Saudi MoH Protocol for Patients Suspected of/Confirmed with COVID-19

Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection

(version 1.5) May 23rd, 2020

Disclaimer: This is a living guidance that is subject to change as more evidence accumulates. It will be updated regularly whenever needed. The guidance should be used to assist healthcare practitioners select the best available pharmacotherapy for COVID-19 infection according the best available and current evidence and is not intended to replace clinical judgement but rather to complement it.

COVID-19 Testing*	Category	Supportive Care	Pharmacotherapy	Precautions
Suspicious Cases (follow case definition published in Saudi CDC guidelines)	**Mild to Moderate:** Symptoms with no shortness of breath	– Treat symptoms – If no hospital admission required, need to follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	– Not required – Do not stop ACEI/ARBs in patients with hypertension, post-MI, or heart failure	– Paracetamol (acetaminophen) is the prefered agent for pain/fever see below table *"Medication Related Information"* – Labs and work-up: CBC, Urea/Electrolytes, Creatinine, CRP, LFTs, Chest X-ray, COVID-19 PCR tests
	Mild to Moderate: Symptoms with no shortness of breath in high risk patients[$] **Mild to Moderate**: Symptoms with shortness of breath in high risk patients[$]	– Treat symptoms – If hospital admission is not required, follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/ – Consult Infectious Disease Specialist	– Case shall be discussed with infectious disease specialist, to initiate empirical antiviral therapy, while awaiting PCR result. – Do not stop ACEI/ARBs in patients with hypertension, post-MI, heart failure *If decision is to treat empirically, follow the treatment option under confirmed by PCR*	
PCR Confirmed Cases	**Asymptomatic**	– Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	– Not required	

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PCR Confirmed Cases	**Mild to Moderate:** Symptoms (no O_2 requirements/no evidence of pneumonia)	– Treat symptoms – Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/	Consider starting any of the following (up to treating consultant's discretion): – Triple combination therapy (for adults): Lopinavir /Ritonavir, Ribavirin and interferon beta-1b for 14-days. Start before 7 days from symptoms appearance. • Lopinavir /Ritonavir ○ Adult Dosing: 400/100 mg (2 tablets of 200/50 mg) every 12 hrs. • Ribavirin ○ Adult Dosing: 400mg every 12hrs • Interferon beta-1b ○ Adult Dosing: 8 MIU on alternative days for 3 doses. – hydroxychloroquine, if no contraindications: ○ Adult Dosing: 400 mg every 12 hours for 1 day, followed by 200 mg BID for 5 – 7 days ○ Pediatrics: Not recommended – If hydroxychloroquine is not available, consider chloroquine ○ Adult Dosing: Chloroquine base 600 mg at diagnosis (equivalent to chloroquine phosphate 1000 mg), followed by 300 mg (equivalent to chloroquine phosphate 500 mg) 12 hours later BID for 5 – 7 days ○ Pediatrics: Not recommended	**Hydroxychloroquine & Chloroquine** see below table *"Medication Related Information"* – Labs and work-up: Same as above with additional G6PD screening if chloroquine will be used. Avoid chloroquine in G6PD – Perform baseline ECG and if initial QTc 450- 500 msec, perform ECG daily, Preform daily electrolytes. – Avoid combination with other QT-prolonging agents e.g. Azithromycin – Use with caution in diabetic patients; hypoglycemia may occur. Insulin requirements may decrease. – Avoid hydroxychloroquine with antacids. Separate administration by at least 4 hours – Hydroxychloroquine can be crushed. Extemporaneous oral suspension recipe is available (see reference). **Lopinavir/ritonavir** see below table *"Medication Related Information"* – Avoid coadministration with drugs that are highly dependent on CYP3A for clearance or with potent CYP3A inducers (check MOH formulary) – Patients with renal and/or hepatic impairment – Current evidence doesn't support using Lopinavir/Ritonavir as monotherapy – Perform baseline ECG, if QT interval is above 480 msec, reduce lopinavir/ritonavir frequency to once a day. **Ribavirin** see below table *"Medication Related Information"* – Anemia associated with ribavirin may worsen underlying cardiac disease and lead to fatal and nonfatal myocardial infarctions. **Interferon beta-1b** see below table *"Medication Related Information"* – If patient has more than 7 days since symptoms appeared, don't administer interferon beta-1b.

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PCR Confirmed Cases	**Critical:** – Symptoms ≥ 1 of the following: ○ ARDS ○ Sepsis ○ Altered consciousness ○ Multi-organ failure – Patient with cytokine release syndrome consider starting Tocilizumab – Criteria for patients at high-risk for developing cytokine storm (1 or more of the following): ○ Serum IL-6 ≥3x upper normal limit ○ Ferritin >300 ug/L (or surrogate) with doubling within 24 hours ○ Ferritin >600 ug/L at presentation and LDH >250 ○ Elevated D-dimer (>1 mcg/mL)	– Treat symptoms – Follow instructions and recommendations published by Saudi CDC https://covid19.cdc.gov.sa/professionals-health-workers/ – ICU admission and management by ICU treating team – Antibiotics and antifungals according to local antibiogram and institutional pneumonia management guidelines/ pathways.	**Do not start hydroxychloroquine or chloroquine**. – Triple combination therapy (for adults): Lopinavir /Ritonavir, Ribavirin and interferon beta-1b for 14-days. Start before 7 days from symptoms appearance. • Lopinavir /Ritonavir ○ Adult Dosing: 400/100 mg (2 tablets of 200/50 mg) every 12 hrs. • Ribavirin ○ Adult Dosing: 400mg every 12hrs • Interferon beta-1b Adult Dosing: 8 MIU on alternative days for 3 doses – Consider Remdesivir *(once available)* ○ Adult Dosing: 200 mg loading dose (IV, within 30 min), followed by 100 mg once daily for 5 to 10 days ○ Pediatric dosing - <40 kg: 5 mg/kg IV load, then 2.5 mg/kg q24h for 5 to 10 days - ≥40 kg: 200 mg IV load, then 100 mg IV q24h for 5 to 10 days – Consider Favipiravir *(once available)* ○ Adult Dosing: 1600 mg/dose twice a day on the first day; followed by 600 mg/dose twice a day for 7 - 10 days – If cytokine release syndrome confirmed, consider tocilizumab ○ Adult Dosing: Single dose 4 – 8 mg/kg (usual dose 400 mg; maximum 800 mg) by	**Hydroxychloroquine & Chloroquine** *(see precautions above)* **Lopinavir/ritonavir** *(see precautions above)* **Ribavirin** *(see precautions above)* **Interferon beta-1b** *(see precautions above)* **Remdesivir (non-formulary and non-SFDA registered)** see below table *"Medication Related Information"* – Exclusion criteria evidence of multiorgan failure, need of inotropes, Creatinine clearance < 30 ml/min, dialysis/hemofiltration, transaminases > 5X ULN, or concomitant use of lopinavir/ritonavir **Favipiravir (non-formulary and non-SFDA registered)** see below table *"Medication Related Information"* – Contraindicated in pregnancy **Tocilizumab** see below table *"Medication Related Information"* – Should perform IL6 and other inflammatory markers testing prior to start (CRP, Ferritin, D-dimer) – Watch for infusion reaction

COVID-19 Testing*	Category	Supportive Care	Pharmacotherapy	Precautions
			IV infusion; repeated within 12 hours for maximum of 2 doses ○ Pediatric Dosing (<18 years): - <30 kg: 12 mg/kg repeated within 12 hours for maximum of 2 doses - ≥30 kg: 8 mg/kg (max: 800 mg/dose) repeated within 12 hours for maximum of 2 doses	

NOTES:

(Hydroxy)chloroquine, lopinavir/ritonavir, and tocilizumab are registered medications in Saudi Arabia and available in MoH formulary for other indications but have not shown proven efficacy in randomized clinical trials as of yet

The use of all the above medications is off-labeled and shall follow the process of filling (Unlicensed/Unapproved Use of Medications form) available in MoH electronic formulary

Pregnancy and Lactation: Management of infection with SARS-COV2 in pregnancy is mainly based on supportive care. Consideration of antiviral therapy should be based on patient condition, safety profile and preference of the patient and treating team. Refer to the MoH COVID-19 guidance in pregnancy

Convalescent Plasma transfusion is available as part of a clinical trial for the following critically ill patients: ≥ 18 years old, confirmed COVID-19 PCR, requiring ICU care or severe or immediately life-threatening care (see severe and critical symptoms above). To enroll your patient, please visit https://plasmaforcovid.com/

Thromboprophylaxis:

Adults:

Thromboprophylaxis with low molecular weight heparin (LMWH) should be considered in ALL patients (including non-critically ill) who require hospital admission for COVID-19 infection, in the absence of any contraindications (active bleeding and platelet count less than 25 x 109/L; monitoring advised in severe renal impairment; abnormal PT or APTT is not a contraindication)

D-Dimer (mcg/mL)	Weight (Kg)	LMWH
< 1	< 100	Enoxaparin 40 mg daily
	100-150	Enoxaparin 40 mg twice daily
	>150	Enoxaparin 60 mg twice daily
> 1	< 100	Enoxaparin 40 mg twice daily
	100-150	Enoxaparin 80 mg twice daily
	>150	Enoxaparin 120 mg twice daily

All doses may need adjustment based on renal function. In the absence of bleeding, coagulopathy is not a contraindication to anticoagulation with heparin/LMWH unless platelets fall below 30 for prophylaxis or below 50 for therapeutic heparin/LMWH.

Patients with Heparin-induced thrombocytopenia (HIT), please follow HIT standard institutional protocol for alternative anticoagulation.

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Pediatrics:

For all COVID-19 suspected / confirmed pediatrics patients requiring hospital admission, Low Molecular Weight Heparin (LMWH) will be started unless contraindicated based on D-dimer level

Patient category	D-dimer level (ug/ml)	Enoxaparin dose (< 2months of age)	Enoxaparin dose (> 2months of age)	Target aXa level (unit/ml)	Monitoring tests
Mild / Moderate	0.5 -1	1.5 mg / kg once daily	1 mg / kg once daily	Not required	With no respiratory symptoms: - daily CBC, D-dimer
	>1	1.5 mg / kg twice daily	1 mg / kg twice daily	0.5 – 1.0	With Respiratory symptoms: - Daily CBC - Renal and liver function, D-dimer, Fibrinogen, Ferritin, LDH, PT, INR, aPTT, Chest X-ray.
Severe / Critical	0.5 -1	1.5 mg / kg once daily	1 mg / kg once daily	Not required	- Daily CBC - Renal and liver function, D-dimer, Fibrinogen, Ferritin, LDH, PT, INR, aPTT, Chest X-ray.
	1-3	1.5 mg / kg twice daily	1 mg / kg twice daily	0.5 – 1.0	
	>3		1 mg / kg twice daily	0.9 – 1.2	

Enoxaparin dose Adjustments:

- **Renal impairment (CrCl 30 to 80 mL/min): No adjustment necessary**
- **Renal impairment (CrCl less than 30 mL/min): reduce usual recommended dose by 50%.**

Enoxaparin dosage titration in pediatrics:

Anti-factor Xa	Dose Titration	Time to Repeat Antifactor Xa Level
<0.35 units/mL	Increase dose by 25%	4 h after next dose
0.35-0.49 units/mL	Increase dose by 10%	4 h after next dose
0.5-1 unit/mL	Keep same dosage	Next day, then 1 week later, then monthly (4 h after dose)
1.1-1.5 units/mL	Decrease dose by 20%	Before next dose
1.6-2 units/mL	Hold dose for 3 h and decrease dose by 30%	Before next dose, then 4 h after next dose
>2 units/mL	Hold all doses until Anti-factor Xa is 0.5 units/mL, then decrease dose by 40%	Before next dose and every 12 h until anti-factor Xa <0.5 units/mL

When to consult hematologist:

- **Heparin-induced thrombocytopenia (HIT), platelets fall below 30 for prophylaxis or below 50 for therapeutic**
- **Bleeding episodes**
- **Bleeding disorders (e.g. Hemophilia, thrombasthenia)**

Abbreviations:

ARDS: Acute respiratory distress syndrome, COVID-19: Coronavirus Disease 2019, CBC: Complete Blood Count, CRP: C-Reactive Protein, IL6: Interleukin 6, LFT: Liver Function Test, PCR: Polymerase Chain Reaction, ECG: Electrocardiogram, G6PD: Glucose-6-Phosphate Dehydrogenase, ACEI: Angiotensin-converting enzyme inhibitors, ARBs: Angiotensin II receptor blockers, MI: Myocardial infarction

Footnotes:

***Testing for SARS-COV2 virus shall be performed in accordance with published case definition by Saudi CDC guidelines.**

$High risk patients have one or more: 1. Elderly (age > 65 years), 2. With underlying end organ dysfunction, 3. Diabetes, 4. History of cardiovascular disease, 5. History of pulmonary disease, 6. Immunocompromised, and/or 7. Pregnancy

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Require dose adjustment	Pregnancy
Paracetamol (acetaminophen)	– Hypersensitivity to acetaminophen or any component of the formulation – Severe hepatic impairment or active liver disease	– Acetaminophen may increase the levels/effects of: Busulfan; Dasatinib; Imatinib; Local Anesthetics; Mipomersen; Phenylephrine (Systemic); Prilocaine; Sodium Nitrite; SORAfenib; Vitamin K Antagonists – The levels/effects of Acetaminophen may be increased by: Alcohol (Ethyl); Dapsone (Topical); Dasatinib; Flucloxacillin; Isoniazid; MetyraPONE; Nitric Oxide; Probenecid; SORAfenib	– Requires dose adjustment with patient with hepatic impairment *See MoH online formulary*	– Oral paracetamol is considered safe in normal therapeutic doses for short-term use as a minor analgesic/antipyretic in pregnancy. Consider Administering IV paracetamol to a pregnant woman only if clearly needed. Carefully assess maternal benefit and fetal risk before administering IV paracetamol during labor and delivery.
Hydroxychloroquine	– Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation. – Preexisting retinopathy	– Avoid concomitant use: Artemether; Lumefantrine; Mefloquine – Hydroxychloroquine may increase the levels/effects of: Antipsychotic Agents (Phenothiazines); Beta-Blockers; Cardiac Glycosides; Dapsone (Systemic); Dapsone (Topical); Haloperidol; Hypoglycemia-Associated Agents; Lumefantrine; Mefloquine; QT-prolonging Agents (Highest Risk) – The levels/effects of Hydroxychloroquine may be increased by: Androgens; Antidiabetic Agents; Artemether; Dapsone (Systemic); Herbs (Hypoglycemic Properties); Maitake; Mefloquine; Monoamine Oxidase Inhibitors; Pegvisomant; Prothionamide; Quinolones; Salicylates; Selective Serotonin Reuptake Inhibitors; Tamoxifen	– No dose adjustment required with patient with hepatic nor renal impairment	– Fetal risk cannot be ruled out. Fetal ocular toxicity has been reported. – Hydroxychloroquine use should be avoided during pregnancy, unless absolutely indicated and only after assessing maternal benefit and fetal risk.
Chloroquine	– Hypersensitivity to chloroquine, 4-aminoquinoline compounds, or any component of the formulation – The presence of retinal or visual field changes of any etiology	– Avoid concomitant use of Chloroquine with any of the following: Agalsidase Alfa; Agalsidase Beta; Artemether; Conivaptan; Fusidic Acid (Systemic); Idelalisib; Lumefantrine; Mefloquine; Pimozide; QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk) – Chloroquine may increase the levels/effects of: Antipsychotic Agents (Phenothiazines); Beta-Blockers; Cardiac Glycosides; Dapsone (Systemic); Dapsone (Topical); Domperidone; Haloperidol; Hypoglycemia-Associated Agents; Local Anesthetics; Lumefantrine; Mefloquine; Ondansetron; Pentamidine (Systemic); Perhexiline; Prilocaine; Primaquine; QT-prolonging Antipsychotics (Moderate Risk); QT-prolonging Class IC Antiarrhythmics (Moderate Risk); QT-prolonging Quinolone Antibiotics (Moderate Risk); Sodium Nitrite – The levels/effects of Chloroquine may be increased by: Abiraterone Acetate; Androgens; Antidiabetic Agents; Aprepitant; Artemether; Asunaprevir; Cimetidine; CloBAZam; Clofazimine; Conivaptan; CYP2D6 Inhibitors (Moderate); CYP2D6 Inhibitors (Strong); CYP3A4 Inhibitors (Moderate); CYP3A4 Inhibitors (Strong); Dacomitinib; Dapsone (Systemic); Duvelisib; Erdafitinib; Fosaprepitant; Fosnetupitant; Fusidic Acid (Systemic); Herbs (Hypoglycemic Properties); Idelalisib; Imatinib; Larotrectinib; Maitake; Mefloquine; MiFEPRIStone; Monoamine Oxidase Inhibitors; Netupitant; Nitric Oxide; Palbociclib; Panobinostat; Peginterferon Alfa-2b; Pegvisomant; Perhexiline; Pimozide; Prothionamide; QT-prolonging Agents (Highest Risk); QT-prolonging Antidepressants (Moderate Risk); QT-prolonging Kinase Inhibitors (Moderate Risk); QT-prolonging Miscellaneous Agents (Moderate Risk); QT-prolonging Moderate CYP3A4 Inhibitors (Moderate Risk); QT-prolonging Strong CYP3A4 Inhibitors (Moderate Risk); Quinolones; Salicylates; Selective Serotonin Reuptake Inhibitors; Simeprevir; Stiripentol; Tamoxifen	– Requires dose adjustment with patient with renal impairment *See MoH online formulary*	– Fetal risk cannot be ruled out. Fetal ocular toxicity has been reported – Administer chloroquine during pregnancy only if the potential maternal benefit outweighs the potential fetal risk

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Require dose adjustment	Pregnancy
Lopinavir/ritonavir	– Hypersensitivity to lopinavir, ritonavir, or any component of the formulation; – Coadministration with drugs that are highly dependent on CYP3A for clearance or with potent CYP3A inducers – Patients with renal and/or hepatic impairment	– Avoid concomitant use of Lopinavir and Ritonavir with any of the following: Acalabrutinib; Ado-Trastuzumab Emtansine; Alfuzosin; Amiodarone; Antihepaciviral Combination Products; Aprepitant; Astemizole; Asunaprevir; Avanafil; Axitinib; Barnidipine; Blonanserin; Bosutinib; Bromocriptine; Budesonide (Systemic); Cisapride; Clarithromycin; Clobetasone; Cobicistat; Cobimetinib; Conivaptan; Dabrafenib; Dapoxetine; Darunavir; Disulfiram; Domperidone; Dronedarone; Elagolix; Eletriptan; Eplerenone; Ergot Derivatives; Everolimus; Flecainide; Flibanserin; Fluticasone (Nasal); Fosamprenavir; Fosaprepitant; Fusidic Acid (Systemic); Glecaprevir and Pibrentasvir; Grazoprevir; Halofantrine; Ibrutinib; Irinotecan Products; Isavuconazonium Sulfate; Ivabradine; Lapatinib; Lefamulin; Lercanidipine; Lomitapide; Lovastatin; Lurasidone; Macitentan; Meptazinol; MetroNIDAZOLE (Systemic); Midazolam; Naloxegol; Neratinib; NiMODipine; Nisoldipine; Palbociclib; PAZOPanib; Pimozide; Propafenone; QuiNIDine; QuiNINE; Radotinib; Ranolazine; Red Yeast Rice; Regorafenib; Revefenacin; RifAMPin; Rivaroxaban; Rupatadine; Salmeterol; Silodosin; Simeprevir; Simvastatin; Sonidegib; St John's Wort; Suvorexant; Tamsulosin; Terfenadine; Ticagrelor; Tipranavir; Tolvaptan; Topotecan; Trabectedin; Triazolam; Udenafil; Ulipristal; VinCRIStine (Liposomal); Vinflunine; Vorapaxar; Voriconazole; Voxilaprevir – Lopinavir and Ritonavir may increase the levels/effects of: Abemaciclib; Acalabrutinib; Ado-Trastuzumab Emtansine; Afatinib; Alfuzosin; Alitretinoin (Systemic); Almotriptan; Alosetron; Alpelisib; ALPRAZolam; Amiodarone; AmLODIPine; Antihepaciviral Combination Products; Apixaban; Aprepitant; ARIPiprazole; ARIPiprazole Lauroxil; Astemizole; Asunaprevir; AtorvaSTATin; Avanafil; Axitinib; Barnidipine; Bedaquiline; Benperidol; Benzhydrocodone; Betamethasone (Ophthalmic); Betrixaban; Bictegravir; Bilastine; Blonanserin; Bortezomib; Bosentan; Bosutinib; Brentuximab Vedotin; Brexpiprazole; Brigatinib; Brinzolamide; Bromocriptine; Budesonide (Nasal); Budesonide (Oral Inhalation); Budesonide (Systemic); Budesonide (Topical); Buprenorphine; BusPIRone; Cabazitaxel; Cabozantinib; Calcifediol; Calcium Channel Blockers (Nondihydropyridine); Cannabidiol; Cannabis; Cariprazine; Celiprolol; Ceritinib; Cilostazol; Cinacalcet; Cisapride; Cladribine; Clarithromycin; Clobetasone; Clorazepate; CloZAPine; Cobimetinib; Codeine; Colchicine; Conivaptan; Copanlisib; Corticosteroids (Orally Inhaled); Corticosteroids (Systemic); Crizotinib; Cyclophosphamide; CycloSPORINE (Systemic); CYP3A4 Substrates (High risk with Inhibitors); Dabigatran Etexilate; Dabrafenib; Daclatasvir; Dapoxetine; Darolutamide; Dasatinib; Deflazacort; Delamanid; Dexamethasone (Ophthalmic); Digoxin; Disulfiram; DOCEtaxel; Dofetilide; Domperidone; DOXOrubicin (Conventional); Dronabinol; Dronedarone; Drospirenone; Dutasteride; Duvelisib; Edoxaban; Elagolix; Eletriptan; Eliglustat; Eluxadoline; Elvitegravir; Encorafenib; Enfuvirtide; Entrectinib; Eplerenone; Erdafitinib; Ergot Derivatives; Erlotinib; Estazolam; Estrogen Derivatives; Eszopiclone; Etizolam; Everolimus; Evogliptin; Fedratinib; FentaNYL; Fesoterodine; Flecainide; Flibanserin; Fluticasone (Nasal); Fluticasone (Oral Inhalation); Fosaprepitant; Fostamatinib; Fusidic Acid (Systemic); Galantamine; Gefitinib; Gilteritinib; Glasdegib; Glecaprevir and Pibrentasvir; Grazoprevir; GuanFACINE; Halofantrine; HYDROcodone; Ibrutinib; Idelalisib; Iloperidone; Imatinib; Imidafenacin; Irinotecan Products; Isavuconazonium Sulfate; Itraconazole; Ivabradine; Ivacaftor; Ivosidenib; Ixabepilone; Ketoconazole (Systemic); Lacosamide; Lapatinib; Larotrectinib; Lefamulin; Lercanidipine; Levobupivacaine; Levomilnacipran; LinaGLIPtin; Lomitapide; Lorlatinib; Lovastatin; Lumefantrine; Lurasidone; Macitentan; Manidipine; Maraviroc; Meperidine; Meptazinol; Methadone; MethylPREDNISolone; MetroNIDAZOLE (Systemic); Midazolam; Midostaurin; MiFEPRIStone; Mirodenafil; Mirtazapine; Naldemedine; Nalfurafine; Naloxegol; Nefazodone; Nelfinavir; Neratinib; Nilotinib; NiMODipine; Nintedanib; Nisoldipine; Olaparib; Ospemifene; Oxybutynin; OxyCODONE; Palbociclib; Panobinostat; Parecoxib; Paricalcitol; PAZOPanib; Pexidartinib; P-glycoprotein/ABCB1 Substrates; Pimavanserin; Pimecrolimus; Pimozide; Piperaquine; Polatuzumab Vedotin; PONATinib; Pranlukast; Praziquantel; PrednisoLONE (Systemic); PredniSONE; Progestins (Contraceptive); Propafenone; Protease Inhibitors; Prucalopride; QT-prolonging Agents (Highest Risk); QUEtiapine; QuiNIDine; QuiNINE; Radotinib; Ramelteon; Ranolazine; Reboxetine; Red Yeast Rice; Regorafenib; Repaglinide; Retapamulin; Revefenacin; Ribociclib; Rifabutin; RifAXIMin; Rilpivirine; Riociguat; Rivaroxaban; RomiDEPsin; Rosuvastatin; Rupatadine; Ruxolitinib; Salmeterol; SAXagliptin; Sibutramine; Sildenafil; Silodosin; Simeprevir; Simvastatin; Sirolimus; Solifenacin; Sonidegib; SORAfenib; SUFentanil; SUNItinib; Suvorexant; Tacrolimus (Systemic); Tacrolimus (Topical); Tadalafil; Talazoparib; Tamsulosin; Tasimelteon; Tegaserod; Telithromycin; Temsirolimus; Tenofovir Disoproxil Fumarate; Terfenadine; Tetrahydrocannabinol; Tetrahydrocannabinol and Cannabidiol; Tezacaftor; Thiotepa; Ticagrelor; Tofacitinib; Tolterodine; Tolvaptan; Topotecan; Toremifene; Trabectedin; TraMADol; TraZODone; Triamcinolone (Systemic); Triazolam; Tricyclic Antidepressants; Udenafil; Ulipristal; Upadacitinib; Valbenazine; Vardenafil; Velpatasvir; Vemurafenib;	– No dose adjustment required with patient with hepatic impairment; however, lopinavir is metabolized by the liver – Requires to be avoided with patient on dialysis *See MoH online formulary*	– Fetal risk cannot be ruled out – Avoid the oral solution of this combination product during pregnancy due to the presence of ethanol as an excipient in the solution.

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Require dose adjustment	Pregnancy
		Venetoclax; Vilazodone; VinBLAStine; VinCRIStine; VinCRIStine (Liposomal); Vindesine; Vinflunine; Vinorelbine; Vorapaxar; Voxilaprevir; Zolpidem; Zopiclone; Zuclopenthixol – The levels/effects of Lopinavir and Ritonavir may be increased by: ARIPiprazole; Cat's Claw; Clarithromycin; Cobicistat; Delavirdine; Enfuvirtide; Fusidic Acid (Systemic); Ketoconazole (Systemic); MetroNIDAZOLE (Topical); P-glycoprotein/ABCB1 Inhibitors; Posaconazole; QuiNINE; Rifabutin; RifAMPin; Simeprevir; Vilanterol		
Remdesivir	– Safety and efficacy not established	– Avoid Concomitant Use: There are no known interactions where it is recommended to avoid concomitant use. – Increased Effect/Toxicity: There are no known significant interactions involving an increase in effect. – Decreased Effect: There are no known significant interactions involving a decrease in effect.	– No dose adjustment studied	– Not studied
Favipiravir	– Hematopoietic tissues such as decreased RBC production, and increases in liver function parameters – Testis toxicity was also noted – Teratogenic	– Acyclovir, Adefovir dipivoxil, Afatinib, Allopurinol, Almotriptan, Alprostadil, Ambrisentan, Aminohippuric acid, Aminophenazone, Amiodarone, Amitriptyline, Amodiaquine, Anastrozole, Antipyrine, Apalutamide, Apixaban, Atorvastatin, Avatrombopag, Avibactam, Azelastine, Baricitinib, Belinostat, Benzyl alcohol, Benzylpenicillin, Betrixaban, Bisoprolol, Bosutinib, Brentuximab vedotin, Brigatinib, Bumetanide, Buprenorphine, Cabazitaxel, Canagliflozin, Captopril, Cefaclor, Cefazolin, Cefdinir, Cefotiam, Ceftibuten, Ceftizoxime, Celecoxib, Cephalexin, Ceritinib, Cerivastatin, Chloroquine, Cholic Acid, Cidofovir, Cimetidine, Cisapride, Citrulline, Clobazam, Clomifene, Cobimetinib, Colchicine, Conjugated estrogens, Copanlisib, Crizotinib, Cyclophosphamide, Cyclosporine, Dabigatran etexilate, Zafirlukast, Zalcitabine, Zidovudine, Zopiclone	– No dose adjustment studied	– Contraindicated
Tocilizumab	– Known hypersensitivity to tocilizumab or any component of the formulation – Active infections	– Avoid Concomitant Use: Anti-TNF Agents; BCG (Intravesical); Belimumab; Biologic Disease-Modifying Antirheumatic Drugs (DMARDs); Cladribine; Natalizumab; Pimecrolimus; Tacrolimus (Topical); Vaccines (Live) – Increased Effect/Toxicity: Anti-TNF Agents; Biologic Disease-Modifying Antirheumatic Drugs (DMARDs); Fingolimod; Leflunomide; Natalizumab; Siponimod; Vaccines (Live) – The levels/effects of Tocilizumab may be increased by: Belimumab; Cladribine; Denosumab; Ocrelizumab; Pimecrolimus; Roflumilast; Tacrolimus (Topical); Trastuzumab – Tocilizumab may decrease the levels/effects of: BCG (Intravesical); Coccidioides immitis Skin Test; CYP3A4 Substrates (High risk with Inducers); Nivolumab; Pidotimod; Sipuleucel-T; Smallpox and Monkeypox Vaccine (Live); Tertomotide; Vaccines (Inactivated); Vaccines (Live) – The levels/effects of Tocilizumab may be decreased by: Echinacea	– Requires dose adjustment with patient with hepatotoxicity *See MoH online formulary*	– Fetal risk cannot be ruled out
Ribavirin	– Autoimmune hepatitis – Coadministration with didanosine; symptomatic hyperlactatemia/lactic acidosis, peripheral neuropathy, pancreatitis, and fatal hepatic failure. – Hemoglobinopathy (eg, thalassemia major and sickle-cell anemia) – Hypersensitivity, including serious skin reactions – Pregnant women or men with pregnant wives – Renal impairment (CrCl less than 50 mL/min)	– Avoid combination: Cladribine and Didanosine – Consider therapy modification: Influenza Virus Vaccine, AzaTHIOprine, Zidovudine – Monitor therapy: Interferons (Alfa) and Vitamin K Antagonists (eg, warfarin)	– Requires dose adjustment *See MoH online formulary*	– Significant teratogenic

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Require dose adjustment	Pregnancy
Interferon beta-1b	– History of hypersensitivity to natural or recombinant interferon beta, albumin (human), or any component of the formulation. – Documentation of allergenic cross-reactivity for interferons is limited. However, because of similarities in chemical structure and/or pharmacologic actions, the possibility of cross-sensitivity cannot be ruled out with certainty. – Pregnancy, decompensated liver disease; current severe depression and/or suicidal ideation	– Avoid combination with Cladribine – Monitor therapy with Zidovudine	– No dose adjustment is required	– Rating Fetal risk cannot be ruled out. – Available evidence is inconclusive or is inadequate for determining fetal risk when used in pregnant women or women of childbearing potential. Weigh the potential benefits of drug treatment against potential risks before prescribing this drug during pregnancy.

Drug Administration in patients with Swallowing Difficulties

Drug	Formulation	Remarks
Lopinavir/ritonavir	Tablets	– Manufacturer does not recommend crushing of tablets. – Exposure of lopinavir was reduced by 45% when the tablet was crushed and administered with food. – Administration through NG tube, doubling lopinavir/ritonavir to 800/200 mg twice daily when crushed could be considered (depending on drug availability) with monitoring of ECG.
	Oral solution	– Administer syrup without dilution otherwise there is a risk of precipitation. – Rinse the administration feeding tube with milk (not water). – As the oral solution contains ethanol and propylene glycol, feeding tubes that are compatible with ethanol and propylene glycol, such as silicone and polyvinyl chloride (PVC) feeding tubes, can be used. – As the oral solution contains alcohol, disulfiram-like reactions may occur with disulfiram or other drugs that produce this reaction (e.g. metronidazole). – Co-administration is contraindicated with disulfiram or metronidazole due to the potential risk of toxicity from propylene glycol.
Favipiravir	Tablets	– Tablets can be crushed and mixed with liquid.
Chloroquine	Tablets	– It is preferable to avoid crushing tablets, however, chloroquine tablets may be crushed and mixed with jam, honey, pasteurised yoghurt, or similar foods.
	Syrup	– Contains propylene glycol, but no recommendations are given in the product label as to compatibility with feeding tubes.
Hydroxychloroquine	Tablets	– Manufacturer does not recommend crushing of tablets, However, some sources suggest that tablets can be crushed and dispersed in water.

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