Recommendations for Drug Therapy for Adults with Severe to Critical COVID-19

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Purpose

This document provides recommendations for health care providers on the appropriate prescribing of dexamethasone, remdesivir, baricitinib and/or tocilizumab for adults 18 years and older for the treatment of severe to critical coronavirus disease 2019 (COVID-19) (see ***COVID-19 Severity Classification*** for the definition).

Recommendations Development

The recommendations are informed by best available evidence retrieved from a systematic literature search conducted between June and October 2024 of peer-reviewed studies, review articles, Canadian guidelines, international guidelines and grey literature. The recommendations were developed by the Ontario Health Infectious Diseases program's guidance working group with consensus-based feedback and contributions from Ontario Health's Infectious Diseases Advisory Committee (IDAC). This document was reviewed by multidisciplinary clinicians and health care administrators from Ontario Health's Primary Care Program, Renal Program, Systemic Treatment Program (Cancer Care), Regional Clinical Vice-Presidents and the Chief Medical Executive.

This guidance document will be updated as required as new evidence and relevant information becomes available.

See the ***Authorship, Contributors and Acknowledgements*** section for additional information about the authors and contributors of this guidance document.

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COVID-19 Severity Classification

The classification of illness severity varies among different references and health authorities. ***Table 1*** outlines the classification of disease severity in Ontario that was adapted from Canadian and international guidelines and supported by the IDAC.[1–7] ***Table 2*** describes the common, less frequent and rare symptoms reported by individuals with COVID-19 during the Omicron era.[8,9]

In the early stages of illness, COVID-19 is commonly associated with symptoms such as runny nose, sneezing, sore throat and headache.[8] Disease progression can lead to lung inflammation with shortness of breath and hypoxia, followed by hyperinflammation characterized by acute respiratory distress syndrome, systemic inflammatory response syndrome, septic shock, coagulation disorders or cardiac failure.[10] Severe and critical COVID-19 is associated with an increased risk of death.[10]

Table 1: COVID-19 Severity Classification

COVID-19 Severity	Definition
Mild	Individuals who have: 1. Any of the signs and symptoms of COVID-19 (***Table 2***) **AND** 2. Oxygen saturation (SpO_2) greater than 92% at rest without supplemental oxygen or no increase in supplemental oxygen from baseline
Moderate	Individuals who have: 1. SpO_2 greater than 92% at rest without supplemental oxygen or no increase in supplemental oxygen from baseline **AND** 2. Evidence of lower respiratory disease during clinical assessment or imaging
Severe	Individuals who **newly require supplemental oxygen* OR** Individuals who require an **increase in supplemental oxygen*** from baseline, with or without worsening or progressive signs and symptoms of COVID-19
Critical	Individuals who require any **new respiratory support*** (e.g., high-flow oxygen [HFO], non-invasive ventilation [NIV], mechanical ventilation [MV], extracorporeal membrane oxygenation [ECMO]), vasopressor or inotropic support

*Supplemental oxygen, respiratory, vasopressor or inotropic support due to COVID-19 and not other underlying conditions

Table 2: Symptoms Associated with COVID-19 During the Omicron Era

Frequency of Symptoms[8,9]	Symptoms[8,9]
Common symptoms (Reported by greater than 50% of individuals)	• Headache • Runny nose • Sneezing • Sore throat
Less frequent symptoms (Reported by 10% to 50% of individuals)	• Chills • Dizziness • Fever • Gastrointestinal symptoms (e.g., nausea, diarrhea, abdominal pain) • Hoarse voice • Joint pain • Muscle pain • New loss of or altered sense of smell • Persistent cough
Rare symptoms (Reported by less than 10% of individuals)	• Chest pain • Confusion/brain fog • Delirium • Irregular heartbeat • Skin changes • Shortness of breath • Swollen glands

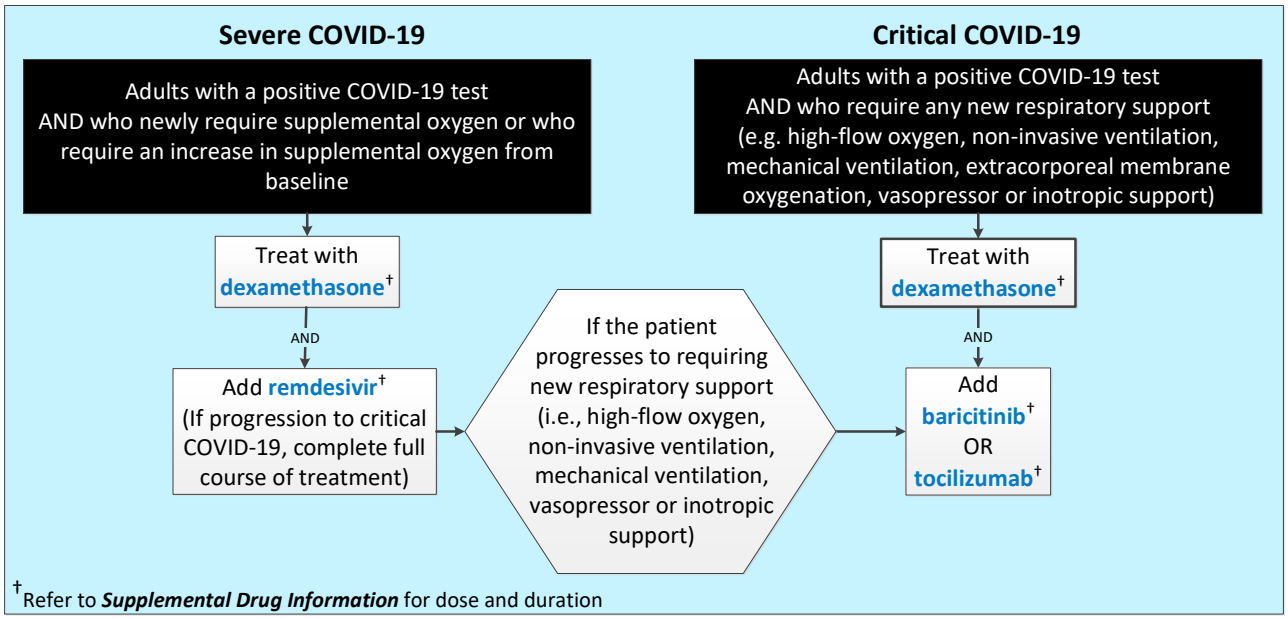
Overview of Treatment for Severe and Critical COVID-19

The goals of treatment in patients with severe or critical COVID-19 are to:

- Prevent mortality[11–13]
- Prevent disease progression[13,14]
- Reduce the time to clinical improvement[14]
- Decrease the risk of serious complications from COVID-19 (e.g., organ damage and/or failure, need for organ support)[1,13]
- Prevent admission to the intensive care unit (ICU)[14]
- Reduce the duration of hospitalization[14]

See ***Figure 1*** for a suggested treatment algorithm.

Figure 1: Treatment Algorithm for Severe and Critical COVID-19



Recommendations for Treatment of Severe and Critical COVID-19

1. **A microbiologically-determined COVID-19 diagnosis is required prior to initiating drug therapy.**
   Patients must have COVID-19 symptoms and a positive test based on polymerase chain reaction (PCR), rapid molecular or rapid antigen test to be eligible for COVID-19 drug therapy.

2. **Dexamethasone is recommended for all patients with severe or critical COVID-19.**
   Dexamethasone is recommended for individuals who newly require supplemental oxygen (e.g., low flow oxygen [LFO]), an increase in supplemental oxygen from baseline, any new respiratory support (e.g., HFO, NIV, MV, ECMO), vasopressor or inotropic support.[1,2,15–17]

3. **Remdesivir is recommended for all patients with severe COVID-19.**
   Remdesivir is recommended in addition to dexamethasone for individuals who newly require supplemental oxygen or an increase in supplemental oxygen from baseline.[1,2,15,17] In patients with severe COVID-19 who are started on remdesivir but progress to critical COVID-19 (e.g., requiring HFO, NIV, MV, ECMO, vasopressor or inotropic support), the full course of remdesivir should still be completed.[1]

4. **Baricitinib or tocilizumab is recommended for all patients with critical COVID-19.**
   Baricitinib or tocilizumab is recommended in addition to dexamethasone for individuals who require any new respiratory support (e.g., HFO, NIV, MV, ECMO), vasopressor or inotropic support.[1,2,15,17]

Clinical Evidence

Systemic Corticosteroids

Systemic corticosteroids mitigate the hyperinflammatory response induced by COVID-19 that can lead to lung injury and multisystem organ dysfunction.[1]

Place in therapy

Systemic corticosteroid therapy is recommended for individuals with severe or critical COVID-19 based on randomized controlled trials that showed treatment with systemic corticosteroids reduced mortality and time to clinical improvement compared with no systemic corticosteroid therapy.[1,2,15–20] In patients who required HFO or NIV, systemic corticosteroid therapy also reduced the risk of progression to MV for individuals not receiving MV at baseline compared with no systemic corticosteroid therapy.[19]

Of the different systemic corticosteroids, dexamethasone is most commonly recommended by COVID-19 treatment guidelines.[1,2,15–17] Dexamethasone was the systemic corticosteroid used in the landmark RECOVERY randomized controlled trial early in the pandemic.[18] The RECOVERY trial established the role of systemic corticosteroids in treating COVID-19 for patients who required oxygen supplementation or respiratory support.[21]

Due to its mechanism of action, the effect of systemic corticosteroids would not be expected to change based on the SARS-CoV-2 variant, an individual's COVID-19 vaccination status or pre-existing immunity.[13] A retrospective study of hospitalized adults with COVID-19 treated with dexamethasone did not find any significant difference for the rate of mortality between the period when the Omicron variant was predominant compared to the pre-Omicron period.[22] A limitation of the retrospective study is that unmeasured confounders (other than the variant of SARS-CoV-2) may impact the accuracy of the estimated effect on mortality.[22]

The initiation of systemic corticosteroid therapy is not recommended for patients with mild to moderate COVID-19 who do not require supplemental oxygen or do not require an increase in supplemental oxygen from baseline due to COVID-19.[1,16] Clinical studies have found the use of systemic steroids in patients with mild to moderate COVID-19 provided no benefit and may increase mortality.[18,23,24] However, patients with mild to moderate COVID-19 who are receiving dexamethasone or an alternative corticosteroid for another underlying condition should continue the drug as directed by their health care provider.[1]

Remdesivir

Remdesivir has demonstrated antiviral activity against SARS-CoV-2 by binding to the viral RNA polymerase and inhibiting viral replication.[25]

The pathogenicity of the circulating variants and subvariants of SARS-CoV-2 and pre-existing immunity of individuals through natural infection and vaccination has evolved over time. Remdesivir maintains equipotent antiviral activity against the ancestral SARS-CoV-2 virus and its variants of concern, including the Omicron variant.[26] However, the expected benefit of remdesivir is likely to be smaller in a better protected population (e.g., individuals with prior immunity).[27,28]

Place in therapy

Severe COVID-19

Remdesivir is recommended for individuals with severe COVID-19.[1,2,15–17]

Randomized control trials and observational studies of patients with severe COVID-19 who had received concurrent therapy with or without systemic corticosteroids reported that remdesivir treatment was associated with decreased mortality and faster clinical improvement compared to no remdesivir treatment.[26,29–32] A meta-analysis of randomized controlled trials found that treatment with remdesivir significantly decreased the risk of progression to NIV or MV compared to no remdesivir treatment in patients with severe COVID-19.[31] Observational studies have reported an association between remdesivir therapy and a shorter duration of hospitalization, decreased ICU length of stay and fewer hospital readmissions compared to no remdesivir therapy in patients with severe COVID-19.[30,33]

For patients with severe COVID-19 who initiated remdesivir therapy but progress to critical COVID-19 (e.g., HFO, NIV, MV, ECMO, vasopressor or inotropic support), completion of the full course of remdesivir is recommended based on the available evidence.[1] Clinical studies of patients with severe COVID-19 who were started on remdesivir finished their course of treatment or stopped at hospital discharge (whichever occurred first), irrespective of clinical improvement or disease progression during their course of therapy.[34–39] The risks and benefits of stopping remdesivir prior to completing the full course of therapy if a patient progresses from severe to critical COVID-19 has not been studied.

Critical COVID-19

There is insufficient evidence to support routine treatment with remdesivir in individuals with critical COVID-19. Consultation with an Infectious Diseases specialist is recommended for immunocompromised patients with persistent symptoms and evidence of ongoing viral replication.[1]

In patients with critical COVID-19 who have received concurrent therapy with or without a systemic corticosteroid, clinical studies that have compared remdesivir therapy to no remdesivir therapy have reported inconsistent results for mortality, time to recovery and the duration of hospitalization.[1,27,29–31,34]

In patients with COVID-19 treated with a systemic corticosteroid and either baricitinib or tocilizumab, one retrospective study evaluated the impact of concurrent remdesivir therapy compared to no remdesivir therapy.[40] This study included patients who required any level of oxygen supplementation or respiratory support.[40] No significant difference was found for mortality in patients who were treated with remdesivir compare to no remdesivir therapy.[40] The study reported mixed findings with regard to improvement in other clinical outcomes.[40] Although remdesivir treatment was associated with faster respiratory recovery (e.g., time to oxygen free status, time to be weaned off supplemental oxygen) compared to no remdesivir treatment, no significant difference was found between the two groups for improvement of COVID-19 disease severity level from baseline at 14 or 28 days after starting treatment.[40]

Baricitinib

Baricitinib is a selective Janus kinase (JAK) 1 and 2 inhibitor that can reduce elevated levels of cytokines associated with the hyperinflammatory phase in COVID-19.[14] It is postulated that the mitigation of systemic inflammation may improve clinical outcomes by preventing progression to acute respiratory distress syndrome, multiorgan failure and death. Baricitinib may also have antiviral activity by interfering with the entry of viruses into host cells.[41,42]

Since baricitinib mainly acts on complications caused by SARS-CoV-2, the generalizability of the clinical evidence for baricitinib is less affected by changes in the circulating SARS-CoV-2 variants, vaccination or natural immunity.[13]

Place in therapy

Severe COVID-19

Baricitinib is not routinely recommended for the treatment of patients with severe COVID-19.[15] In exceptional circumstances where a patient with severe COVID-19 presents with clinical signs and symptoms that suggests a worsening course of illness, consultation with an Infectious Diseases specialist is strongly recommended to inform individualized treatment decisions.[15]

Critical COVID-19

Baricitinib is recommended as a treatment option in addition to dexamethasone for all individuals with critical COVID-19 (e.g., requiring HFO, NIV, MV, ECMO, vasopressor or inotropic support).[1,2]

In the subgroup of patients with critical COVID-19 who required HFO or NIV, randomized control trials and observational studies found a survival benefit for baricitinib therapy compared to no baricitinib therapy.[43–45] The survival benefit of baricitinib was consistent in studies where concurrent treatment with a systemic corticosteroid was prevalent and in studies where concurrent treatment with a systemic corticosteroid varied because they were started prior to dexamethasone becoming a part of usual care.[27,43–45] A randomized controlled trial found that baricitinib therapy reduced the duration of hospitalization and the risk of progression to MV or ECMO among patients who were receiving NIV at baseline compared to no baricitinib therapy.[43] Over 95% of patients in this study received concurrent therapy with a systemic corticosteroid.[43] A retrospective study of patients with COVID-19 who required HFO or NIV and treated with a systemic corticosteroid reported the addition of baricitinib was associated with fewer ICU admissions compared to no baricitinib.[44]

In the subgroup of patients with critical COVID-19 who required MV or ECMO, a meta-analysis of randomized controlled trials found baricitinib therapy significantly decreased mortality compared to no baricitinib therapy.[45] However, randomized controlled trials and observational studies did not find any significant difference between baricitinib therapy and no baricitinib therapy for other clinical outcomes such as time to clinical improvement or the duration of hospitalization.[43,46,47] Over 86% of the patients in these clinical studies received concurrent therapy with a systemic corticosteroid.[43,46,47]

Tocilizumab

Tocilizumab is a monoclonal antibody that blocks interleukin-6 (IL-6)-mediated inflammation.[48] Elevated IL-6 levels have been associated with increased COVID-19 severity because hyperactivation of the immune response impairs oxygen diffusion and may lead to lung injury or multiorgan failure.[48] Since tocilizumab acts on complications caused by SARS-CoV-2 rather than attempting to neutralize the virus itself, the generalizability of the clinical evidence for tocilizumab is less affected by changes in the circulating SARS-CoV-2 variants, vaccination or natural immunity.[13]

Place in therapy

Severe COVID-19

Tocilizumab is not routinely recommended for the treatment of patients with severe COVID-19.[15] In exceptional circumstances where a patient with severe COVID-19 presents with clinical signs and symptoms that suggests a worsening course of illness, consultation with an Infectious Diseases specialist is strongly recommended to inform individualized treatment decisions.[15]

Critical COVID-19

Tocilizumab is recommended as a treatment option in addition to dexamethasone for individuals with critical COVID-19.[1,2,15–17]

In the subgroup of patients with critical COVID-19 who required HFO or NIV, a meta-analysis of randomized controlled trials found that tocilizumab treatment decreased mortality, time to clinical improvement, progression to MV among patients who were not receiving MV at baseline, progression to cardiovascular system support and the need for renal replacement therapy compared to no tocilizumab treatment.[49] Concurrent therapy with systemic corticosteroids was variable in the studies included in the meta-analysis because some were started prior to release of the RECOVERY trial results after which dexamethasone became a part of usual care.[27,49,50]

The supporting evidence for tocilizumab use in patients with critical COVID-19 patients who require MV, ECMO, vasopressor or inotropic support is limited. No clinical trial has demonstrated that tocilizumab improved clinical outcomes in this specific subgroup of patients.[49–53] In randomized controlled trials and observational studies that compared tocilizumab therapy compared to no tocilizumab therapy in patients with COVID-19 who required any oxygen supplementation or respiratory support that included individuals who received MV, ECMO, vasopressor or inotropic support, inconsistent results have been reported for mortality, hospital length of stay, ICU length of stay, ICU admissions and time to clinical improvement.[49,52,54–59] Concurrent therapy with systemic corticosteroids was variable in the studies included in the meta-analysis because some were started prior to release of the RECOVERY trial results after which dexamethasone became a part of usual care.[27,49,50]

Comparison of Baricitinib and Tocilizumab in Patients with Critical COVID-19

The data from randomized controlled trials that have directly compared baricitinib and tocilizumab is extremely limited. The evidence to guide the use of baricitinib or tocilizumab in patients with critical COVID-19 is primarily derived from observational studies that have indirectly compared the two drugs. In the absence of robust clinical trial evidence, selection between the two drugs will depend on patient-specific factors (e.g., route of administration, contraindications, etc).[60]

Patients who require HFO or NIV

Treatment with either baricitinib or tocilizumab in addition to systemic corticosteroids is recommended for individuals with critical COVID-19 who require HFO or NIV.[1,2,14–16]

Although the United States' (US) National Institutes of Health COVID-19 guidelines noted a preference for baricitinib over tocilizumab in individuals who require HFO or NIV based on the totality of the data for baricitinib treatment, there are limitations to the evidence that is currently available.[1] There are two retrospective studies that have compared the use of baricitinib and tocilizumab in the patients who require HFO or NIV. A large retrospective study in which over 81% of patients had received concurrent therapy with a systemic corticosteroid, found baricitinib therapy was associated with significantly lower mortality compared to tocilizumab therapy.[61] Another retrospective study found no significant difference for the time to clinical improvement when baricitinib therapy was compared to tocilizumab therapy in this subgroup of patients.[62] Although information about concurrent systemic corticosteroid use for patients in this study has not been published, the study was conducted after the results of the RECOVERY trial was released and dexamethasone became a part of usual care[27,62]

Additional evidence is derived from studies that have compared the use of baricitinib and tocilizumab in patients who required any oxygen supplementation or respiratory support, including HFO or NIV. An open-label, randomized controlled trial that compared baricitinib with tocilizumab found baricitinib therapy was non-inferior to tocilizumab therapy for hospitalization length of stay and progression to MV or death.[63] The same study also reported no significant difference between the two treatment groups for clinical disease progression.[63] All the patients in this study received concurrent therapy with dexamethasone as part of usual care.[63]

Observational studies that have compared baricitinib therapy with tocilizumab therapy in patients who required any oxygen supplementation or respiratory support, including HFO or NIV, have reported mixed results. A retrospective study noted an association between baricitinib therapy and a lower incidence of admission to the ICU compared with tocilizumab therapy.[64] However, the lack of propensity score-matched analysis of the results to help mitigate the impact of potential selection bias and confounding variables is a limitation of the study.[65] In other observational studies, neither baricitinib nor tocilizumab was consistently associated with a clinical benefit for outcomes such as mortality, progression to MV, duration of MV, duration of hospitalization, time to clinical improvement or ICU length of stay when compared against one another.[42,42,61,62,64,66–71]

Patients who require MV, ECMO, vasopressor or inotropic support

Treatment with baricitinib or tocilizumab is recommended in addition to systemic corticosteroid therapy for individuals with COVID-19 who require MV, ECMO, vasopressor or inotropic support.[1,2,14–17]

In this subgroup of patients, only observational studies have compared the use of baricitinib with tocilizumab. A retrospective study reported an association between baricitinib therapy and faster time to clinical improvement compared to tocilizumab therapy.[62] However, other studies that compared baricitinib treatment with tocilizumab treatment for patients who require MV, ECMO, vasopressor or inotropic support have shown inconsistent results for mortality. One retrospective study found baricitinib therapy was associated with a mortality benefit compared with tocilizumab therapy, but another retrospective study found no significant difference between the two drugs.[61,72]

Patients with severe COVID-19 who progress to critical COVID-19

Some individuals with severe COVID-19 who have started systemic corticosteroids and remdesivir may experience a progression to critical COVID-19.[1] In this clinical scenario, patients should continue and complete their course of systemic corticosteroids and remdesivir.[1,17] Furthermore, the addition of baricitinib or tocilizumab is recommended for the treatment of critical COVID-19.[1]

The use of baricitinib compared to tocilizumab in patients with critical COVID-19 who received concurrent therapy with a systemic corticosteroid and remdesivir is not well-studied. The limited available evidence from observational studies is summarized below. Selection between the two agents in the absence of robust clinical evidence will depend on patient-specific factors (e.g., route of administration, contraindications, etc).[60]

Patients who require HFO or NIV

Two retrospective studies have compared baricitinib to tocilizumab in patients who required HFO or NIV.[73,74] All the patients in both studies received concurrent therapy with a systemic corticosteroid and over 85% of the patients received concurrent therapy with remdesivir.[73,74] No significant difference for mortality was reported when baricitinib was compared to tocilizumab.[73,74] One of the studies with data for time to respiratory improvement found no significant difference between baricitinib and tocilizumab for this clinical outcome.[73]

Patients who require MV, ECMO, vasopressor or inotropic support

An observational study that compared baricitinib with tocilizumab in individuals with critical COVID-19 who required MV, ECMO, vasopressor or inotropic support found no significant difference between baricitinib and tocilizumab for mortality.[74] All the patients in the study received concurrent therapy with a systemic corticosteroid and over 85% of patients had also received remdesivir.[74]

Use of Tocilizumab in Individuals with Critical COVID-19 Treated with Systemic Corticosteroids and Baricitinib

There is insufficient evidence to recommend the addition of tocilizumab as part of combination therapy with baricitinib and systemic corticosteroids for treatment of critical COVID-19.

Clinical trials have not evaluated the impact of tocilizumab therapy in patients with critical COVID-19 who have already received a systemic corticosteroid plus baricitinib.[1] There is a potential for greater risk of secondary infections when multiple immunomodulators are used together.[1]

Use of Baricitinib in Individuals with Critical COVID-19 Treated with Systemic Corticosteroids and Tocilizumab

There is insufficient evidence to recommend the addition of baricitinib to systemic corticosteroids and tocilizumab for the treatment of critical COVID-19.

The RECOVERY trial included patients who required any oxygen supplementation or respiratory support, including HFO, NIV, MV or ECMO.[43] In the subgroup analysis of patients who had all received tocilizumab, no significant difference was found for mortality between the patients treated with baricitinib therapy compared to no baricitinib therapy. [43] Although the results of the subgroup analysis was not stratified for patients who had also received concurrent systemic corticosteroids therapy, more than 95% of patients in the trial received concurrent therapy with a systemic corticosteroid as part of usual care.[43]

An observational study found similar results in patients with COVID-19 who required any level of oxygen supplementation or respiratory support, including those who had received HFO, NIV or MV.[48] All patients in this study were treated with systemic corticosteroids and tocilizumab as part of usual care.[48] The addition of baricitinib therapy was not associated with decreased mortality, decreased progression to mechanical ventilation or death compared to no baricitinib therapy.[48]

Supplemental Drug Information

Dexamethasone

Health Canada approved indication

Dexamethasone for the treatment of severe and critical COVID-19 is an off-label indication in Canada.[75–77]

Dose and duration for COVID-19

The recommended dose for dexamethasone is 6 mg orally (PO) or intravenously (IV) for 10 days or until discharge (if sooner).[1,15] No dose adjustment of dexamethasone is recommended for obese individuals.[78]

Dexamethasone doses greater than 6 mg are not recommended for the treatment of COVID-19 unless the patient has another clinical indication for higher doses of the drug (e.g., refractory septic shock, history of chronic steroid use, obstetric use for fetal lung maturation).[79] In a meta-analysis of randomized controlled trials that compared higher doses of dexamethasone (greater than 6 mg per day) with usual doses of 6 mg per day for the treatment of COVID-19, no significant difference for mortality was found.[80] Other studies that compared dexamethasone doses of 10 mg or higher per day against doses of 6 to 8 mg per day to treat COVID-19 also reported no significant difference for mortality between the higher doses and the lower doses.[17,20,81,82]

If dexamethasone is not available, an equivalent dose of another systemic corticosteroid may be considered.[1] However, the evidence supporting their use may not be as strong compared to dexamethasone, as some clinical trials of the other corticosteroids were stopped early due to low enrollment following the publication of the RECOVERY trial results.[1] If a patient has a contraindication to dexamethasone or if dexamethasone is not available, the following alternatives are recommended:

- Prednisone 40 mg PO daily for 10 days or until discharge (if sooner)[1]
- Methylprednisolone 32 mg IV daily for 10 days or until discharge (if sooner)[1]
- Hydrocortisone 50 mg IV every 6 hours for 10 days or until discharge (if sooner)[17,83,84]

Dose adjustment for renal impairment

No dose adjustment is recommended for dexamethasone in individuals with renal impairment.[85]

Dose adjustment for hepatic impairment

No dose adjustment is provided in the manufacturer's labelling for dexamethasone in individuals with hepatic impairment.[75–77]

Administration considerations

Dexamethasone tablets may be crushed and mixed with water for administration to individuals who have difficulty swallowing tablets or for administration via enteral feeding tubes.[86,87]

Dexamethasone has high bioavailability and similar plasma concentrations are achieved after enteral and intravenous intake.[60] The oral formation is preferred when there are no significant concerns about enteral absorption in individuals who can tolerate oral or enteral intake.[16] Intravenous administration is recommended when tablets or oral solutions cannot be used.[16]

Prescribing window

The optimal timing of dexamethasone therapy with respect to time from the onset of COVID-19 symptoms is unknown.[19,20,88] The initiation of dexamethasone is recommended when patients with COVID-19 require new supplemental oxygen or respiratory support, or an increase supplemental oxygen support from baseline due to COVID-19.[15,17]

Clinically relevant contraindications

Dexamethasone is contraindicated in the following individuals: people who are hypersensitive to dexamethasone or to any ingredient in the formulation, people with systemic fungal infections, people who are receiving concurrent vaccination with live vaccines, people with gastric or duodenal ulcers and people with advanced glaucoma who have a cup to disk ratio of greater than 0.8.[75–77]

This list of contraindications is not exhaustive, refer to the dexamethasone product monographs under the ***Additional Resources*** section for more information.

Clinically relevant drug-drug interactions

Dexamethasone may increase cyclosporine concentrations by inhibiting cyclosporine metabolism.[77] Monitoring of cyclosporine levels is recommended for individuals receiving concurrent therapy with dexamethasone.[77]

Both increases and decreases in phenytoin levels have been reported with dexamethasone concurrent therapy.[77] Monitoring of phenytoin levels is recommended for individuals receiving dexamethasone and phenytoin.[77]

Dexamethasone may inhibit the response to warfarin.[77] International normalized ratio (INR) monitoring is recommended for individuals receiving concurrent therapy with dexamethasone and warfarin.[77]

The list of drug-drug interactions noted above is not exhaustive. Refer to the dexamethasone product monographs and the University of Liverpool's COVID-19 drug interactions checker under the ***Additional Resources*** section for more information.

Clinically relevant potential adverse effects

Systemic dexamethasone treatment is generally safe.[89] Some adverse effects that have been reported for dexamethasone include hyperglycemia, gastrointestinal bleeding, neuromuscular weakness and neuropsychiatric effects (e.g., depression, insomnia).[17,77] However, the generalizability of the evidence may be limited because the data was extrapolated from studies where dexamethasone was used to treat non-COVID-19 medical conditions.[17]

The use of dexamethasone or other systemic corticosteroids may increase the risk of opportunistic fungal infections (e.g., aspergillosis, mucormycosis) and reactivation of latent infections (e.g., hepatitis B virus infection, herpes simplex virus and varicella zoster virus infections, strongyloidiasis, tuberculosis).[1] Using dexamethasone alone or in combination with other immunosuppressants, such as tocilizumab or baricitinib, could also theoretically increase the risk of secondary infections.[1] However, clinical trials have not reported a significant difference in the rates of secondary infections between patients who received corticosteroids (including dexamethasone) in combination with another immunomodulatory agent compared to those who received corticosteroids alone.[1]

The list of potential adverse effects listed above is not exhaustive, refer to the dexamethasone product monographs under the ***Additional Resources*** section for more information.

Remdesivir

Health Canada approved indication

Remdesivir is approved for the treatment of hospitalized adult and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with COVID-19 pneumonia who require supplemental oxygen.[25] Remdesivir is also approved for the treatment of non-hospitalized adult and pediatric patients (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing and who are at high risk for progression to severe COVID-19, including hospitalization or death.[25]

Dose and duration for COVID-19

Remdesivir 200 mg IV on day 1, then 100 mg IV daily on days 2 to 5 (or until hospital discharge, whichever is sooner) is recommended for the treatment of severe COVID-19.[25] No dose adjustment of remdesivir is recommended in obese individuals.[78]

Dose adjustment for renal impairment

No dosage adjustment is required for patients with any degree of renal impairment, including patients who require dialysis.[25] Remdesivir can be administered without regard to the timing of dialysis.[25]

Dose adjustment for hepatic impairment

No dosage adjustment is recommended for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B or C).[25]

Prescribing window

The optimal timing to initiate remdesivir therapy for individuals with severe COVID-19 is unknown. Evidence suggests that the benefit of remdesivir is greatest when the drug is given early in the course of COVID-19 based on its mechanism of action.[1,34]

Clinically relevant contraindications

Remdesivir is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation.[25]

Clinically relevant drug-drug interactions

The concomitant use with hydroxychloroquine or chloroquine is not recommended as they may reduce remdesivir's antiviral activity.[25]

Other clinically significant drug-drug interactions are not expected with remdesivir as it is a minor substrate of CYP3A4, OATP1B1 and P-glycoprotein.[1,25]

Clinically relevant potential adverse effects

Remdesivir is generally well tolerated.[27] The frequency of adverse drug effects reported for remdesivir was comparable to usual care in clinical trials.[27] Reported adverse effects include gastrointestinal symptoms (e.g., nausea), elevated transaminase levels (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST]) and an increase in prothrombin time without a change in the INR.[1,25]

There have been rare reports of hypersensitivity reactions with remdesivir, such as infusion-related reactions or anaphylaxis.[25,90] Signs and symptoms of hypersensitivity reaction may include hypotension, hypertension, tachycardia, bradycardia, hypoxia, fever, dyspnea, wheezing, angioedema, rash, nausea, vomiting, diaphoresis, or shivering.[90] For patients who experience remdesivir infusion-related reactions but not anaphylaxis, slower infusion rates with a maximum infusion time of up to 120 minutes, may potentially prevent the signs and symptoms.[25]

The list of potential adverse effects listed above is not exhaustive, refer to the remdesivir product monograph under the ***Additional Resources*** section for more information.

Baricitinib

Health Canada approved indication

Baricitinib for the treatment of critical COVID-19 is an off-label indication in Canada.[91,92]

Dose and duration for COVID-19

The recommended dose for baricitinib is 4 mg daily.[91] Baricitinib may be administered orally or via an enteral feeding tube (e.g., orogastric tube [OG], nasogastric tube [NG] or gastrostomy tube [GT]).[91] No dose adjustment of baricitinib is recommended for obese individuals.[78] Large clinical trials of baricitinib had included a significant number of obese individuals who received the standard recommended dose of baricitinib.[41,93]

The recommended treatment duration of baricitinib is up to 14 days, until the patient has clinically improved and no longer requires supplemental oxygen for COVID-19, or until hospital discharge, whichever is sooner.[79] The optimal duration of baricitinib treatment for COVID-19 is unknown. Clinical trials used treatment durations ranging from 10 to 14 days or until hospital discharge, whichever came first.[43,47,60,93] Early discontinuation of baricitinib for patients who have clinically improved and no longer require supplemental oxygen is a recommendation based on expert opinion.[94]

Dose adjustment for renal impairment

Table 3 provides baricitinib dosing recommendations for the treatment of COVID-19 in adults with renal impairment.[91]

Table 3: Baricitinib dosage recommendations for adults with renal impairment

Renal Function or Renal Replacement Modality	Baricitinib Dose
Estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m^2 to less than 90 mL/min/1.73 m^2	4 mg PO/OG/NG/GT daily[91]
eGFR 30 to less than 60 mL/min/1.73 m^2	2 mg PO/OG/NG/GT daily[91]
eGFR 15 to less than 30 mL/min/1.73 m^2	2 mg PO/OG/NG/GT every other day[‡91]
eGFR less than 15 mL/min/1.73 m^2	Not recommended[91]
Dialysis	Not recommended[91]

[‡]The dosage recommendation for individuals with eGFR 15 to less than 30 mL/min/1.73 m^2 is based on the RECOVERY trial.[43] Although the US product monograph recommends baricitinib 1 mg PO/OG/NG/GT daily in this patients population, the 1 mg tablet is not available in Canada and there are safety concerns with splitting baricitinib 2 mg tablets.[91,92] See the ***Administration Considerations*** section for baricitinib for additional information.

Dose adjustment for hepatic impairment

No dose adjustment is recommended for baricitinib in the manufacturer's labelling for individuals with mild to moderate hepatic impairment.[91] The use of baricitinib has not been studied in individuals with COVID-19 and severe hepatic impairment.[91]

Administration considerations

Intact tablets of baricitinib are not considered hazardous.[91] However, it is unknown if powder from the crushed tablet may constitute a reproductive hazard to the preparer.[91] If baricitinib tablets are crushed, proper control measures (e.g., ventilated enclosure) or personal protective equipment (e.g., N95 respirator) are required.[91] For patients who cannot swallow, baricitinib tablets can be dispersed in water for oral administration or administration via OG/NG/GT.[91]

Refer to the baricitinib product monograph under the ***Additional Resources*** section for more information on preparation instructions for alternative administration in patients unable to swallow tablets.

Prescribing window

Baricitinib therapy may be initiated in patients with critical COVID-19 irrespective of the time from COVID-19 symptom(s) onset.[41,43,47,93] Treatment with baricitinib should be started at the same time as systemic corticosteroids.[60]

Use of inflammatory markers to guide baricitinib initiation

There is insufficient evidence to support the use of inflammatory markers to guide the initiation of baricitinib therapy in patients with critical COVID-19.

Some clinical trials have used inflammatory markers (e.g., C-reactive protein [CRP], D-dimer, lactate dehydrogenase, ferritin) to guide the initiation of baricitinib therapy because COVID-19-induced hyperinflammation is associated with increased disease severity.[42,47,93] However, the selection of specific inflammatory markers and their respective threshold levels have been inconsistent between different clinical trials and guidelines.[43,47,79,93] Currently, there is no consensus on which clinical or laboratory parameters reliably predict a patient's risk of disease progression to guide baricitinib therapy.[1]

Clinically relevant contraindications

Baricitinib is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation.[91]

Clinically relevant precautions

Baricitinib is not recommended for individuals with an ALT or AST greater than five times the upper limit of normal and drug-induced liver injury is suspected, for individuals with an absolute neutrophil count (ANC) less than 0.5 x 10^9/L or absolute lymphocyte count (ALC) less than 0.2 x 10^9/L.[91,94]

Baricitinib is also not recommended for patients with COVID-19 who have any other concurrent active infection (e.g., bacterial, fungal or viral infection).[91] The use of baricitinib has not been well-studied in this population as many of the clinical trials excluded patients with COVID-19 who had another active infection at baseline.[43,47,93]

Clinically relevant drug-drug interactions

Baricitinib is a substrate of the OAT3 drug transporter.[95] Co-administration with strong OAT3 inhibitors (e.g., probenecid) can increase plasma baricitinib concentrations.[95] The following dosage modifications for baricitinib are recommended for individuals treated concurrently with a strong OAT3 inhibitor:

- If the recommended dose is 4 mg once daily, reduce the dose to 2 mg once daily[91]
- If the recommended dose is 2 mg once daily, reduce the dose to 1 mg once daily[91]
- If the recommended dose is 1 mg once daily, consider discontinuing the interacting drug that is a strong OAT3 inhibitor[91]

Refer to the baricitinib product monograph and the University of Liverpool's COVID-19 drug interactions checker under the ***Additional Resources*** section for more information.

Clinically relevant adverse effects

In clinical studies of patients with COVID-19, baricitinib treatment was generally well tolerated.[45,46,58,96] Some adverse effects that have been reported for baricitinib include elevated liver enzymes (e.g., ALT, AST), elevated creatine phosphokinase, thrombocytosis (e.g., platelets greater than 600 x 10^9/L) and neutropenia.[91] Rare cases of intestinal perforation have been reported in patients with COVID-19 treated with baricitinib.[91]

Serious adverse effects

Secondary infections:

- With all immunomodulatory agents, the risk of secondary infection is a potential concern.[21] Secondary infections, including opportunistic infections, have been reported in patients treated with baricitinib for COVID-19.[91] However, clinical trials found that the overall incidence of infections, serious infections and opportunistic infections were similar between patients treated with baricitinib compared to placebo.[91] Data from meta-analyses of randomized controlled trials and observational studies that included patients with COVID-19 treated with or without systemic corticosteroid therapy reported similar findings.[58,96,97] Some clinicians have suggested that patients with COVID-19 who receive baricitinib therapy may not be at a significantly increased risk of secondary infection due to the relatively short course of therapy for this indication.[21]

Thrombosis:

- Although venous thromboembolism (VTE) has been observed in some patients with COVID-19 who were treated with baricitinib, clinical trials and observational studies of patients with COVID-19 have reported comparable rates of VTE in patients treated with baricitinib compared to no baricitinib therapy.[58,91,96,97] Some clinical trials excluded individuals who were at higher risk of VTE (e.g., individuals who had a VTE within 12 weeks prior to study enrollment or patients with a history of more than one VTE event).[47,93] This limitation may restrict the generalizability of the results to individuals who are at increased risk of thrombosis.

Clinicians should consider the risks and benefits of baricitinib therapy to inform individualized treatment decisions for patients with critical COVID-19.[91] Consult with specialists as required to determine the most appropriate treatment for critical COVID-19 (e.g., infectious diseases, hematology).

The list of potential adverse effects listed above is not exhaustive, refer to the baricitinib product monograph under the ***Additional Resources*** section for more information.

Tocilizumab

Health Canada approved indication

Tocilizumab is approved for the treatment of adults with COVID-19 who are receiving systemic corticosteroids and require supplemental oxygen, NIV, MV or ECMO.[98]

Dose and duration for COVID-19

Table 4 provides dosage recommendations for tocilizumab based on the best available evidence, safety and logistical considerations.

Table 4. Tocilizumab dosing recommendations

Patient Weight	Tocilizumab Dosing in Non-drug Shortage Situations (Single Dose IV)	Tocilizumab Dosing in Drug Shortage Situations (Single Dose IV)
Less than or equal to 40 kg	8 mg/kg[50,99]	8 mg/kg[50]
Greater than 40 kg to less than or equal to 65 kg	400 mg[50,99]	400 mg[100]
Greater than 65 kg to less than or equal to 90 kg	600 mg[50,99]	400 mg[100]
Greater than 90 kg	800 mg[50,99]	400 mg[100]

The efficacy and safety of tocilizumab dosing using a weight-based dosing strategy (e.g., 8 mg/kg up to a maximum of 800 mg) or a weight-based dose banding strategy (8 mg/kg for weight equal or less than 40 kg; 400 mg for weight greater than 40 and equal or less than 65 kg; 600 mg for weight greater than 65 and equal or less than 90 kg; 800 mg for weight greater than 90 kg) are supported by clinical evidence from the REMAP-CAP and RECOVERY trials.[50,101] Although the two dosing strategies have not been directly compared in a clinical trial, a pharmacokinetic simulation study predicted comparable tocilizumab exposures for weight-based dosing and weight-based dose banding.[102] It is unclear if there are any advantages for weight-based dosing compared to weight-based dose banding for mortality and other clinical outcomes. The weight-based dose banding strategy has practical and safety advantages such as reducing dosing errors and avoiding unnecessary drug waste.

In drug shortage situations, observational studies that have compared weight-based dosing (8 mg/kg up to a maximum of 800 mg) and fixed-dosed strategies (e.g., 400 mg for all patients irrespective of weight) did not find any significant difference for mortality, duration of hospitalization or ICU length of stay when a fixed dose of 400 mg was compared with weight-based dosing.[103–106] However, unmeasured confounders in the observational studies (e.g., differences in baseline characteristics between patients in the two treatment groups, changes in supportive care over time) may limit the validity of the comparison between weight-based dosing and a fixed dose of 400 mg.[103] There have not been any studies that have compared the weight-based dosing banding strategy with the fixed-dose strategy.

No dose adjustment of tocilizumab is recommended for obese individuals. Most clinical trials of tocilizumab that used either a weight-based dosing strategy or weight-based dose banding strategy had implemented a maximum dose cap of 800 mg, irrespective of the patient's weight.[50,51,101,107] During drug shortage situations, observational studies that had implemented a fixed dose regimen of tocilizumab 400 mg also included patients who were obese.[103,106] However, the inclusion of patients with extreme obesity (e.g., body mass index 40 kg/m^2 and higher) in the studies was limited.[78]

Use of a second dose of tocilizumab

A second dose of tocilizumab is not recommended due to insufficient clinical evidence to support repeated dosing.[83]

Neither the REMAP-CAP nor the RECOVERY trials provided sufficient information to determine the role of a second dose in patients who did not respond to the first dose.[100] Observational studies reported similar benefits between a single tocilizumab dose compared to multiple doses.[94,108,109] An observational study reported that treatment with multiple doses of tocilizumab was associated with higher odds of pneumonia compared to a single dose.[108] The study investigators postulated that the risk of pneumonia could be related to the potential immunosuppressive effects of tocilizumab.[108]

Dose adjustment for renal impairment

No dosage adjustment is required for patients with mild renal impairment.[98] The use of tocilizumab has not been studied in individuals with moderate or severe renal impairment.[98]

Dose adjustment for hepatic impairment

No dose adjustment is provided in the manufacturer's labelling for tocilizumab in patients with hepatic impairment.[98] The use of tocilizumab has not been studied in individuals with hepatic impairment.[98]

Prescribing window

The optimal timing for tocilizumab administration is unknown.[55,110] The initiation of tocilizumab therapy for patients with critical COVID-19 is recommended within 14 days of hospital admission or within 14 days of a new COVID-19 diagnosis if the infection was nosocomially-acquired based on the REMAP-CAP study protocol.[101] Treatment with tocilizumab should be started at the same time as systemic corticosteroids for patients with critical COVID-19.[60]

Use of inflammatory markers to guide tocilizumab initiation

The use of inflammatory markers, such as CRP levels, is not recommended to guide the initiation of tocilizumab therapy.

CRP is an inflammatory biomarker that has been correlated with serum IL-6 concentrations.[50] Early clinical studies of COVID-19 had reported CRP levels were associated with disease severity and prognosis.[50] Although the RECOVERY trial used a CRP level of 75 mg/L and higher as evidence of systemic inflammation, the threshold value for CRP used to guide tocilizumab initiation by other clinical trials has varied.[17] Data is conflicting for the potential association between decreased mortality and the initiation of tocilizumab in patients with COVID-19 whose baseline CRP levels are 75 mg/L or higher. A meta-analysis of randomized controlled trials of patients with COVID-19 that compared tocilizumab treatment with no tocilizumab treatment assessed the mortality rates of patients stratified by CRP levels.[49] Although a survival benefit was reported for tocilizumab treatment in patients with CRP levels 75 to less than 150 mg/L compared to no tocilizumab treatment, no survival benefit was observed for patients treated with tocilizumab who had CRP levels less than 75 mg/L, nor CRP levels equal or greater than 150 mg/L compared to no tocilizumab treatment.[49] Another open-label randomized controlled trial of patients with COVID-19 reported similar hazard ratios for mortality in patients whose baseline CRP level was 81 mg/L or lower compared to patients whose baseline CRP level was 82 mg/L or higher.[56] There is no consensus on which clinical or laboratory parameters reliably predict a patient's risk of disease progression to guide tocilizumab therapy.[1]

Clinically relevant contraindications

Tocilizumab is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation in the Canadian product monograph.[98] The use of tocilizumab is also contraindicated in patients with an active infection other than COVID-19 (e.g., active bacterial, fungal or viral infection) because its use has not been well studied in this population.[98] Many of the clinical trials excluded patients who had another active infection at baseline.[50,56,59,111–119]

Clinically relevant precautions

The use of tocilizumab is not recommended in patients with COVID-19 and elevated ALT or AST that is greater than or equal to 10 times the upper limit of normal, platelet count less than 50×10^9/L or ANC less than 1×10^9/L.[98]

Tocilizumab should be used with caution in individuals at increased risk for gastrointestinal perforation (e.g., patients with a history of gastrointestinal ulceration or diverticulitis).[120]

Clinically relevant drug-drug interactions

Tocilizumab may increase the metabolism of co-administered drugs that are substrates of CYP450 isoenzymes 3A4, 1A2, 2C9 or 2C19.[1,98] Therapeutic drug monitoring for treatment effect or concentration of the co-administered drug may be warranted for drugs with a narrow therapeutic index (e.g., calcium channel blockers, theophylline, warfarin, phenytoin, cyclosporine or benzodiazepines).[98] Since tocilizumab has an elimination half-life of 13 days, the effect of tocilizumab on CYP450 enzyme activity may persist for several weeks after stopping therapy.[98]

Refer to the ***Additional Resources*** section for more information about potential drug-drug interactions from the tocilizumab product monograph and the University of Liverpool's COVID-19 drug interactions checker.

Clinically relevant adverse effects

Common adverse effects related to tocilizumab are generally mild, such as headache, dizziness or injection site reactions.[17] Elevated liver enzymes (e.g., ALT, AST) and rare cases of neutropenia or thrombocytopenia have been reported.[1,98] Gastrointestinal perforation have been observed in patients with COVID-19 treated with tocilizumab but are uncommon.[120] Venous thromboembolic events have been reported in patients with COVID-19 treated with tocilizumab, but a meta-analysis of randomized controlled trials and a retrospective study did not find an association between tocilizumab therapy and the development of thromboembolic events with COVID-19.[58,121] The generalizability of the retrospective study may be limited because it excluded individuals who were at higher risk of VTE (e.g., people who had a history of thrombosis or have risk factors for thrombosis), However, that was not a limitation of the clinical trials in the meta-analysis.[56,101,113,114,118,121–123]

Serious adverse events

Secondary infections:

- The risk of secondary infection is a potential concern with tocilizumab because it is an immunomodulatory agent.[21] Although serious secondary infections such as tuberculosis, bacterial or fungal infections have been reported following tocilizumab use in patients with COVID-19, no excess secondary infections were seen among patients treated with tocilizumab plus corticosteroids compared with no tocilizumab therapy in randomized controlled trials.[1] This was consistent with the results of a meta-analysis of randomized controlled trials that found no significant difference between tocilizumab therapy compared to no tocilizumab therapy for the risk of serious infections in patients with COVID-19.[58]

Clinicians should consider the risks and benefits of tocilizumab therapy to inform individualized treatment decisions for patients with critical COVID-19 who have another active serious infection (e.g., bacterial, fungal or viral co-infection other than COVID-19).[60] Consult an Infectious Diseases specialist as required to determine the most appropriate treatment for critical COVID-19.

The list of potential adverse effects listed above is not exhaustive. Refer to the tocilizumab product monograph under ***Additional Resources*** for more information.

Additional Resources

- Ontario Health COVID-19 treatment website:
  Clinical guidance information on drug therapies for the treatment of COVID-19 in adults
- Ministry of Health: COVID-19 information and resources
- US National Institute of Health COVID-19 treatment guidelines
- Public Health Ontario:
  - COVID-19 Data and surveillance
  - Outbreak preparedness, prevention and management in congregate living settings
- Resources for information on oxygen delivery systems
  (e.g., low-flow oxygen systems, high-flow oxygen systems):
  - BCcampus Open Publishing
  - Open Critical Care
- Public Health Agency of Canada:
  National Advisory Committee on Immunization COVID-19 immunization guidance
- US National Institute of Health COVID-19 treatment guidelines
- Dexamethasone product monographs
  - Dexamethasone tablets product monograph
  - Dexamethasone elixir product monograph
  - Dexamethasone sodium phosphate injection product monograph
- University of Liverpool COVID-19 drug interactions checker
- Baricitinib product monograph: The link to the US baricitinib product monograph is provided because it contains information about its use for COVID-19 treatment. The Canadian baricitinib product monograph does not include information about its use for COVID-19 treatment because the drug has not been approved by Health Canada for this indication.
- Remdesivir product monograph
- Tocilizumab product monograph

Questions

For any questions on the contents of this document, please contact the Provincial Drug Reimbursement Programs (PDRP) at OH-CCO_InfoPDRP@ontariohealth.ca.

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Infectious Diseases Advisory Committee (IDAC)

About IDAC

The Ontario Health Infectious Diseases Advisory Committee (IDAC) provides Ontario Health with timely evidence-based clinical and health system guidance on infectious diseases matters. It is a multidisciplinary committee comprised of health care professionals practising throughout Ontario who specialize or have a focus in treating infectious diseases in the hospital or community setting.

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