and 4 days (IQR 1–8) in the standard of care group (p=0.007). A meta-analysis showed faster viral clearance at day 7 with favipiravir, and clinical improvement by day 14, but studies included were heterogenous in design and no difference in mortality was noted[112].

Evidence of significant clinical benefit of favipiravir is still lacking and we do not recommend its use outside of a clinical trial.

7. We do not recommend the use of other non-corticosteroid immunomodulators (e.g. IL-1, BTK, GM-CSF inhibitors) outside of a clinical trial. (Ungraded).

Besides corticosteroids, tocilizumab and the JAK inhibitors e.g. baricitinib, tofacitinib, the role of non-steroid immunomodulators in the treatment of COVID-19 is still unclear., e.g. IL-1, and other immunomodulators e.g. BTK inhibitors are unclear at this point[113,114]. Further data are awaited.

Anti-Granulocyte macrophage colony-stimulating factor (GM-CSF) monoclonal antibodies directly binds GM-CSF and prevents signalling through its receptor, and downstream activation and trafficking of myeloid cells and elevation of chemokines (e.g. IP-10, MCP-1, IL-8), cytokines (IL-6, IL-1) and other markers of systemic inflammation (CRP, D-dimer, ferritin) and various anti-GM-CSF antibodies have been studied including lenzilumab, mavrilimumab, and otilimab. Lenzilumab improved the likelihood of survival without ventilation by 54% in the mITT population (HR: 1.54; 95%CI: 1.02-2.31, p=0.041, preprint data)[115], and there were some indications in a preplanned sub analysis in a otilimab trial for a survival benefit in patients $\geq$ 70 years (65.1% with otilimab vs 45.9% in placebo, P = 0.009), but this was an unadjusted analyses, and this was not confirmed in Part 2 (N=350 randomised) where the model-adjusted difference was 0.9% (95% CI –9.3, 11.2; p=0.86)[116]. no mortality benefit was found in a small trial (n=40) with mavirilimumab[117]. Further data are needed for the anti- GM-CSF antibodies.

8. **We do not recommend the use of cellular therapies such as mesenchymal stem cell infusion or donor lymphocyte infusions outside of a clinical trial (Level II, Grade C, Weak).**

Few data are available for lymphocyte infusion therapies [118] and larger confirmatory trials are needed for mesenchymal stem cell infusion therapy[119,120].

9. **We do not recommend the use of ivermectin for the treatment or prophylaxis for COVID-19 (Level I, Grade A, Strong).**

Many clinical studies have limitations such as methodological limitations including small sample sizes, varying dosing regimens of ivermectin, open-label design, and poorly defined disease severity and outcome measures. One RCT of 476 patients with mild COVID-19 did not find any different in time to symptom resolution with a 5-day course of ivermectin, compared to placebo[121]. In another open-label RCT (n=490) of high-risk patients with mild to moderate COVID-19 conducted in Malaysia, oral ivermectin at 0.4mg/kg body weight daily for 5 days in early illness did not prevent progression to severe disease[122]. An RCT in Singapore also did not show a protective effect of a single 12 mg dose of oral ivermectin in preventing COVID-19[123]. Toxicities associated with misuse and overdose include rash, nausea, vomiting, abdominal pain, severe hepatitis, and even death. The COVID-OUT RCT also did not find benefit of ivermectin in preventing serious SARS-CoV-2 infection[100], and the ACTIV-6 RCT also did not demonstrate any differences between ivermectin and placebo for time to recovery in patients with mild to moderate COVID-19[124].

10. **We do not recommend post- or pre- exposure chemoprophylaxis for COVID-19 with hydroxychloroquine (Level I, Grade B, Moderate).**

One RCT involving 821 subjects found no benefit with post-exposure prophylaxis[125], although this study had some limitations (only 15% of COVID-19 cases confirmed by PCR, and a delay of 3 or more days between exposure and starting preventive treatment). Another randomised controlled trial conducted in Singapore with 3037 participants in a dormitory setting with a COVID-19 outbreak, looked at hydroxychloroquine, iodine-spray and Vitamin C/Zinc, and found absolute risk reductions of COVID-19 infection with oral hydroxychloroquine (21%, 2–42%) and povidone-iodine throat spray (24%, 7–39%)[123]. This trial was however, open label, and cluster-randomised (not individually randomised) and infection-pressure might not have been homogenous across groups. A separate meta-analysis (not including the Singaporean study [123]) of over 4000 participants in 4 studies found that hydroxychloroquine might have trivial to

no effect on suspected, probable, or laboratory confirmed infection[126]. The pre-exposure prophylaxis trial with hydroxychloroquine, Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine [HERO-HCQ] results only enrolled 1360 of a planned 15,000 health care workers and was terminated, and failed to find any benefit (albeit underpowered)[127].

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