Dosing and Pharmacologic Considerations

for Medications Under Investigation Against COVID-19

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. While it provides collated information on dosing regimens, relative contraindications, and other pharmacotherapy considerations for medications that are currently being investigated as therapy against COVID-19, 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. All pharmacological therapies against COVID-19 are still experimental, and their therapeutic benefit has not been established. As such, the Guidelines currently do not recommend that these agents be routinely used outside of clinical trials for COVID-19. Should they be utilized, however, clinicians must 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 Note

Drug availability may be limited by shortages or allocations. It is advised that drug access be verified prior to considering the use of any of these agents as availability continues to be an evolving issue.

Click below to jump to the relevant section:

Remdesivir

Note: not approved by Health Canada (Online application for access available here)

Contraindications and Warnings	Investigational COVID-19 Dosing and Administration	Drug Interactions For more information: Liverpool COVID-19 Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications: Unknown **Warnings:** Based on clinical trial exclusion criteria, use with caution if evidence of:[1] - Multi-organ failure - Vasopressor requirement to maintain blood pressure - ALT levels >5X ULN - Creatinine clearance <30 mL/min - Dialysis or CRRT - Use of other experimental antiviral agents for COVID-19	**Supplied as:** 100mg IV vials **Pediatric and Adult Dosing:**[1,2] **<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 Possible 5 day duration for fast responders (currently in trials vs. 10 days) **Pregnancy:** No data; being actively studied in this population **Breastfeeding:** No data **Renal Dysfunction:** No data *Renal Replacement Therapy*: No data[3] **Hepatic Dysfunction:** No data **Extracorporeal membrane oxygenation (ECMO):** No dosing guidance available*	**Check relevant drug interaction resource prior to use (see link in heading)** Avoid strong inducers of CYP enzymes (such as rifampin)[4]	Preclinical studies indicate transient grade 1 or grade 2 increases in AST and ALT[5,6] Acute kidney injury[6,7] Hypotension and cardiac arrest have been reported during loading dose.[7] Serious adverse events from preliminary clinical data:[6] - Multiple-organ dysfunction syndrome - Septic shock - Hypotension	Investigational agent with relatively unknown adverse event profile. **Ongoing:** (During therapy) - CBC - Electrolytes - Renal function - LFTs As usage of remdesivir will be limited to Gilead expanded access and/or the Special Access Program, or clinical trials - monitoring parameters will be defined by the company.[1] Once reliable toxicity data becomes available, this document will be updated.

*During compassionate use of standard dose remdesivir in 4 patients on ECMO, 3 out of 4 patients remained alive at 21 days. No conclusion of dose appropriateness can be derived from this data.[6]

Lopinavir/Ritonavir: Kaletra (LPV/r)

Contraindications and Warnings	Investigational COVID-19 Dosing and Administration	Drug Interactions For more information: Liverpool COVID-19 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[8] Known hypersensitivity to any of LPV/r ingredients **Warnings:** Significant drug interactions (see drug interactions column)[9] 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	**Supplied as:** film-coated tablets (100mg LPV/25mg r, 200mg LPV/50mg r), oral solution (80mg LPV/ 20mg/mL r) **Pediatric Dosing:**[11] **<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)[12][13] **Pregnancy:** 400 mg/100 mg PO BID[14] - Generally considered safe in pregnancy – low placental transfer, unknown teratogenicity[15] - Oral solution contraindicated in pregnancy **Breastfeeding:** Limited data; excreted in low quantities in breastmilk and considered to be safe[8] **Renal Dysfunction:** Dose adjustment not required *Renal Replacement Therapy*: Dose adjustment not required[3] **Hepatic Dysfunction:** Oral solution should be used with caution **ECMO:** No data; may require dose adjustment on an individualized basis **Administration:**	**Check relevant drug interaction resource prior to use (see link in heading)** [9,14,15] 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 (eg. 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 eg. cancer chemotherapy)	**Baseline:**[5] - 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)

ART regimen is not recommended. Consultation with an HIV expert is recommended. Caution in patients with known prolonged QT interval[10]	- Oral solution should be taken with food - Tablets can be taken with or without food - Avoid crushing tablets due to ~46% decreased absorption[16] - Use oral solution if possible - note oral solution is incompatible with polyurethane enteral feeding tubes[17,18] - If NG administration required and unable to use solution, consider crushing tablets and increasing dose[17] or alternate formulation within a study protocol.[23]			

***** 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 (eg. propofol)

Hydroxychloroquine sulfate (HCQ)

Contraindications and Warnings	Investigational COVID-19 Dosing and Administration	Drug Interactions For more information: Liverpool COVID-19 Interactions	Documented Adverse Effects	Monitoring Parameters
Absolute Contraindications:[19,20,21] Hypersensitivity to aminoquinoline derivatives Pre-existing retinopathy **Warnings:**[19,20,21] 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[22,23,24,25,26,27] **Pediatric Dosing**:** Most experts recommend a dosing regimen that includes: - A loading dose on Day 1 and a total duration of no more than 5 days[28,29,30] **Pregnancy:** No dose adjustment; may be administered during pregnancy. Current evidence suggests that hydroxychloroquine crosses the placenta, but is likely safe in pregnancy. [31,32,33] **Breastfeeding:** Excreted in low quantities in breastmilk and considered to be safe[19] **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[3] **Hepatic Dysfunction:** Dose adjustment not required	**Check relevant drug interaction resource prior to use (see header for link)** *Pharmacodynamic:*[4,19,20,21] - 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:**[19,20,21,34] *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:**[19,20,21] *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	**Baseline:**[19,20,21] - 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

	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 - Oral suspension may be compounded by pharmacy if required		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).	

*** 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[22]
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)[23]
c) French publication: 200 mg PO TID x 10 days[24]
d) Chinese pilot trial: 400 mg PO daily x 5 days[25]
e) Canadian arm of REMAP-CAP: 400 mg PO q8h x 9 doses, then 200 mg PO q12h to max of 10 days[26]
f) Pharmacokinetic modelling study: 800 mg once daily on day 1, followed by 200 mg BID for 7 days[27]

**** 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)[28,29]
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)[30]

Tocilizumab

Contraindications and Warnings	Investigational COVID-19 Dosing and Administration	Drug Interactions For more information: Liverpool COVID-19 Interactions	Documented Adverse Effects	Monitoring Parameters
Contraindications in the package insert may not apply (eg. thrombocytopenia) in the setting of COVID-19 **Absolute contraindications:** - Patients with other active infections (ie. ideal to test and treat latent tuberculosis prior to dosing)[35,36] **Warnings:** - Pre-existing CNS demyelinating disorders	**Supplied as:** 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. **Doses under investigation for COVID-19:** a) **Adult Patients:** 400 mg IV x1[37] b) **Pediatric and Adult Patients:** 4-8 mg/kg IV x1 (single dose not to exceed 800 mg, or may use 400 mg standard dose) infused over 1 hour, may repeat 1x dose in 12 hours[38] **Pediatric and Adult dosing for cytokine release syndrome (CRS):**[39] **<30kg:** 12 mg/kg (max 800 mg) **≥30kg:** 8 mg/kg (max 800mg) May repeat up to 3 doses (at least 8h apart) if no clinical improvement after first dose **Pregnancy:** Potential for placental transfer, risk generally increases as pregnancy progresses **Breastfeeding:** Expected exposure in breastmilk (no human data), consider risk/benefit to infant[40] **Renal Dysfunction:** Dose adjustment not required *Renal Replacement Therapy*: Dose adjustment not required[3] **Hepatic Dysfunction:** recommend to stop drug if ALT/AST >5X ULN **ECMO:** No data; may require dose adjustment on an individualized basis	**Check relevant drug interaction resource prior to use (see link in heading)** *Pharmacodynamic:* May cause additive immunosuppression when administered with concomitant immunosuppressive agents eg. anti-TNF agents, biologic disease modifying antirheumatic drugs (DMARDs), tacrolimus, cyclosporine, etc. [4,35,36] *Pharmacokinetic:* Tocilizumab may decrease serum concentrations of CYP substrates (effect may persist several weeks after stopping therapy) *Other:* Avoid concomitant administration of live and inactivated vaccines	**Common:**[35,36] *CNS*: Headache *Cardiac*: Hypertension *Gastrointestinal*: Diarrhea *Hepato/biliary/pancreatic:* Increased ALT/AST, hypercholesterolemia *Hematological:* Thrombocytopenia, neutropenia (more common in children <30kg) *Other:* Infusion related reactions, nasopharyngitis **Severe:** Drug induced liver injury, some acute liver injuries requiring transplant[41] Hypersensitivity reactions (anaphylaxis, SJS) GI perforations Invasive infections (disseminated fungal, TB, bacterial and viral pathogens)[42]	**Baseline:**[35,36] (Recommended if feasible and time permits) - Latent TB (consider IGRA/Quanitferon) - Hepatitis B testing - LFTs - Lipids - CBC with differential (neutrophils, platelets) - Vaccine assessment - Consider monitoring inflammatory biomarkers (IL-6, ferritin, CRP, ESR, etc) **Ongoing:**[35,36] - LFTs before redosing - CBC with differential (neutrophils, platelets) - New onset infection - Abdominal symptoms - Signs/symptoms of CNS demyelinating disorders - Infusion related reactions

References

Remdesivir

1. Gilead Sciences. COVID-19. Accessed April 1, 2020. Available at: https://www.gilead.com/purpose/advancing-global-health/covid-19

2. 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

3. Acute Kidney Injury. http://www.nephjc.com/news/covidaki

4. Liverpool Drug Interactions Group. Interactions with experimental COVID-19 Therapies. [Updated 2020; Accessed March 29, 2020] Available at: https://www.covid19-druginteractions.org/

5. 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

6. 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

7. 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

8. 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

9. University of Liverpool. HIV Drug Interactions. [Updated March 2020; Accessed March 29, 2020] Available at: https://hiv-druginteractions.org

10. 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

11. SickKids Drug Handbook and Formulary. Available at: http://www.sickkids.ca/Pharmacy/SickKids-Drug-Handbook-and-Formulary/index.html

12. 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

13. 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

14. 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

15. Tseng A. Handbook of HIV Drug Therapy, 2013 .[Updated 2020; Accessed March 29, 2020] Available at: https://hivclinic.ca/.

16. 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

17. Kaletra. FDA Label [Updated Aug 2019, Accessed March 30, 2020]. Available at:https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021251s057,021906s052lbl.pdf

18. 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

19. 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

20. 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

21. 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

22. 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

23. 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

24. 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

25. 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

26. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP), NCT02735707

27. 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

28. 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

29. 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

30. Downes K, Chiotos K, Fitzgerald JC, et al. Rational Dosing of Hydroxychloroquine for Treatment of COVID-19. Pre-Print 2020

31. 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.

32. 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

33. 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

34. 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

Tocilizumab

35. ACTEMRA® tocilizumab Product Monograph. [Updated March 2020, Accessed April 1, 2020] Available at: https://www.rochecanada.com/PMs/Actemra/Actemra_PM_E.pdf

36. 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

37. Xiaoling Xu, Mingfeng Han, Tiantian Li et al. Effective Treatment of Severe COVID-19 Patients with Tocilizumab. 2020. *chinaXiv*:202003.00026v1 (Pre-print)

38. China National Health Commission. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment (7th edition) Available at: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html

39. Società Italiana di Malattie Infettive e Tropicali Sezione Regione Lombardia. [Updated March 2020, Accessed April 1, 2020] Available at: http://www.simit.org/medias/1569-covid19-vademecum-13-03-202.pdf

40. Actemra® Tocilizumab. MotherToBaby. Available at: https://mothertobaby.org/ongoing-study/actemra/. Registry telephone number: 877-311-8972

41. Important Safety Information on ACTEMRA® (tocilizumab) - Risk of Hepatotoxicity
https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2019/69991a-eng.php

42. 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