Ontario COVID-19 Clinical Practice Guidelines

Dosing and Pharmacologic Considerations

for Medications Approved or Under Investigation for Management of COVID-19 Infection

Introduction and Scope of this Document

This document is intended to accompany the Ontario Clinical Practice Guidelines for Antimicrobial and Immunomodulatory Therapy in Patients with COVID-19. This document provides collated information on dosing regimens, relative contraindications, and other pharmacotherapy considerations for medications that are approved or under investigation for management of COVID-19 infection. This document does not serve as an endorsement or recommendation for any of the therapeutic options, nor is the information provided within exhaustive; it is recommended that clinicians use their best clinical judgement with respect to treatment selection and monitoring for potential adverse drug effects. Pharmacological therapies for the management of COVID-19 are based on evolving clinical evidence, therefore enrolling in clinical trials if available is encouraged. Clinicians should always consider the risk/benefit profile for their individual patient, discuss these risks with the patient or caregiver before initiating therapy, and closely monitor for any treatment benefit and adverse effects.

Important Notes

- **Drug availability may be limited by shortages or allocations.** It is advised that drug access be verified prior to considering use of these agents as drug availability continues to evolve.
- **Immunomodulatory agents may affect vaccine response, and vice-versa.** Refer to the pharmacodynamic interactions section within individual drug tables for specific details and considerations on potential vaccine interactions.

Click the drug name below to jump to the relevant section:

Antiviral Therapy

- Remdesivir
- Ribavirin
- Hydroxychloroquine
- Lopinavir/Ritonavir (Kaletra®)

Immunomodulatory Therapy

- Dexamethasone
- Tocilizumab
- Bamlanivimab
- Baricitinib
- Interferons

Recommended in specific patient populations

Not recommended outside of approved clinical trials

Not recommended for treatment of COVID-19

Remdesivir

Can be considered for moderately ill adult patients. Preference should be given to enrolling in eligible clinical trials evaluating remdesivir.

Health Canada authorization with conditions, pending results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization.

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: Hypersensitivity to this drug or component of the formulation **Warnings:** Based on clinical trial exclusion criteria and conditions of Health Canada authorization, avoid use in:[1, 2] - ALT or AST >5X ULN - Creatinine clearance <30 mL/min* - Dialysis or CRRT* Coadministration with hydroxychloroquine (see drug interactions section)[3]	**Supplied as:**[1] Injection Solution 100mg/20mL single use vial* Lyophilized Powder 100mg vial for dilution* **Pediatric and Adult Dosing:**[2,3,4,5] **<40 kg:** 5 mg/kg **loading** dose; then 2.5 mg/kg IV q24h **≥40 kg:** 200 mg IV x1; then 100 mg IV q24h **Duration of Therapy:**[6] **Non-Severe:** 5 days for patients not requiring mechanical ventilation or ECMO; may extend up to a total of 10 days if no clinical improvement **Severe:** may extend up to a total of 10 days for patients requiring mechanical ventilation or ECMO **Pregnancy:** No human data; being actively studied in this population **Breastfeeding:** No data **Renal Dysfunction:** Not recommended for eGFR <30ml/min.[3,4] No dose adjustment recommended for eGFR ≥30ml/min. *Renal Replacement Therapy*: No data[7] **Hepatic Dysfunction:** No data **Extracorporeal membrane oxygenation (ECMO):** No dose adjustment recommended.	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use**[8] Avoid strong inducers of CYP enzymes (such as rifampin)[8] Due to antagonism observed in vitro, concomitant use of remdesivir with hydroxychloroquine is not recommended[2]	**Clinical and observational studies** - Nausea - Headache - Rash - Transient increases in AST and ALT[9,10] - Acute kidney injury[9,10] - Infusion-related reactions including hypotension Serious adverse events from preliminary clinical data:[10, 11] - Multiple-organ dysfunction syndrome - Septic shock - Hypotension	**Baseline:** - SCr - LFTs **Ongoing:** (During therapy) - CBC - Electrolytes - Renal function - LFTs

* Avoid/limit use in renal impairment due to sulfobutylether-β-cyclodextrin sodium salt (SBECD), a renally cleared excipient found in the IV product. Injection solution contains 6 g SBECD per 100 mg vial; whereas the lyophilized powder formulation contains 3 g SBECD per 100 mg vial. For pediatric patients <40 kg, remdesivir lyophilized powder is used to limit cyclodextrin exposure to less than 300 mg/kg.

Lopinavir/Ritonavir (Kaletra®, LPV/r)

Not recommended for the treatment of COVID-19

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: Oral solution contraindicated in pregnancy and hepatic/renal impairment due to risk of excipients (ethanol and propylene glycol) accumulation and toxicity[12] Known hypersensitivity to any of LPV/r ingredients **Warnings:** Significant drug interactions (see drug interactions column)[13] Avoid use in solid organ transplant, and patients receiving GVHD treatment or prophylaxis due to significant drug interactions with immunosuppressants Immediate initiation of ART for newly diagnosed HIV in patients with COVID is generally not recommended. LPV/r monotherapy or substitution in an existing ART regimen is not recommended. Consultation with an HIV expert is recommended. Caution in patients with known prolonged QT interval[14]	**Supplied as:** film-coated tablets (100mg LPV/25mg r, 200mg LPV/50mg r), oral solution (80mg LPV/20mg/mL r) **Pediatric Dosing:**[15] **<6 months:** 300 mg/m^2/dose LPV PO BID (Dose limit: 800 mg/day) **6 months to 12 yrs:** 230-300 mg/m^2/dose LPV PO BID (Dose limit: 800 mg/day) **>12 yrs or ≥35 kg**: 400 mg LPV PO BID **Alternative Pediatric Dosing:** 10 mg/kg/dose LPV PO BID (maximum 800 mg/day) **Adult Dosing:** 400 mg/100 mg PO BID (up to 10-14 days)[16,17] **Pregnancy:** 400 mg/100 mg PO BID[18] - Generally considered safe in pregnancy – low placental transfer, unknown teratogenicity[19] - Oral solution contraindicated in pregnancy **Breastfeeding:** Limited data; excreted in low quantities in breastmilk and considered to be safe[12] **Renal Dysfunction:** Dose adjustment not required *Renal Replacement Therapy*: Dose adjustment not required[7] **Hepatic Dysfunction:** Oral solution should be used with caution **ECMO:** No data; may require dose adjustment on an individualized basis **Administration:** - Oral solution should be taken with food - Tablets can be taken with or without food - Avoid crushing tablets due to ~46% decreased absorption[20] - Use oral solution if possible - note oral solution is incompatible with polyurethane enteral feeding tubes[21,22]	**For drug interaction information, check Liverpool COVID-19 Interactions and other relevant resources prior to use** [13,18,19] LPV/r are strong inhibitors and substrates of CYP3A4 and P-glycoprotein, and can result in significant drug interactions **Note:** If used in solid organ transplant patients concomitantly receiving immunosuppressive agents (e.g. tacrolimus, cyclosporine), consider dose adjustment*	**Common:** *Gastrointestinal*: - Diarrhea - Nausea/vomiting **Severe:** - Liver dysfunction - Pancreatitis - Arrhythmias - Hypersensitivity - Neutropenia and thrombocytopenia (may be exacerbated in patients at risk for neutropenia e.g. cancer chemotherapy)	**Baseline:**[12] - ECG - LFTs - Cholesterol and triglycerides** **Ongoing:** (weekly if in hospital) - ECG - LFTs - Skin rash - Blood glucose - Additional clinical monitoring of potentially interacting drugs (therapeutic drug monitoring where appropriate and available)

	- If NG administration required and unable to use solution, consider crushing tablets and increasing dose[21] or alternate formulation within a study protocol.			

***** Dose adjustment of tacrolimus in adults to 0.5 mg - 1 mg PO weekly may be adequate, as proposed by some institutions

****** Has been reported with long term use of LPV/r, and can be exacerbated with concomitant medications (e.g. propofol)

Hydroxychloroquine sulfate (HCQ)

Not recommended for the treatment of COVID-19

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications:[23,24,25] - Hypersensitivity to aminoquinoline derivatives - Pre-existing retinopathy **Warnings:**[23,24,25] - Known prolonged QTc interval - Known G6PD deficiency (Note: this is a very uncommon cause of adverse event and routine screening prior to initiation is generally not required)	**Supplied as:** 200mg PO tablets **Adult Dosing:** *Various dosing regimens reported or being utilized in clinical trials** Most adult regimens include: - A loading dose of 800-1600 mg, followed by a total daily dose of 400-800 mg, divided BID or TID for 5-10 days[26,27,28,29,30,31] **Pediatric Dosing**:** Dosage regimen being utilized: A loading dose on Day 1 and a total duration of no more than 5 days[32,33,34] **Pregnancy:** No dose adjustment; may be administered during pregnancy. Current evidence suggests that hydroxychloroquine crosses the placenta, but is likely safe in pregnancy. [35,36,37] **Breastfeeding:** Excreted in low quantities in breastmilk and considered to be safe[23] **Renal Dysfunction:** Dose adjustment not required, but recommend more frequent monitoring for glycemic and cardiac adverse effects. Consider dose adjustment if adverse events occur. *Renal Replacement Therapy*: Dose adjustment not required[7] **Hepatic Dysfunction:** Dose adjustment not required **ECMO:** No data, may require dose adjustment on an individualized basis **Administration** - Tablets should not be crushed for administration via enteral feeding tubes unless film coating has been removed	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use**[8] *Pharmacodynamic:*[8,23,24,25] - QTc prolonging agents - Antidiabetic agents *Pharmacokinetic:* - CYP3A4, 2C8 substrate therefore inhibitors may increase HCQ levels - CYP2D6 inhibitor therefore may increase other drug levels Cyclosporine (increased cyclosporine level) Antacids; separate doses from antacids by ≥4 hours	**Common:**[23,24,25,38] *Gastrointestinal:* Abdominal pain, nausea (may take with food to alleviate) *Ophthalmic:* Blurring of vision, diminished colour vision (dose dependent) *CNS:* Headache, dizziness, nervousness, vivid dreams, insomnia *Endocrine:* Hypoglycemia *Dermatologic:* Skin rash, pruritus **Severe:**[23,24,25] *CNS:* Extrapyramidal effects – usually resolve on stopping *Ophthalmic:* Retinopathy more common with prolonged use. Ophthalmologic exam is not required for short term use *Cardiac*: Cardiotoxicity (including cardiomyopathy, cardiac failure) secondary to dysrhythmias (QTc or QRS prolongation) *Hematologic*: Rare reversible agranulocytosis, aplastic anaemia, neutropenia, thrombocytopenia (may be exacerbated in patients at risk for neutropenia eg. cancer chemotherapy).	**Baseline:**[23,24,25] - ECG - LFTs - Blood Glucose **Ongoing:** (weekly if in hospital) - ECG - LFTs - Blood glucose (may need to increase monitoring while on HCQ in patients with diabetes) - Renal function

	- Oral suspension may be compounded by pharmacy if required			

*** Adult dosing regimens for hydroxychloroquine proposed in the literature:**

a) *In vitro* data: 400 mg PO BID x 1 day, followed by 200 mg PO BID x 4 days[26]
b) Canadian arm of SOLIDARITY trial (CATCO): 800 mg PO BID (separated by 6 hours) x 1 day, then 400 mg PO BID x 10 days (or until discharge, whichever comes first)[27]
c) French publication: 200 mg PO TID x 10 days[28]
d) Chinese pilot trial: 400 mg PO daily x 5 days[29]
e) Canadian arm of REMAP-CAP: 400 mg PO q8h x 9 doses, then 200 mg PO q12h to max of 10 days[30]
f) Pharmacokinetic modelling study: 800 mg once daily on day 1, followed by 200 mg BID for 7 days[31]

**** Pediatric dosing regimens for hydroxychloroquine proposed in the literature:**

a) Physiologically-based pharmacokinetic modelling: 6.5 mg/kg/dose PO BID x 2 doses (max 400 mg/dose), then 3.25 mg/kg/dose PO BID x 4 days (max 200 mg/dose)[32,33]
b) Acute malaria dosing: 13 mg/kg/dose PO once (max 800 mg/dose), then 6.5 mg/kg/dose PO at 6, 24, and 48 hours after initial dose (max 400 mg/dose)[34]

Ribavirin

Not recommended outside of approved clinical trials

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: - Pregnancy and breastfeeding - Hemoglobinopathies (e.g. thalassemia or sickle-cell anemia) - Concomitant use with didanosine - Known hypersensitivity **Warnings:** - Patients with preexisting cardiac disease who develop anemia while on treatment are at risk of cardiac status deterioration - Risk of fetal death and birth defects: women (and men with female partners of childbearing age) should be counselled on the use of effective contraception for at least 6 months after ribavirin treatment is completed.[39]	**Hazardous Drug: Refer to product monograph for safe handling of oral[39] and inhaled[40] medication** **Supplied as:** *Inhalation:* 6 g/vial *Oral:* 200 mg, 400 mg, 600 mg tablets *Intravenous:* 1.2 g/12 mL vial (available in Canada through the Special Access Program) **Adult and Pediatric Dosing:** *Various dosing regimens and routes (PO, IV, inhalation) reported or being utilized in clinical trials* Inhaled ribavirin poses risk to both patient and healthcare workers. Administration by inhalation in ventilated patients can cause drug precipitation within the ventilatory apparatus, requiring appropriate nebulizer, RT administration and AGMP precautions.[41] **Pregnancy:** Contraindicated **Breastfeeding:** No data, unknown if excreted in breastmilk. Avoid use. **Renal Dysfunction (IV, PO only):** CrCl 30-60 mL/min: dose reduce by 50% CrCl <30 mL/min: dose reduce by 75%[42,43] *Renal Replacement Therapy*:[44] IHD: Dose reduce as for CrCl <10mL/min CRRT: No data **ECMO:** Limited data; No dosing guidance available[45,46] **Hepatic Dysfunction:** Dose adjustment not required	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use[8]** *Pharmacodynamic:* May cause additive myelosuppression when administered with concomitant myelotoxic agents eg. azathioprine, clozapine, ganciclovir, linezolid, etc. *Pharmacokinetic:* Didanosine (fatal hepatic failure, peripheral neuropathy, pancreatitis, and symptomatic hyperlactatemia/lactic acidosis have been reported) Warfarin (ribavirin may decrease efficacy of warfarin for up to 1 month after discontinuation)	**Systemic:** Hemolytic anemia (dose-dependent, reversible; greater risk with doses greater than 1-2 g, may appear as early as 3-5 days after initiation)[42,43] Electrolyte abnormalities, in particular:[47] - Hypocalcemia - Hypomagnesemia - Hyperammonemia Bone marrow suppression (reversible) Pancreatitis Transaminitis **Inhalation related:** *Cardiovascular* - Bradycardia - Chest pain - Hypotension - Tachycardia *Respiratory* - Bronchospasm - Apnea - Severe dyspnea - Cyanosis - Dry cough	**Baseline:** - Confirm negative pregnancy testing, if applicable **Ongoing:** (During therapy) - CBC - Electrolytes (particularly calcium and magnesium) - ECG - LFTs

*** Adult dosing regimens for ribavirin proposed in the literature for SARS-CoV-1 and SARS-CoV-2 (with or without other investigational agents):**

Inhaled:

a) 50 mg/mL aerosolized and administered over 1 hour twice a day for up to 6 days[48]
b) 100 mg/mL aerosolized and administered over 30 minutes twice a day for up to 6 days[48]

Systemic:

a) 400mg PO Q12H up to 14 days (in combination with LPV/r and Interferon beta-1b)49
b) 400 mg IV every 8 hours for 3 days, then 1200 mg orally (with food) twice daily for 7 days[42]

**** Pediatric dosing regimens for ribavirin proposed in the literature for other indications:**

Systemic:[51,52]

a) Loading dose 33 mg/kg IV, one time only (maximum 2 g/dose)
→ 6 hours after loading dose, start IV doses of 16 mg/kg (maximum 1 g/dose) every 6 hours for 4 days
→ 8 hours after the last dose of 16 mg/kg, start IV doses of 8 mg/kg (maximum 500 mg/dose) every 8 hours for 3 to 6 days, depending on the clinical course

Interferons (IFNs): IFN Beta-1a (B-1a), IFN Beta-1b (B-1b), IFN Lambda (λ)

Not recommended outside of approved clinical trials

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: - Patients with decompensated liver disease - Pregnancy - Known hypersensitivity **Warnings:** - SARS CoV2: use caution if started beyond 7 days of symptom onset (concern about pro-inflammatory effect) - Patients with severe depression - Pre-existing CHF, CAD, or arrhythmias - Pre-existing thyroid dysfunction, significant liver disease, alcohol abuse - Pre-existing seizure disorder Women should be counselled to take adequate contraceptive measures	**Supplied as:** *IFN B-1a*: 0.11 mg/vial and 0.44 mg/vial supplied with diluent for reconstitution *IFN B-1a*: 0.3 mg/0.5 mL pre-filled syringe *IFN B-1b:* 0.3 mg/vial supplied with diluent for reconstitution *IFN λ:* 0.18 mg/syringe (not currently marketed in Canada) **Adult dosing:** *Various dosing regimens and routes (IV, SC) reported or being utilized in clinical trials** **Pediatric Dosing:** Dosing not established in <18 years-old **Pregnancy:** Contraindicated, may increase risk of spontaneous abortion **Breastfeeding:** No data, unknown if excreted in breastmilk. **Renal Dysfunction:** Dose adjustment not required *Renal Replacement Therapy*: No data **ECMO:** No data **Hepatic Dysfunction:** Dose adjustment not required, use with caution in pre-existing liver dysfunction	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use**[8] *Pharmacodynamic:* May cause additive myelosuppression when administered with concomitant myelosuppressive agents *Pharmacokinetic:* May reduce activity of hepatic cytochrome P450 dependent enzymes.	**Common:** - Injection site reactions - Flu-like symptoms - Menstrual disorders - Abdominal pain - Loss of appetite - Asthenia **Severe:** - Psychiatric side effects: depression/anxiety (onset as early as 1 week, typically develop at week 4);[53] other psychiatric side effects with prolonged use - Lymphopenia - Neutropenia - AST/ALT >5X ULN	**Baseline:** - Confirm negative pregnancy testing, if applicable **Ongoing:** (During therapy) - CBC - LFTs - Heart failure signs and symptoms - Injection site reactions - Flu-like symptoms - Additional clinical monitoring of potentially interacting drugs (therapeutic drug monitoring where appropriate and available

*** Adult dosing regimens for IFN B-1a proposed in the literature (with or without other investigational agents):**

a) Canadian arm of REMAP-CAP: 10 mcg IV bolus once daily for 6 days or until ICU discharge, whichever occurs first[54]
b) DisCoVeRy (French trial): 44 mcg SC on day 1, day 3 and day 6 (total of 3 doses over 6 days)[55]

*** Adult dosing regimens for IFN B-1b proposed in the literature (with or without other investigational agents):**

a) 0.25 mg (8 MIU) on alternate days from symptom onset until 7th day of symptoms (patients had less than 7 days of symptom onset)
eg. If started on day 1-2 from symptom onset the patient received 3 doses. If started on day 3-4, the patient received 2 doses. If started on day 5-6 the patient received 1 dose.[56]
b) Hong Kong triple therapy study: 0.25 mg SQ daily x 3 days on day 1-3[57]
c) Mcmaster study ACT trial: 0.25 mg SQ on days 1, 3, 5 and 7[58]

*** Adult dosing regimens for IFN λ proposed in the literature:**

a) ILIAD: 0.18 mg SQ (For ambulatory patients; single dose on day 0. For hospitalized patients; doses on day 0 and day 7)[59]

Dexamethasone

Recommended for critically ill and moderately ill adult patients with suspected or confirmed COVID-19

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: - Hypersensitivity to dexamethasone[64] **Warnings:** - May cause reactivation or exacerbation of fungal or latent infections (eg. tuberculosis, Hepatitis B, herpesvirus, strongyloides)[65,66] - Refer to CATMAT guideline recommendations regarding screening, assessment and considerations for initiating pre-emptive therapy in high risk patients.	**Supplied as:**[67] *Oral*: 0.5 mg, 0.75 mg, 4 mg tablets; 0.5 mg/5 mL elixir *Intravenous*: 4 mg/mL, 10 mg/mL **Adult Dosing:**[64] 6 mg PO/IV once daily for 10 days (or until discharge)[1] **Pediatric Dosing*:** 0.15 mg/kg PO/IV once daily (maximum 6 mg) for 10 days (or until discharge)[68] **Pregnancy**:** Dexamethasone crosses the placenta, alternative equivalent corticosteroids are recommended (see below) **Breastfeeding**:** Dexamethasone is not well studied, alternative equivalent corticosteroids are recommended (see below) **Renal Dysfunction:** Dose adjustment not required for renal dysfunction or renal replacement therapy (IHD, CRRT)[69,70] **ECMO***:** Dose adjustment not required[64,68] **Hepatic Dysfunction:** Dose adjustment not required[69]	**For drug interaction information, check Liverpool COVID-19 Interactions[8] prior to use** *Pharmacodynamic:*[69,70] - Antihyperglycemics - Fluoroquinolones - Amphotericin B (increased hypokalemia) - NSAID *Pharmacokinetic:*[69] Dexamethasone is a substrate of CYP3A4 (major) and P-glycoprotein - Strong **inhibitors** of CYP3A4: increased dexamethasone levels - Strong **inducers** of CYP3A4 (e.g. phenytoin): reduced dexamethasone levels Dexamethasone is a weak-to-moderate inducer of CYP and may decrease levels of substrates (e.g. caspofungin)	Long term side effects of corticosteroids are **likely not** observed given short duration of treatment (10 days or until discharge) **Common:**[78, 79] - Hyperglycemia - Insomnia, depression, euphoria - Gastritis - Impaired wound healing **Severe:**[78, 79] - GI bleeding - Psychosis, behaviour changes - Secondary superinfections[74, 75]	**Baseline:**[69,70] - Blood glucose - GI symptoms (gastritis, ulcers, GI bleed history) - Neuropsychiatric status (sleep, mood, behaviour) **Ongoing:** (During therapy)[69,70] - Blood glucose - GI symptoms - Neuropsychiatric status - Signs of secondary superinfections - Additional clinical monitoring of potentially interacting drugs (therapeutic drug monitoring where appropriate and available) - Signs of adrenal insufficiency for patients at risk (eg. baseline corticosteroid use, recent high doses of corticosteroids)

*__Pediatric bioequivalent regimens proposed in the literature:__[68]

a) For preterm infants less than 40 weeks GA: Hydrocortisone 0.5 mg/kg IV q12h for 7 days, then 0.5 mg/kg IV once daily for 3 days
b) Prednisolone 1 mg/kg PO/NG once daily (maximum 40 mg)
c) Methylprednisolone sodium succinate 0.8 mg/kg IV once daily (maximum 32 mg)

**__Pregnancy and breastfeeding bioequivalent regimens proposed in the literature: pregnancy and breastfeeding patients__.

a) Prednisolone 40 mg PO once daily or Hydrocortisone 80 mg IV BID[68]
b) In the RECOVERY trial, 0.1% of patients were pregnant (6 patients) and none were breastfeeding.[64]

***In the RECOVERY trial, 16% of patients were either mechanically ventilated or receiving ECMO.[64]

Interleukin-6 Inhibitors (Tocilizumab & Sarilumab)

A single dose of tocilizumab (preferred vs. sarilumab) can be considered for critically ill patients who have been recently (i.e. within 24 h) placed on ventilatory support due to COVID-19

Contraindications and Warnings	Investigational COVID-19 Dosing and Administration	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Contraindications in the package insert (e.g. thrombocytopenia, non-COVID-19 active infections) may not apply due to single dose for COVID-19 vs chronic dosing. *COVID-19 clinical trials of IL-6 inhibitors have excluded:*[71] - *platelets < 50* - *AST/ALT > 5X ULN* - *current or expected neutropenia or immune suppression (disease or drug related)* **Absolute contraindications:**[71,72,73,74] Tocilizumab and sarilumab: - Hypersensitivity to either agent or its components **Warnings:** Tocilizumab and Sarilumab: - May cause reactivation or exacerbation of fungal or latent infections (eg. tuberculosis, Hepatitis B, herpesvirus, strongyloides)[75] - Patients at risk of gastrointestinal perforation (e.g. concurrent diverticulitis or concomitant NSAID or corticosteroid use)	**Supplied as:** Tocilizumab: IV (80 mg/4mL, 200 mg/10mL, 400 mg/20mL) and SQ (auto-injector and prefilled syringe) dosage forms. IV dosage form and dosing differ from the SQ product. Sarilumab:150 mg/1.14 mL or 200 mg/1.14 mL solution for SQ injection (pre-filled syringe or pen) **Doses under investigation for COVID-19:** Tocilizumab: **Adult patients:** 8 mg/kg IV x1 (single dose not to exceed 800 mg) infused over 1 hour. Some studies report repeating 1x dose in 12-48 hours[71] **Pediatric dosing for cytokine release syndrome (CRS):**[75] **<30 kg:** 12 mg/kg (max 800 mg) **≥30kg**: 8 mg/kg **Pregnancy:** Potential for placental transfer, risk generally increases as pregnancy progresses. Fetal risk cannot be ruled out. **Breastfeeding:** Expected exposure in breastmilk (no human data), consider risk/benefit to infant[85] **Renal Dysfunction:** Dose adjustment not required *Renal Replacement Therapy*: Dose adjustment not required[7] **Hepatic Dysfunction:** recommend to stop drug if ALT/AST >5X ULN **ECMO:** No data; may require dose adjustment on an individualized basis	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use**[8] Tocilizumab and Sarilumab: *Pharmacodynamic:* Avoid concomitant administration of live and inactivated vaccines May cause additive immunosuppression when administered with concomitant immunosuppressive agents e.g. anti-TNF agents, biologic disease modifying antirheumatic drugs (DMARDs), tacrolimus, cyclosporine, etc. [7,71,72] *Pharmacokinetic:* Il-6 inhibitors may decrease serum concentrations of CYP substrates (effect may persist several weeks after stopping therapy)	Tocilizumab and Sarilumab: **Common:**[71,72,73] *CNS*: Headache, injection site reactions *Hepato/biliary/pancreatic:* Increased ALT/AST, hypercholesterolemia *Hematological:* Thrombocytopenia, neutropenia (more common in children <30kg) *Other:* Infusion related reactions, upper respiratory tract infections (pharyngitis) **Severe:** Drug induced liver injury, some acute liver injuries requiring transplant[79] Hypersensitivity reactions (anaphylaxis, SJS) GI perforations Invasive infections (disseminated fungal, TB, bacterial and viral pathogens)[80] Tocilizumab only: *Cardiac*: Hypertension *Gastrointestinal*: Diarrhea	Tocilizumab and Sarilumab: **Baseline:**[71,72,73] (Recommended if feasible and time permits) - Latent TB (consider IGRA/Quantiferon) - Hepatitis B testing - LFTs - Lipids - CBC with differential (neutrophils, platelets) - Vaccine assessment - Consider monitoring inflammatory biomarkers (e.g. IL-6, ferritin, CRP, ESR) **Ongoing:**[71,72,73] - LFTs before redosing - CBC with differential (neutrophils, platelets) - New onset infection - Abdominal symptoms - Infusion related reactions Tocilizumab only: - Signs/symptoms of CNS demyelinating disorders

Tocilizumab: - Pre-existing CNS demyelinating disorders[72,73]	Sarilumab: **Adult patients:** 400 mg IV x1 dose[71] **Pediatric patients:** Dosing not established in <18 years-old **Pregnancy: not recommended:** Potential for placental transfer, risk generally increases as pregnancy progresses. Fetal risk cannot be ruled out (monograph recommends contraception for 3 months following treatment)[73] **Breastfeeding:** Expected exposure in breastmilk (no human data), consider risk/benefit to infant[76] **Renal Dysfunction:** Dose adjustment not required for mild to moderate renal dysfunction; no data in severe renal dysfunction[73,87] *Renal Replacement Therapy*: No data **Hepatic Dysfunction:** recommend to stop drug if ALT/AST >5X ULN; no data on dose adjustment in hepatic failure **ECMO:** No data; may require dose adjustment on an individualized basis			

Baricitinib

Not currently recommended outside of a clinical trial

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: - Hypersensitivity to this drug or component of the formulation[81] **Warnings:** - Avoid use in those with: ALC <200 cells/uL ANC <500 cells/uL ALT/AST >5X ULN - May increase risk of serious infections (e.g. latent TB, viral hepatitis) - May increase risk of thrombosis (study excluded recent history of VTE), GI perforation, lymphoma/ malignancy - Limited data with concurrent use of corticosteroids* (potential increased risk of infection)[82,83]	**Supplied as:** 2 mg tablets (oral route) **Adult Dosing:** (in combination with remdesivir) 4 mg PO/NG daily for 14 days or until discharge (whichever comes first) **Pediatric Dosing:** Not recommended for those <18 years[81] ** **Pregnancy:** Limited data, placental transfer expected **Breastfeeding:** Limited data, transfer into breast milk may be expected **Renal Dysfunction:** eGFR 30 to <60 mL/min: 2 mg PO/NG daily eGFR 15 to <30 mL/min: 1 mg PO/NG daily[83] eGFR <15 mL/min: not recommended *Renal Replacement Therapy:* not recommended **ECMO:** No dose adjustment recommended **Hepatic Dysfunction:** Recommend to stop drug if ALT/AST >5X ULN	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use[8]** *Pharmacodynamic:* - Avoid concomitant use with live vaccines - COVID-19 vaccine (mRNA vaccines): may diminish the therapeutic effect of these vaccines[84] - May cause additive immunosuppression when administered with concomitant immunosuppressive agents *Pharmacokinetic:* - Strong OAT3 inhibitors (eg. probenecid), may increase baricitinib exposure	**Common:** - Upper respiratory tract infection, urinary tract infection - Nausea - Herpes zoster infection - Increased LFTs - Increased CPK **Severe:** - Liver injury - Thromboembolism - Lymphoma/malignancy - Increased lipids - Severe infections - Anemia - Lymphocytopenia - Neutropenia - GI perforation	**Baseline:** - Scr/eGFR - LFTs - CBC - Lipids **Onoing:** (During therapy) - Hypersensitivity reactions - Scr/eGFR - LFTs - CBC - CPK (if symptoms of muscle weakness/pain) - New infections - Abdominal symptoms - Skin exams - Clinical concern for thrombosis

* In the ACTT-2 study, only 10.9% of baricitinib patients were on concurrent steroids[82]

** Although not studied in setting of COVID-19, the FDA EUA outlines Pediatric Dosing (in normal renal function) based on limited data for other indications[83]:
≥ 9 years: 4 mg PO/NG daily (in combination with remdesivir)
2-8 years: 2 mg PO/NG daily (in combination with remdesivir)

Bamlanivimab

Not recommended outside of approved clinical trials

Health Canada authorization with conditions, pending results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization[85]
Infusion site logistics (eg. administration and monitoring requirements) should be considered prior to decision for administration of this drug [86,87]

Contraindications and Warnings	Dosing and Administration for Management of COVID-19	Drug Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: Hypersensitivity to this drug or component of the formulation **Warnings:** Administer in settings in which health care providers have immediate access to medications to treat and manage a severe reaction[85,86] Limited data in elderly patients >65 years old*	Refer to product monograph for details regarding specific instructions regarding dilution, reconstitution and administration (eg. filter, flushing, monitoring)[86] **Supplied as:** Solution for IV infusion: 700 mg/20 mL (20 mL) (preservative free) **Treatment Dosing:** **Adults ≥40 kg:** 700 mg IV x1 (over 60min). Administer as soon as possible after a positive SARS-CoV-2 test and within 10 days of symptom onset[86,88,89] **Pediatrics ≥40 kg:** safety and efficacy has not been established; not recommended due to current lack of safety and efficacy data[90] **Adults and Pediatrics <40 kg:** not recommended **Prophylaxis Adult Dosing:** Currently under investigation** **Pregnancy:** Potential for placental transfer, unknown risk to fetus **Breastfeeding:** exposure in breastmilk theorized to be limited due to large molecule size (no human data), consider risk/benefit to infant[91] **Renal Dysfunction:** No dosage adjustment recommended **ECMO:** No data available	**For drug interaction information, check Liverpool COVID-19 Interactions prior to use**[8] *Pharmacodynamic:*[86] - COVID-19 vaccine (adenovirus vector and mRNA vaccines): delay administration of these vaccines until at least 90 days after treatment with bamlanivimab (may diminish the therapeutic effect of these vaccines) *Pharmacokinetic:* N/A	**Common:**[86] - Infusion related reactions - Dizziness - Headache - Pruritus **Severe:**[86] - Hypersensitivity including Type I hypersensitivity reaction anaphylaxis, flushing and facial swelling - Infusion related reactions	**Baseline:** N/A **Ongoing:** (During therapy) - Infusion-related reactions (e.g. fever, chills, hypotension, rash, pruritus), and hypersensitivity/ anaphylaxis during infusion and for 1 hour following completion of infusion completion[86]

	Hepatic Dysfunction: No dosage adjustment recommended (not studied in moderate/severe)			

***** The BLAZE-1 randomized controlled trial (bamlanivimab +/- etesivimab vs placebo) in Mild to Moderate COVID-19 only included a very small number of elderly patients: ≥65 years old (11%), and >75 years old (3%)[88,89]
Elderly patients ≥65 years old who received bamlanivimab monotherapy (n; % of study group): 700mg (11; 10.9%), 2800mg (8; 7.5%), 7000mg (14; 13.9%)
Elderly patients ≥65 years old who received combination therapy, bamlanivimab 2800mg + eteseivimab 2800mg = 13% (11.6%)

****** The BLAZE-2 randomized controlled trial is still underway (phase 3, bamlanivimab +/- etesivimab vs placebo) studying prevention of SARS-CoV-2 infection and COVID-19 in skilled nursing and assisted living facility residents and staff (with at least one confirmed case of SARS-CoV-2 infection among residents or facility staff no more than 7 days prior to randomization).[92]

References

Remdesivir

1. Gilead Sciences. Remdesivir Product Monograph. Available at: http://www.gilead.ca/application/files/2015/9594/6448/VEKLURY_English_PM_e240551-GS-000.pdf
2. Gilead Sciences. COVID-19. Accessed April 1, 2020. Available at: https://www.gilead.com/purpose/advancing-global-health/covid-19
3. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Remdesivir (GS-5734). Gilead. Available at: https://www.fda.gov/media/137566/download
4. Remdesivir. (Pediatric and Neonatal Lexi-Drugs) In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated March 2020, Accessed April 1, 2020] Available at: http://online.lexi.com.myaccess.library.utoronto.ca/lco/action/doc/retrieve/docid/patch_f/6925182?cesid=5YOVsW6PiLM&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dremdesivir%26t%3Dname%26va%3Dremd#doa
5. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 — Final report. N Engl J Med. 2020. DOI:10.1056/NEJMoa2007764
6. 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. DOI:10.1056/NEJMoa2015301
7. Acute Kidney Injury. http://www.nephjc.com/news/covidaki
8. Liverpool Drug Interactions Group. Interactions with experimental COVID-19 Therapies. [Updated 2020; Accessed March 29, 2020] Available at: https://www.covid19-druginteractions.org/
9. Wang Y, Zhou F, Zhang D. Evaluation of the Efficacy and Safety of Intravenous Remdesivir in Adult Patients with Severe Pneumonia caused by COVID-19 virus Infection: study protocol for a Phase 3 Randomized, Double-blind, Placebo-controlled, Multicentre trial. [Updated Feb 2020; Accessed April 1, 2020], Available at: https://www.researchsquare.com/article/rs-14618/v1
10. J. Grein, N. Ohmagari, D. Shin, G. Diaz, E. Asperges, A. Castagna TF, G. Green, M.L. Green, F.-X. Lescure, E. Nicastri, R. Oda, K. Yo, E. Quiros-Roldan, A. Studemeister, J. Redinski, S. Ahmed, J. Bernett, D. Chelliah DC, S. Chihara, S.H. Cohen, J. Cunningham, A. D'Arminio Monforte SI, et al. Compassionate Use of Remdesivir for Patients with Severe Covid-19. *NEJM*. 2020. doi:10.1056/NEJMoa2007016
11. Mulangu, S, Dodd L, Davey R et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med. 2019; 381:2293-2303

Lopinavir/Ritonavir

12. Kaletra Product Monograph. AbbVie Corporation. [Updated September 2019; Accessed March 29, 2020]. Available at: https://www.abbvie.ca/content/dam/abbvie-dotcom/ca/en/documents/products/KALETRA_PM_EN.pdf
13. University of Liverpool. HIV Drug Interactions. [Updated March 2020; Accessed March 29, 2020] Available at: https://hiv-druginteractions.org
14. Drugs to be avoided by congenital long QT patients. CredibleMeds. [Updated March 2020, Accessed March 30, 2020] Available at: https://crediblemeds.org/pdftemp/pdf/DrugsToAvoidList.pdf
15. SickKids Drug Handbook and Formulary. Available at: http://www.sickkids.ca/Pharmacy/SickKids-Drug-Handbook-and-Formulary/index.html
16. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New Engl J Medicine. 2020. doi:10.1056/nejmoa2001282
17. National Health Commission (NHC) of the People's Republic of China. The diagnosis and treatment guide of COVID-19 pneumonia caused by new coronavirus infection 7th Edition, published March 3rd, 2020. Available at: http://www.gov.cn/zhengce/zhengceku/2020-03/04/content_5486705.htm
18. Lopinavir/ritonavir (Kaletra, LPV/r). Recommendations for the Use of Antiretroviral Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States. [Updated Dec 2019, Accessed March 29, 2020] Available at: https://aidsinfo.nih.gov/contentfiles/glchunk/glchunk_212.pdf
19. Tseng A. Handbook of HIV Drug Therapy, 2013 .[Updated 2020; Accessed March 29, 2020] Available at: https://hivclinic.ca/.
20. Best BM, Capparelli EV, Diep H, et al. Pharmacokinetics of lopinavir/ritonavir crushed versus whole tablets in children. J Acquir Immune Defic Syndr. 2011 Dec 1;58(4):385-91
21. Kaletra. FDA Label [Updated Aug 2019, Accessed March 30, 2020]. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s057,021906s052lbl.pdf
22. Liverpool Drug Interactions Group. Experimental COVID-19 Therapies: Administration in Case of Swallowing Difficulty. [Updated March 2020, Accessed April 1, 2020] Available at: https://www.covid19-druginteractions.org/

Hydroxychloroquine

23. Hydroxychloroquine (Systemic). In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated March 25th 2020; Accessed March 25th, 2020]. Retrieved from URL:http://online.lexi.com.myaccess.library.utoronto.ca/lco/action/doc/retrieve/docid/patch_f/7057?cesid=5rEJOx4UD4C&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dhydroxychloroquine%26t%3Dname%26va%3Dhydrox
24. Hydroxychloroquine Antimalarial—Disease Modifying Antirheumatic Drug (DMARD): CPhA Monograph. [Updated August 2019; Accessed March 25th, 2020]. Retrieved from URL: https://www-e-therapeutics-ca.myaccess.library.utoronto.ca/search#m702499n00006
25. PLAQUENIL® Drug Product Monograph. sanofi-aventis Canada Inc. [Updated August 26th, 2019; Accessed March 25th, 2020]. Retrieved from URL: http://products.sanofi.ca/en/plaquenil.pdf
26. Yao X, Ye F, Zhang M et al. In vitro antiviral activity and projection of optimized dosing design of hydroxychloroquine for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;ciaa237. ODI:10.1093/cid/ciaa237

27. World Health Organization. Public health emergency SOLIDARITY trial of treatments for COVID-19 infection in hospitalized patients. (Canadian arm of the SOLIDARITY trial is the CATCO trial). Available at: http://www.isrctn.com/ISRCTN83971151
28. Gautret P, Lagier J-C, Parola P et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Pre Print published online 19 Mar 2020. Available at: https://www.mediterranee-infection.com/wp-content/uploads/2020/03/hydroxychloroquine fina DOI IJAA.pdf. Accessed March 20,2020
29. Chen J, Liudan P, Liu L, et al. Preliminary study of hydroxychloroquine sulfate in treating common coronavirus disease (COVID-19) patients in 2019. J of Zhejiang University (Medical Ed) 2020;49(1):0-0 doi:10.3785/j.issn.1008-9292.2020.03.03
30. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP), NCT02735707
31. Perinel S, Launay M, Botelho-Nevers E, et al. Towards Optimization of Hydroxychloroquine Dosing in Intensive Care Unit COVID-19 Patients. Clin Infect Dis, 2020 , ciaa394, https://doi.org/10.1093/cid/ciaa394
32. Hydroxychloroquine (Pediatric and Neonatal Lexi-Drugs) In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated March 2020, Accessed April 1, 2020] Available at: http://online.lexi.com.myaccess.library.utoronto.ca/lco/action/doc/retrieve/docid/pdh_f/129665?cesid=0F4Uf3xSDuw&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dhydroxychloroquine%26t%3Dname%26va%3Dhydroxy#dop
33. Chen Z, Hu, J, Zhang z. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial https://www.medrxiv.org/content/10.1101/2020.03.22.20040758v2
34. Downes K, Chiotos K, Fitzgerald JC, et al. Rational Dosing of Hydroxychloroquine for Treatment of COVID-19. Pre-Print 2020
35. Sperber K, Hom C, Chao C, Shapiro D, Ash J. Systematic review of hydroxychloroquine use in pregnant patients with autoimmune diseases. Pediatr Rheumatol Online J. 2009; 7: 9.
36. Clowse M, Magder L, Witter F, Petri M. Hydroxychloroquine in Lupus Pregnancy. Arthritis Rheum. 2006; 54(11):3640-3647 https://onlinelibrary.wiley.com/doi/epdf/10.1002/art.22159
37. Nathalie Costedoat-Chalumeaua N, Amouraa Z, Huonga D , Lechatb P, Piettea JC. Safety of hydroxychloroquine in pregnant patients with connective tissue diseases. Review of the literature. Autoimmun Reviews 2005; 4(2):111 – 115 Available at: https://www.ncbi.nlm.nih.gov/pubmed/15722258
38. Hansen HS, Schuman SG. Hydroxyhcloroquine-Induced Retinal Toxicity. American Academy of Ophthalmology EyeNet Magazine. June 2011; 33–35 Available at: https://www.aao.org/eyenet/article/hydroxychloroquine-induced-retinal-toxicity

Ribavirin

39. PrIBAVYR™ Drug Product Monograph. [Updated March 2015, Accessed May 26th, 2020] Available at: https://pdf.hres.ca/dpd_pm/00029996.PDF
40. Pr VIRAZOLE® Drug Product Monograph. [Updated July 2014, Accessed May 26th, 2020] Available at: https://pdf.hres.ca/dpd_pm/00026097.PDF
41. Health and Safety Practices Survey of Healthcare Workers- Aerosolized Medications. National Institute for Health and Safety. [Accessed June 1st, 2020] Available at: https://www.cdc.gov/niosh/topics/healthcarehsps/aerosolizedmeds.html
42. Koren G, King S, Knowles S, Phillips E. Ribavirin in the treatment of SARS: A new trick for an old drug? CMAJ May 13, 2003 168 (10) 1289-1292;
43. Knowles S, Phillips E, Dresser L, Matukas L. Common Adverse Events Associated with the Use of Ribavirin for Severe Acute Respiratory Syndrome in Canada. Clin Inf Dis. 2003; 37:1139–42
44. Smith J, Jenh Hsu, A. John Hopkins ABX guide: Ribavirin. The Johns Hopkins University. [Updated March 2018, Accessed May 26th, 2020] Available at: www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540479/all/Ribavirin.
45. Shah A, Peahota M, Thoma B, Kraft W. Medication Complications in Extracorporeal Membrane Oxygenation. College of Pharmacy Faculty Papers. 2017. Paper 31. Available at: https://jdc.jefferson.edu/pharmacyfp/31
46. Sherwin, Heath, Watt. Pharmacokinetics and Dosing of Anti-infective Drugs in Patients on Extracorporeal Membrane Oxygenation: A Review of the Current Literature. Clinical Therapeutics. 2016;38(9).
47. MacKay I, Garrah J, Tabah B et al. Adverse Drug Reactions Associated with the use of Ribavirin in the Treatment of Severe Acute Respiratory Syndrome (SARS). Can J Clin Pharmacol 2005. 12(1): e165-e179
48. An Open-Label Study to Evaluate the Safety and Efficacy of VIRAZOLE® (RIBAVIRIN FOR INHALATION SOLUTION, USP) in Hospitalized Adult Participants With Respiratory Distress Due to COVID-19 (NCT04356677)
49. Hung I, Lung KC, Tso E et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. Published Online May 8, 2020 https://doi.org/10.1016/ S0140-6736(20)31042-4
50. Khalili J, Zhu H, Mak N, Yan Y, Zhu Y. Novel coronavirus treatment with ribavirin: Groundwork for an evaluation concerning COVID-19. J Med Virol. 2020;1–7
51. Riner A, Chan-Tack K, Murray J. Original Research: Intravenous Ribavirin—Review of the FDA's Emergency Investigational New Drug Database (1997–2008) and Literature Review, Postgraduate Medicine. 2009. 121:3, 5-15, DOI: 10.3810/ pgm.2009.05.2014
52. Gavin P, Katz B. Intravenous Ribavirin Treatment for Severe Adenovirus Disease in Immunocompromised Children. Pediatrics. 2002. 110(1)

Interferons

53. Lucaciu L, Dumitrascu DL. Depression and suicide ideation in chronic hepatitis C patients untreated and treated with interferon: prevalence, prevention, and treatment. Annals of Gastroenterology (2015) 28, 440-447
54. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP)(NCT02735707)
55. Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) (NCT04315948)
56. Hung I, Lung KC, Tso E et al. Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. Lancet. Published Online May 8, 2020 https://doi.org/10.1016/ S0140-6736(20)31042-4
57. Double Therapy With IFN-beta 1b and Hydroxychloroquine (NCT04350281)

58. Anti-Coronavirus Therapies to Prevent Progression of Coronavirus Disease 2019 (COVID-19) Trial (ACT COVID19) (NCT04324463)
59. Interferon Lambda for Immediate Antiviral Therapy at Diagnosis in COVID-19 (ILIAD) (NCT04354259)
60. PrREBIF® Drug product monograph. [Date Approved February 27, 2006, Accessed June 5, 2020]. Available at: https://pdf.hres.ca/dpd_pm/00004308.PDF
61. PrBETASERON® Drug product monograph. [Updated August 8, 2016, Accessed May 28, 2020] Available at: https://www.bayer.ca/omr/online/betaseron-pm-en.pdf
62. PrAvonex® Drug product monograph. [Date prepared June 16, 2016, Accessed June 6, 2020]. Available at: https://www.biogen.ca/content/dam/corporate/en_CA/pdfs/products/AVONEX/AVONEX_PM_E.pdf
63. Arabi Y, Shalhoub S, Mandourah Y et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis . 2020 Apr 15;70(9):1837-1844. doi: 10.1093/cid/ciz544.

Dexamethasone

64. The RECOVERY Collaborative Group. Effect of Dexamethasone in Hospitalized Patients with COVID-19 - Preliminary Report. N Engl J Med. 2020. Available at: https://www.nejm.org/doi/10.1056/NEJMoa2021436
65. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. [Updated Jun 25, 2020; Accessed Jul 16, 2020]. Available at: https://www.covid19treatmentguidelines.nih.gov/.
66. Dexamethasone. In: Health Canada Drug Product Database. Health Canada. Accessed Jul 16, 2020. Retrieved from URL: https://health-products.canada.ca/dpd-bdpp/dispatch-repartition.do;jsessionid=37A2D581A22077A7DED4AFAAFAC16CDC.
67. Randomised Evaluation of COVID-19 Therapy (RECOVERY) - Protocol. Version 7.0 Jun 18, 2020. Available at: https://www.recoverytrial.net/files/recovery-protocol-v7-0-2020-06-18.pdf.
68. Dexamethasone (Systemic). In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated Jul 16, 2020; Accessed Jul 16, 2020]. Retrieved from URL: http://online.lexi.com.myaccess.library.utoronto.ca/lco/action/doc/retrieve/docid/patch_f/1772961?cesid=7oAfmSG79E9&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Ddexamethasone%26t%3Dname%26va%3Ddexamethasone
69. Corticosteroids: Systemic (CPhA Monograph). In: RxTx. Ottawa, ON: Canadian Pharmacists Association. [Updated Aug 1, 2018; Accessed Jul 16, 2020]. Retrieved from URL: https://www.e-therapeutics.ca/search.
70. Ashley C, Currie A. Dexamethasone. In: The Renal Drug Handbook. Radcliffe, 2009, p. 223.

Tocilizumab and Sarilumab

71. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP), Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. 2021. Available at: https://doi.org/10.1101/2021.01.07.21249390
72. ACTEMRA® tocilizumab Product Monograph. [Updated March 2020, Accessed April 1, 2020] Available at: https://www.rochecanada.com/PMs/Actemra/Actemra_PM_E.pdf
73. Tocilizumab. In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated March 2020, Accessed April 1, 2020] Available at: http://online.lexi.com.myaccess.library.utoronto.ca/lco/action/doc/retrieve/docid/patch_f/2125139?cesid=9tC4AilqU0w&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dtocilizumab%26t%3Dname%26va%3Dtociliz#doa
74. KEVZARA® Sarilumab Product Monograph. [Updated August, 2019, Accessed January 24th, 2021] Available at: https://products.sanofi.ca/en/Kevzara-en.pdf
75. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. Infectious Diseases Society of America. 2020. [Updated Jun 25, 2020; Accessed Jul 16, 2020]. Retrieved from URL: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/
76. Actemra® Tocilizumab. MotherToBaby. Available at: https://mothertobaby.org/ongoing-study/actemra/. Registry telephone number: 877-311-8972
77. Sarilumab. In: Lexi-Drugs. Hudson, OH: Lexi-Comp, Inc. [Updated January 22, 2021, Accessed January 24, 2021] Available at: https://www.wolterskluwer.com/en/solutions/lexicomp. Subscription required to view.
78. Sarilumab. In: IBM Micromedex®, In Depth Answers. Greenwood Village (CO): IBM Corporation; [Updated 2021, Accessed January 24, 2021]. Available from: www.micromedexsolutions.com. Subscription required to view.
79. Important Safety Information on ACTEMRA® (tocilizumab) - Risk of Hepatotoxicity https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/69991a-eng.php
80. ACTEMRA® (tocilizumab) Human interleukin-6 receptor inhibitor Risk Evaluation and Mitigation Strategy (REMS). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/125276REMS.pdf

Baricitinib

81. Baricitinib: Canadian Monograph: https://pdf.hres.ca/dpd_pm/00055893.PDF
82. Kalil A. et al. for the ACTT-2 Study Investigators. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. 2020 Dec 11; NEJM. doi: 10.1056/NEJMoa2031994. Online ahead of print. https://www.nejm.org/doi/10.1056/NEJMoa2031994
83. U.S. FDA Fact Sheet EUA of Baricitinib: https://www.fda.gov/media/143823/download
84. NACI Guidelines: https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/recommendations-use-covid-19-vaccines.html#a7

Bamlanivimab

85. Health Canada EUA and English Product Labeling https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2020/74573a-eng.php
86. Bamlanivimab. Canadian Monograph: http://pi.lilly.com/ca/bamlanivimab-ca-pm.pdf
87. CADTH Drug Implementation Advice: Bamlanivimab for Mild-to-Moderate Symptoms of COVID-19 (Jan 14, 2021): https://cadth.ca/sites/default/files/covid-19/HD0004-bamlanivimab-post-panel-final-jan14.pdf
88. Chen P et al. for the BLAZE-1 Investigators. SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with COVID-19. NEJM. 2021 Jan 21;384(3):229-237. doi: 10.1056/NEJMoa2029849. Epub 2020 Oct 28.
89. Gottlieb RL, et al. Effect of Bamlanivimab as Monotherapy or in Combination With Etesevimab on Viral Load in Patients With Mild to Moderate COVID-19: A Randomized Clinical Trial. JAMA. 2021 Jan 21. Epub ahead of print.
90. Wolf J et al (PIDS). Initial Guidance on Use of Monoclonal Antibody Therapy for Treatment of COVID-19 in Children and Adolescents. J Pediatric Infect Dis Soc. 2021 Jan 3;piaa175. doi: 10.1093/jpids/piaa175. Online ahead of print.
91. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006-. Bamlanivimab. [Updated 2020 Nov 21]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK564281/
92. Eli Lilly Press Release on Initial results from BLAZE-2 Study [Updated 2021 Jan 21, Accessed 2021 Jan 25]. Available from: https://investor.lilly.com/news-releases/news-release-details/lillys-neutralizing-antibody-bamlanivimab-ly-cov555-prevented