COVID-19 Vaccines and Therapeutics Quick Guide

By Pharmaceutical Society of Singapore (PSS) Infectious Diseases Special Interest Group (IDSIG).

This quick guide summarizes the key points and evidences for pertinent COVID-19 vaccines and therapeutics and the team hopes it will support pharmacists in recommending COVID-19 vaccinations and providing care for patients with COVID-19.

Table 1: Summary COVID-19 vaccines available under the National Vaccination Programme

Vaccine name and type	Summary of evidence	Activity against strains	Schedule and administration	Common ADRs	Contra-indications and precautions	Ref
Pfizer/ BioNTech Comirnaty mRNA	Symptomatic, laboratory confirmed COVID-19 - Relative risk: 0.09 (0.07–0.1) - Absolute Effect: 3,840 fewer per 100,000 Hospitalization for COVID-19 - Relative risk: 0.02 (0.00–0.12) - Absolute Effect: 154 fewer per 100,000 Deaths due to COVID-19 - Relative risk: 0.17 (0.02–1.39) - Absolute Effect: 25 fewer per 100,000	Delta strain Vaccine effectiveness against symptomatic disease >80% after 9 weeks from the completion of the primary series and reaches >90% for up to 10 weeks after the booster dose. Omicron strain Vaccine effectiveness against symptomatic disease >65% after 4 weeks from the completion of the primary series and reaches >55% for up to 9 weeks after the booster dose.	Adult/Adolescent (Aged 12+) **Primary:** Two 0.3mL (30 mcg) doses at 0 and 21 days **Booster:** One 0.3mL (30 mcg) dose taken 5-9 months from last dose of primary series **2nd Booster:** One 0.3mL (30 mcg) at least 5 months after 1st booster - Recommended for persons aged 80 years and above, persons living in aged care facilities and persons aged 12 and above who are medically vulnerable and at higher risk of severe COVID-19 - Offered to persons aged 50-79 y/o Pediatric (Aged 5-11) **Primary:** Two 0.2mL (10 mcg) doses at 0 and 21 days Pediatric (Aged 6 months – 4 y/o)* **Primary:** Three 0.2 mL (3 mcg) doses at 0, 21 and 77+ days ***Not yet approved in Singapore, under review by MOH**	Injection site pain, swelling, redness, tiredness, headache, muscle pain, chills, joint pain, fever	Contra-indication People with severe allergic reaction to COMIRNATY, or other inactivated vaccines or components of the vaccine. Precaution Myocarditis and pericarditis Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose. Observed risk is highest in males 12-17. All vaccinated persons, in particular adolescents and younger men, should avoid exercise or strenous physical activity for two weeks after the vaccination.	1-5
Moderna/ Spikevax mRNA	Symptomatic, laboratory confirmed COVID-19 - Relative risk: 0.07 (0.05–0.09) – Absolute Effect: 4,885 fewer per 100,000 Hospitalization for COVID-19 - Relative risk: 0.04 (0.01-0.31) - Absolute Effect: 163 fewer per 100,000 Deaths due to COVID-19 - Relative risk: 0.14 (0.01 -2.79) - Absolute Effect: 18 fewer per 100,000	Delta strain Vaccine effectiveness against symptomatic disease >80% and reached >95% with booster. Omicron strain The vaccine effectiveness with primary series reduces over time from 75.1% (95% CI, 70.8 to 78.7) after 2 to 4 weeks to 14.9% (95% CI, 3.9 to 24.7) after 25 or more weeks. The booster vaccine increased effectiveness to 70.1% (95% CI, 69.5 to 70.7) after 2 to 4 weeks. This waned to 60.9% (95% CI, 59.7 to 62.1) after 5 to 9 weeks	Adult (Aged 18+) **Primary:** Two 0.5mL (100mcg) doses at 0 and 28 days **Booster:** One 0.25mL (50mcg) given at least 5 months after completion of the primary series 2nd Booster: One 0.25ml (50mcg) dose given at least 4 months after first booster dose.	Pain at the injection site, fatigue, headache, myalgia, arthralgia, chills, nausea/ vomiting, axillary swelling/ tenderness, fever, injection site swelling and redness.	Contra-indication People with severe allergic reaction to Spikevax, or other inactivated vaccines or components of the vaccine.	2,3,4,6

Vaccine name and type	Summary of evidence	Activity against strains	Schedule and administration	Common ADRs	Contra-indications and precautions	Ref
Sinovac-CoronaVac β-propio-lactone-inactivated vaccine	Efficacy against symptomatic COVID-19: 51-84% Efficacy against hospitalisations due to COVID-19: 100%	<u>Delta strain</u> Efficacy against symptomatic COVID-19: 59%, [95% CI; 47.5-69.6] <u>Omicron strain</u> Insufficient data at present	<u>Adult (Aged 18+)</u> **Primary:** Three 0.5mL (600SU of inactivated SARS-CoV-2 virus) doses at 0, 28 and 118 days (3rd dose should be 90 days after 2nd dose)	Injection site pain, fever, pruritus, myalgia, cough	<u>Contra-indication</u> People with severe allergic reaction to Coronavac, or other inactivated vaccines or components of the vaccine. Considered for use in persons who are medically ineligible to receive mRNA vaccines and the Novavax/Nuvaxovid vaccine.	5-8
Novavax/ Nuvaxovid Protein subunit	Efficacy against symptomatic COVID-19: 90% Efficacy against severe COVID-19: 100%	<u>Delta strain</u> Limited data. 80% efficacy demonstrated in trial conducted on adolescents aged 12-17, during a period where delta variant was dominant. Of note, adolescents had greater antibody responses compared to adults aged 18 and above. <u>Omicron strain</u> Insufficient data at present	<u>Adult (Aged 18+)</u> **Primary:** Two 0.5mL (5mcg of SARS-CoV-2 spike protein) doses at 0 and 21 days **Booster:** One 0.5mL (5mcg of SARS-CoV-2 spike protein) given 5-9 months from last dose of primary series	Injection site tenderness, injection site pain, fatigue, myalgia, headache, malaise, arthralgia, nausea/vomiting.	<u>Contra-indication</u> People with severe allergic reaction to Coronavac, or other inactivated vaccines or components of the vaccine.	5,9

Other Considerations

<u>Pregnant or breastfeeding women</u>

Internationally, a large number of pregnant and breastfeeding women have received a COVID-19 vaccination. The Expert Committee on COVID-19 Vaccination (EC19V) has examined studies done to monitor women who were vaccinated when they were pregnant, and their babies. These studies were done on women at different trimesters of pregnancy and there is no evidence to suggest that the Pfizer-BioNTech/ Comirnaty or Moderna/Spikevax COVID-19 vaccine may cause harm to pregnant women or their babies.

Both Pfizer-BioNTech/ Comirnaty and Moderna/Spikevax COVID-19 vaccines are mRNA vaccines. As mRNA vaccines are not live vaccines, they are biologically unlikely to adversely affect breastfed babies. In addition, the breast milk of vaccinated mothers may help to protect their babies from COVID-19 due to antibodies in breast milk. There have also been no vaccine-related side effects reported in the babies who were breastfed by mothers who received the vaccine while breastfeeding

There is currently limited data in pregnant women for both Sinovac-CoronaVac and Novax/Nuvaxovid. Nevertheless, The Sinovac-CoronaVac vaccine is an inactivated vaccine, while Novavax/Nuvaxovid is a protein subunit vaccine. These vaccine technologies are routinely used in many other vaccines with a documented good safety profile, including in pregnant women.

Table 2: Summary of COVID-19 therapeutics available in healthcare institutions in Singapore[10]

Medication and Class	Dose*	Place in therapy	Summary of evidence	Notes for pharmacists	Ref
Antivirals					
Remdesivir RNA-dependent RNA polymerase inhibitor	200mg IV on Day 1, followed by 100mg IV daily from Day 2 via intravenous infusion. Total of 5 to 10 days. It should be given within 7-10 days of onset of illness.	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression. - Monotherapy b) Severe illness (requiring supplemental oxygen) - Combination therapy (Remdesivir + Dexamethasone) c) Critical illness (on invasive ventilation or ECMO) - Remdesivir may be considered but utility is likely limited.	<u>Efficacy:</u> a) Mild to moderate illness Remdesivir resulted in a 87% reduction in the risk of composite COVID-19 related hospitalisation or all-cause death with remdesivir vs placebo. Remdesivir also reduced the risk of COVID-19-related medically attended visits or all-cause deaths at day 28 by 81%. [PINETREE study] b) Severe illness i) Remdesivir significantly shortened the time to recovery in COVID-19 hospitalised adults (10 days vs 15 days, p<0.001) when compared to placebo. Remdesivir can also reduce progression to high flow oxygen, non-invasive or invasive ventilation. Trend of reduction in mortality was greatest for hospitalised patients requiring supplemental oxygen but not non-invasive, invasive ventilation or ECMO). [ACTT-1 study] ii) Efficacy of a 5-day regimen of remdesivir in severe COVID-19 was similar to that of a 10-day regimen [GS-US-540-5773 study] <u>Safety:</u> Hypersensitivity reactions including infusion-related and anaphylactic reactions have been observed, mostly during and within the hour following administration. Extending infusion time to 120 minutes may mitigate this. Other adverse effects include nausea, increase in ALT/AST and bradycardia. Monitor LFTs and heart rate prior to initiation and regularly while on remdesivir.	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. There is a risk of reduced antiviral activity when remdesivir is administered with chloroquine phosphate or hydroxychloroquine sulfate.	11-16
Molnupiravir Mutagenesis - induced Inhibition of replication by RNA-dependent RNA polymerase inhibitor	800mg every 12 hours for 5 days It should be given within 5 days of onset of illness.	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression.	<u>Efficacy:</u> Studied in non-hospitalised adults with mild-moderate Covid-19 disease with at least 1 risk factor for severe disease progression. Molnupiravir reduces risk of hospitalisation or death through day 29, 6.8% vs 9.7% in placebo, with a relative risk reduction of 30% (95% CI 1% to 51%). [MOVe-OUT] <u>Safety</u> Adverse events include diarrhea, nausea and dizziness.	Do not use in women of childbearing potential or who are pregnant or breast feeding. In females and males, avoid unprotected intercourse for 4 days and 3 months after the last dose of molnupiravir respectively. Do not use in patients < 18 years of age due to effect on bone/cartilage growth.	17

*For adults with normal renal and hepatic function.

Medication and Class	Dose*	Place in therapy	Safety/Efficacy	Notes for pharmacists	Ref
Nirmatrelvir/ ritonavir [Paxlovid] Protease inhibitors	Nirmatelvir 300mg / Ritonavir 100mg BD for 5 days It should be given within 5 days of onset of illness in mild-moderate COVID-19.	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression.	Efficacy: Studied in unvaccinated, non-hospitalised adults with mild-moderate disease at risk for progression to severe Covid-19 disease. - Use of Paxlovid within 5 days of symptoms onset had reduced the risk of Covid-19 related hospitalisation or death from any cause by almost 90% vs placebo [EPIC-HR] At the end of therapy, viral load was reduced by approximately 10-fold relative to placebo if initiated within 5 days of initial symptoms. Safety: Adverse events include dysgeusia, diarrhea, hypertension and myalgia.	eGFR 30-60 ml/min: ↓ dose to Nirmatelvir 150 mg/ Ritonavir 100 mg BD. Use is CONTRAINDICATED in patients with eGFR <30 ml/min, or severe hepatic impairment (Child-Pugh C). Numerous interactions with drugs which depend on CYP3A for clearance or which induce CYP3A4. Prior to dispensing, please check a drug-interaction database for potential drug interactions (e.g. https://www.covid19-druginteractions.org/checker). Do not crush/break tablets.	18-20
Immunomodulators					
Dexa-methasone Steroid	6mg PO or IV for up to 10 days	a) Severe illness (requiring supplemental oxygen but not invasive ventilation or ECMO), used alone or in combination with remdesivir and/or baricitinib. b) Critical illness (requiring mechanical ventilation or ECMO), used alone or in combination with tocilizumab or baricitinib.	Efficacy a) Severe illness Amongst patient hospitalised with COVID-19 and requiring supplemental oxygen without invasive mechanical ventilation, dexamethasone given for 10 days, compared to standard of care, significantly lowered 28-day mortality (23.3% vs. 26.2%; [95% CI 0.72 to 0.94]) [RECOVERY trial] b) Critical illness i) Amongst patients on mechanical ventilation, dexamethasone given for 10 days, compared to standard of care, significantly lowered 28-day mortality (29.3% vs 41.4%, [95% CI 0.51 to 0.81]) [RECOVERY trial] ii) The meta-analysis by REACT working group found that, amongst critically ill patients, treatment with corticosteroids, compared to usual care or placebo, was associated with lower 28-day all-cause mortality (OR, 0.66 [95% CI, 0.53-0.82]). Safety Caution in patients with concurrent infections. Monitor for hyperglycaemia, psychiatric effects, gastrointestinal bleeding, sepsis and heart failure.	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 8hourly)	21-22

*For adults with normal renal and hepatic function

Medication and Class	Dose*	Place in therapy	Safety/Efficacy	Notes for pharmacists	Ref
Baricitinib Janus kinase (JAK) inhibitor	4mg PO once daily, for up to 14 days	a) Severe illness (requiring supplemental oxygen but not invasive ventilation or ECMO), used alone or in combination with remdesivir and/or baricitinib. b) Critical illness (requiring mechanical ventilation or ECMO), in combination with dexamethasone.	<u>Efficacy</u> Amongst patients critically ill with COVID-19, baricitinib given for up to 14 days, compared to placebo, in combination with standard of care, significantly reduced 28-day all-cause mortality by 46%, and 60-day mortality by 44%. [exploratory trial with similar design to COV-BARRIER trial] <u>Safety</u> Serious infections, venous thrombosis, including pulmonary embolism were reported amongst patients receiving baricitinib in the COV-BARRIER trial and the exploratory trial respectively. Prophylaxis for venous thromboembolism is recommended unless contraindicated. Monitor liver function test and full blood count prior to initiation and regularly while on baricitinib.	Not recommended for patients with active tuberculosis infections, who are on dialysis, have end-stage renal disease, or have acute kidney injury.	23-25
Tocilizumab Interleukin-6 (IL-6) inhibitor	8mg/kg IV ONCE (up to maximum of 800mg per dose). A repeat dose may be given after 12-24 hours.	a) Critical illness (requiring mechanical ventilation or ECMO), in combination with dexamethasone.	<u>Efficacy</u> Amongst critically ill patients with COVID-19 receiving organ support in ICU, tocilizumab compared to placebo, was associated with a higher median number of respiratory and cardiovascular organ support-free days (10 days vs 0 days, adjusted odds ratio 1.64 [95% credible interval, 1.25-2.14]) and reduced in-hospital mortality (27% versus 36%; adjusted odds ratio 1.64 [95% credible interval, 1.14-2.35]. [REMAP-CAP trial] <u>Safety</u> Serious adverse events reported in the tocilizumab group include secondary bacterial infection, bleeding events, cardiac events and deterioration in vision. 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.	26-30

*For adults with normal renal and hepatic function

Medication and Class	Dose*	Place in therapy	Safety/Efficacy	Notes for pharmacists	Ref
Viral-neutralising, antibody-based therapies					
Tixagevimab-cilgavimab [Evusheld] Monoclonal antibody to SARS-CoV-2 spike protein	Prophylaxis: currently 150mg Tixagevimab/ 150mg Cilgavimab as two injections (one in each gluteal muscle); in literature 300mg Tixagevimab/ 300mg Cilgavimab has been used for PrEP. Treatment: 300mg Tixagevimab/ 300mg Cilgavimab, IM as two injections (one in each gluteal muscle) It should be given within 7 days of onset of illness in mild-moderate COVID-19	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression. b) Pre-exposure prophylaxis. c) Post-exposure prophylaxis.	<u>Efficacy</u> <u>Treatment</u> In patients with mild to moderate illness, Evusheld reduced the risk of progression or all-cause death by 50-67% when compared against placebo within 5-7 days of symptoms onset. [TACKLE trial] <u>Pre-exposure prophylaxis</u> Evusheld resulted in a 77% [95% CI 46-90] reduction in COVID-19 incidence compared to placebo ($p<0.001$) among unvaccinated adults with pre-specified co-morbidities, aged 60 or older or at increased risk of COVID-19 infection. [PROVENT trial] <u>Post-exposure prophylaxis</u> In a pre-planned subgroup analysis of participants who were PCR negative at time of dosing, Evusheld reduced the risk of COVID infection by 73% [95% CI 27 – 90] if given within 8 days after exposure. [STORMCHASER trial] <u>Safety</u> Hypersensitivity reactions, including infusion-related and anaphylactic reactions have been observed. Monitor patients during and for 1 hour post administration. Other adverse effects include headache, fatigue, cough and cardiovascular events such as myocardial infarction and cardiac failure. Risk of cross-hypersensitivity with COVID-19 vaccine containing excipients such as polysorbate 80 or polyethylene glycol. Caution when used in individuals with bleeding disorders since it is administered via IM.	Evusheld is expected to have activity against the Omicron variant. Lack of studies on drug interaction but drug—drug interactions are unlikely. Evusheld is authorised via the pandemic special access route (PSAR) for PrEP and available via the special access route (SAR) for treatment for COVID-19. Requesting doctors to take full responsibility of its use for treatment of COVID-19. Risk, benefits and potential adverse effects should be discussed, documented and consented by the patient.	31-33

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Medication and Class	Dose*	Place in therapy	Safety/Efficacy	Notes for pharmacists	Ref
Sotrovimab Monoclonal antibody to SARS-CoV-2 spike protein	1000mg IV single dose infusion It should be given within 7 days of onset of illness in mild-moderate COVID-19	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression.	Efficacy i) In non-hospitalized patients with symptomatic, mild to moderate COVID-19 with at least 1 risk factor for progression, the use of IV 500mg sotrovimab vs. placebo, resulted in a 79% relative risk reduction for progression to hospitalization >24 hours or death, adjusted relative risk: 0.21, [95% CI, 0.09-0.50]. [COMET-ICE trial] ii) In hospitalized COVID-19 patients the use of neutralising monoclonal antibody therapies (sotrovimab and BRII-196 plus BRII-198) did not result in more favourable outcomes compared to placebo on either the scale that measured pulmonary status or extrapulmonary complications of COVID-19. Primary outcome of sustained clinical recovery by day 90 was also similar in all groups (88% in sotrovimab group [adjusted rate ratio (aRR) 1.12; [95% CI 0.91-1.37], 88% in BRII-196+BRII-198 group aRR: 1.08; [95% CI 0.88-1.32] versus 85% in placebo group aRR: 1.12; [95% CI 0.91-1.37]). [ACTIV-3/TICO study group] iii) Takashita et al. reported lower neutralizing activity against Omicron variants for sotrovimab and an increased dose of 1000mg has been recommended by manufacturer based on safety and PK/PD data. This higher dose is also currently being studied in RECOVERY trial. Safety Common adverse effects include diarrhoea and infusion-related reaction. Do not administer via intravenous push. Patients should be monitored during and for at least 1 hour after infusion is complete. Serious reactions reported include hypersensitivity reactions. Consider slowing or stopping the infusion along with appropriate supportive care. Anaphylaxis has been reported. If occurs, immediately discontinue administration and initiate appropriate therapy.		34-38
Casirivimab and imdevimab (REGEN-COV) Monoclonal antibody to SARS-CoV-2 spike protein	600mg of casirivimab and 600mg of imdevimab administered together as a single IV infusion NOTE: Subcutaneous route is only approved for PEP It should be given within 10 days of onset of illness in mild-moderate COVID-19	a) Mild to moderate illness (not requiring supplemental oxygen), and at high risk of progression. b) Post-exposure prophylaxis.	Efficacy Treatment Outpatients, with onset of COVID-19 symptoms ≤7 days and risk factors for severe illness, were randomized them to receive either 2.4g or 1.2g REGEN-COV or placebo. COVID-19-related hospitalization or death from any cause occurred in 1.3% of patients in REGEN-COV 2.4g group vs. 4.6% in placebo group (relative risk reduction of 71.3%; p<0.001) and 1.0% of patients in REGEN-COV 1.2g group vs. 3.2% in placebo group (relative risk reduction of 70.4%; p=0.002). Median time to resolution of symptoms was 4 days shorter in any REGEN-COV group vs. placebo (10 days vs. 14 days; p<0.001) Post-exposure prophylaxis Household contacts of COVID-19 infected persons were randomized to receive SC 1.2g REGEN-COV or placebo in 1:1 manner. Symptomatic COVID-19 infection developed in 1.5% in REGEN-COV group vs. 7.8% in placebo group (relative risk reduction 81.4%; p<0.001). Safety Common adverse effects reported in trials include infusion-related/injection site reaction and headache. Patients should be monitored during the infusion and for at least 1 hour after the infusion is completed. Serious reactions reported include hypersensitivity reactions.	**Not indicated for Omicron variant infections.**	39-42

*For adults with normal renal and hepatic function.

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