INESSS
LE SAVOIR PREND FORME

JANUARY 2022

COVID-19
USE OF BARICITINIB

This clinical tool is intended primarily for clinicians. It is provided for information purposes only and should not replace the judgment of the clinician who performs activities reserved under a statute or a regulation. The contents are based on a rapid ongoing review of the scientific literature available when it was being developed and it is supported by the knowledge and experience of Québec clinicians who contributed to its development. INESSS remains on the lookout for any new data that might warrant changes to this tool, which is intended to complement other INESSS publications. For further details, go to inesss.qc.ca/COVID-19.

CLINICAL PRESENTATION

- For a list of symptoms and signs of the 2019 coronavirus disease (COVID-19), see the table here.
- Severe forms of the disease include a viral pneumonia that can progress to an acute respiratory distress syndrome (ARDS) and then to complications associated with elevated levels of pro-inflammatory cytokines.

CLINICAL PROGRESSION SCALE

WHO ORDINAL SCALE[1]	Classification	
	Stage	Score
1. Ambulatory; asymptomatic, viral RNA detected 2. Ambulatory; symptomatic, independent 3. Ambulatory; symptomatic, assistance needed	**Mild**	**1, 2 or 3**
4. Hospitalized; no oxygen therapy[2] 5. Hospitalized; oxygen by mask or nasal prongs (O_2+) 6. Hospitalized; oxygen by noninvasive ventilation (NIV) **OR** high-flow oxygen (O_2++)	**Moderate**	**4 or 5**
7. Hospitalized; intubation **AND** invasive mechanical ventilation, $pO_2/FiO_2 \geq 150$ **OR** $SpO_2/FiO_2 \geq 200$ [O_2+++]) 8. Hospitalized; invasive mechanical ventilation, $pO_2/FIO_2 < 150$ ($SpO_2/FiO_2 < 200$) **OR** vasopressor 9. Hospitalized; invasive mechanical ventilation, $pO_2/FiO_2 < 150$ [O_2+++]) **AND** vasopressor **OR** dialysis **OR** ECMO 10. Deceased	**Severe to critical**	**6, 7, 8, or 9**

1. *WHO Working Group. A minimal common outcome measure set for COVID-19 clinical research. The Lancet Infectious Diseases 2020;20(8):e192-e7.*
2. If the person is hospitalized for isolation only (oxygen therapy or medical care not required), classify them as ambulatory.

Acronyms and symbols: pO_2: partial pressure of oxygen; FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation; ECMO: extracorporeal membrane

JAK INHIBITORS

- Janus kinase (JAK) inhibitors are molecules capable of inhibiting one or more JAK family enzymes, that is, JAK1, JAK2, JAK3 and TYK2.
- Because of their association with the receptors for several cytokines and their involvement in the phosphorylation of STAT (signal transducer and activator of transcription) proteins, JAKs play a key role in the JAK-STAT signaling pathway, whose activation notably leads to the gene expression of inflammatory markers.
- The results of several studies showed that the patients who developed a severe or critical form of COVID-19 had higher levels of several cytokines whose expression is regulated by JAKs (namely, IL-2, IL-4, IL-6, IL-7, IL-10, TNF-α, or IFN-γ) than the patients who had a moderate form. There is a significant association between high levels of these inflammatory cytokines and unfavourable clinical outcomes, such as ICU admission, ARDS and death.

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TREATMENT-RELATED LABORATORY TESTS

- For the relevant laboratory tests in the context of COVID-19 in adults, consult the table available here.

LABORATORY TESTS BEFORE AND AFTER INITIATING TREATMENT WITH BARICITINIB

Test	Before initiation	After initiation
C-reactive protein (CRP)	√	PRN[1]
Liver function tests	√	PRN[1]
Renal function	√	PRN[1]
Complete blood count (CBC)	√	PRN[1]

1. Unless required by the person's condition, it is preferable to limit the frequency of certain tests that are normally ordered and to combine blood draws to reduce the risk of exposure for the staff who collect the samples and to rationalize the use of personal protective equipment and medical supplies.

POSITIONS

- Based on the current state of knowledge (summary in Appendices I et II),
  - Baricitinib reduces mortality in hospitalized COVID-19 patients receiving noninvasive oxygen therapy[2] and with systemic inflammation characterized by an elevation above the local upper limit of normal of at least one of the following markers at the start of treatment: CRP, ferritin and D-dimers (COV-BARRIER study).
  - The impact of baricitinib on mortality is independent of systemic corticosteroids being part of the standard of care.
  - Although a class effect is likely, the data are much more robust for baricitinib than for the other JAK inhibitors.
- Treatment with a systemic corticosteroid should be initiated in persons with COVID-19 who require low-flow oxygen therapy, high-flow oxygen therapy, invasive or noninvasive mechanical ventilation, ECMO, or the use of a vasopressor or an ionotrope. For the recommendations regarding the use of systemic corticosteroids, consult the corresponding clinical tool.
- Treatment with tocilizumab or sarilumab should be initiated in persons with COVID-19 who require low-flow oxygen therapy, high-flow oxygen therapy, invasive or noninvasive mechanical ventilation, ECMO, or the use of a vasopressor or an ionotrope. For the recommendations regarding the use of tocilizumab or sarilumab, consult the corresponding clinical tool.

⚠ Given the risk of shortage, baricitinib is the preferred alternative when tocilizumab and sarilumab are not available.

- Other drugs with immunomodulatory properties (e.g., biotherapies against the IL-1 pathway or against granulocyte-macrophage colony-stimulating factor [GM-CSF]) are currently being investigated. For the current state of scientific knowledge regarding different therapeutic drugs, go to inesss.qc.ca/COVID-19.

IMPORTANT CONSIDERATIONS

Due to the lack of available clinical data, scientific uncertainty remains regarding:
- persons under 18 years of age and pregnant women
- the clinical benefits of the other JAK inhibitors (e.g., ruxolitinib, tofacitinib, nezulcitinib

The concomitant use of baricitinib with tocilizumab or with sarilumab is not recommended because of the increased risk of adverse effects, such as an opportunistic infection.

Regardless of the shortage risk, participation in research efforts remain important and should be encouraged if the context so permits, especially in academic settings. Acquiring and consolidating knowledge are key to identifying and positioning value-added therapies within the therapeutic arsenal against COVID-19.

2. Low-flow oxygen, high-flow oxygen or noninvasive ventilation.

STAGE	Mild	Moderate O_2 +	Severe to critical O_2 ++	Severe to critical O_2 +++
Score at initiation of treatment with baricitinib	1-2-3	4	5	6	7-8-9
Adults	✗	✗	To be preferred if access to tocilizumab or sarilumab is restricted ✓ In addition to dexaméthasone if systemic inflammation	To be preferred if access to tocilizumab or sarilumab is restricted ✓ In addition to dexaméthasone if systemic inflammation	✗
< 18 years	✗	✗	? Tocilizumab preferred	? Tocilizumab preferred	✗
Pregnancy	✗	✗	? Tocilizumab preferred	? Tocilizumab preferred	✗

✓ Should be initiated for this population **in combination with standards of care that include dexamethasone or an equivalent corticosteroid, in the presence of systemic inflammation (e.g. CRP ≥ 75 mg/L) AND if tocilizumab or sarilumab are not available**, unless there is a contraindication. Based on the current state knowledge: clinical benefit in terms of mortality; low risk of major adverse effects. Level of scientific evidence for the efficacy of baricitinib: moderate.

✗ Use is not recommended for this population because of lower biological plausibility, scientific uncertainty regarding the potential benefits according to the stage of the infection, risks that could outweigh the benefits, or because other treatment options could be more beneficial. Level of scientific evidence for the efficacy of baricitinib: insufficient.

? Populations mainly excluded from studies. Treatment could be considered on a case-by-case basis for these populations in exceptional situations if the benefits outweigh the risks. Enrollment in a research study remains, however, an option. Level of scientific evidence for the efficacy and safety of JAK. inhibitors in the context of COVID-19: insufficient.

Symbols and acronym: O_2+: oxygen therapy by mask or nasal prongs; O_2++: high-flow nasal oxygen therapy OR noninvasive mechanical ventilation; O_2+++: oxygen therapy with invasive mechanical ventilation or ECMO.

CONDITIONS OF USE

ADULT		
DRUG	**DOSAGE**	**DURATION OF TREATMENT**
Baricitinib[1]	4 mg QD PO (or crushed for nasogastric tube[2] administration)	14 days or until discharge from hospital
	For Patients with an estimated glomerular filtration rate (eGFR) ≥ 30 to < 60 m/min/1.73m² 2 mg QD PO (or crushed for nasogastric tube[2] administration)	
	eGFR ≥ 15 to < 30 m/min/1.73m² 1 mg QD PO (extemporaneous preparation[3])	

1. Off-label use.
2. The U.S. monograph states that the tablets can be placed in a container containing about 30 mL of room temperature water with gentle swirling to dissolve them. Once they have dissolved sufficiently to pass through the tip of a syringe, the contents can be collected in an appropriate syringe and administered immediately through the nasogastric tube. The initial container should then be rinsed with at least 15 ml of room temperature water, with the contents then drawn up into the syringe and administered immediately through the nasogastric tube.
3. The 1 mg format is not available in Canada. Extemporaneous preparation is required. Refer to the monograph for the manufacturer's recommendations regarding the preparation. Closer monitoring of renal function, liver function tests and CBC could be relevant in this context. Dose not studied in COV-BARRIER.

⚠ For exceptional use in a child, consult a pediatric specialist.

⚠ For exceptional use in a pregnant woman, consult a maternal fetal medicine specialist.

INFORMATION ON BARICITINIB

Contraindications	• History of allergy to any component of the formulation • Active infection • ALT or AST > five times the upper normal limit • Neutropenia < 1,000 cells /µL • Lymphopenia < 200 cells /µL • Estimated glomerular filtration rate (eGFR) < 15 ml/min/1.73m^2
Precautions	• Symptoms and signs or suspicion of thrombosis • Gastrointestinal perforations • Increased ALT or AST level with suspected treatment-related liver damage • Estimated glomerular filtration rate (eGFR) ≥ 15 to < 60 ml/min/1.73m^2 • Hemoglobin level < 80 g/L
Most common adverse effects	• Secondary infections • Thromboembolic complications • Elevated liver transaminases • Neutropenia • Thrombocytopenia
Drug interactions (list not exhaustive)	• Potent OAT3 inhibitors, potent immunosuppressants, other JAK inhibitors, and biologic DMARDs

DISCONTINUATION CRITERIA

- Treatment with baricitinib should be discontinued in the following situations:
  - The presence of a severe secondary infection or the occurrence of clinical manifestations suggestive of a thromboembolic complication.
  - If CBC, eGFR, ALT or ALT reach thresholds where baricitinib is contraindicated.

MAIN REFERENCES

Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. The Lancet Respiratory medicine 2021;

Ely EW, Ramanan AV, Kartman CE, de Bono S, Liao R, Piruzeli MLB, et al. Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomized, Placebo-Controlled Trial. medRxiv 2021:2021.10.11.21263897.

Guimarães PO, Quirk D, Furtado RH, Maia LN, Saraiva JF, Antunes MO, et al. Tofacitinib in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021;

FACT SHEET FOR HEALTHCARE PROVIDERS EMERGENCY USE AUTHORIZATION (EUA) OF BARICITINIB [site Web]. 2021. Available at: https://www.fda.gov/media/143823/download#:~:text=The%20U.S.%20Food%20and%20Drug%20Administration%20(FDA)%20has%20issued%20an,oxygen%2C%20non%2Dinvasive%20or%20invasive (consulted January 31, 2022).

NIH. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines [website]. 2021. Available at: https://www.covid19treatmentguidelines.nih.gov/ (consulted January 31, 2022).

National COVID-19 Clinical evidence taskforce. Australian guidelines for the clinical care of people with COVID-19 [site Web]. National Health and Medical Research Council (NHMRC); 2021. Available at: https://app.magicapp.org/#/guideline/L4Q5An/section/L0OPkj (consulted January 31, 2022).

IDSA. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 Infection [website]. 2021. Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ (consulted January 31, 2022).

BCCDC. Clinical Reference Group Recommendations: Therapies for COVID-19 [website]. 2021. Available at: http://www.bccdc.ca/health-professionals/clinical-resources/covid-19-care/clinical-care/treatments (consulted January 31, 2022).

Van Ierssel S, Dauby N, Bottieau E, Huits R. Interim Clinical Guidance For Adults With Suspected Or Confirmed Covid-19 In Belgium [website]. Belgium: 2021. Available at: https://epidemio.wiv-isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf (consulted January 31, 2022).

Therapeutics and COVID-19: living guideline [site Web]. 2022. Available at: https://app.magicapp.org/#/guideline/nBkO1E/section/nByvRL (consulted January 31, 2022).

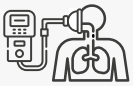
Clinical practice guideline summary: recommended drugs and biologics in adult patients with COVID-19 [site Web]. 2022. Available at: https://covid19-sciencetable.ca/sciencebrief/clinical-practice-guideline-summary-recommended-drugs-and-biologics-in-adult-patients-with-covid-19-version-9-0/ (consulted January 31).

APPENDIX I

WHAT DO THE SCIENTIFIC DATA SAY AT THIS TIME ABOUT SCORE 4 TO 6 HOSPITALIZED COVID-19 PATIENTS (JANUARY 31, 2022)

CHARACTERISTICS OF THE POPULATION INCLUDED IN THE RANDOMIZED CONTROLLED TRIAL

- Infected with the original SARS-CoV-2 virus (or the alpha variant circulating at the time of recruitment in this clinical trial) - confirmed by RT-PCR
- Not vaccinated
- Hospitalized without oxygen therapy, with low-flow oxygen or with high-flow oxygen (scores 4-5-6)
- At least one inflammatory marker above the local upper limit of normal (C-reactive protein, ferritin, D-dimers, lactate dehydrogenase)
- Intervention:
  - Baricitinib 4 mg QD PO (or crushed for nasogastric tube administration) for 14 days vs. placebo (or until discharge from hospital)
- Characteristics of the participants:
  - Mean age 57.8 years (± 14.3 years); score 4 = 12.3%; score 5 = 63.4%; score 6 = 24.4%; corticosteroids in the standard of care = 79%.

PARAMETERS EXAMINED	COV-BARRIER N = 1,525
PRIMARY ENDPOINT	
 **or** 	The proportion who **progressed to high-flow oxygen, invasive or noninvasive mechanical ventilation, or all-cause mortality (by day 28)** comparable between the baricitinib and placebo groups (27.8% vs. 30.5%).
SECONDARY ENDPOINT	
	43% reduction in the adjusted hazard ratio for **all-cause mortality (by day 28)**, with a reduction that could be in the range of 22% to 59%, based on the 95% confidence interval (CI), p=0.0018. Absolute risk reduction: 5% Number needed to treat to prevent one death (by day 28) more than in the placebo group: 20 (95% CI: 15-46) (baseline risk = 13%).

SAFETY IN THE STUDY POPULATION

Safety profile: possible secondary infections

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APPENDIX II

WHAT DO THE SCIENTIFIC DATA SAY AT THIS TIME ABOUT SCORE 7 AND ABOVE HOSPITALIZED COVID-19 PATIENTS (JANUARY 31, 2022)

CARACTÉRISTIQUES DE LA POPULATION INCLUSE DANS L'ESSAI COMPARATIF À RÉPARTITION ALÉATOIRE

- Infected with the original SARS-CoV-2 virus (or the alpha variant circulating at the time of recruitment in this clinical trial) - confirmed by RT-PCR
- Not vaccinated
- Hospitalized with invasive mechanical ventilation or ECMO at the start of treatment (scores 7 and above)
- At least one inflammatory marker above the local upper limit of normal (C-reactive protein, ferritin, D-dimers, lactate dehydrogenase)
- Interventions
  - Baricitinib 4 mg QD crushed for nasogastric tube administration for 14 days vs. placebo (or until discharge from hospital)
- Characteristics of the participants:
  - Mean age 58.6 years (± 13.8 yeas); invasive mechanical ventilation = 96%; ECMO = 4%; corticosteroids in the standards of care = 86.1%.

PARAMETERS EXAMINED	ADDENDUM TO COV-BARRIER N = 101
EXPLORATORY ENDPOINT	
	46% reduction in the adjusted hazard ratio for **mortality (by day 28)**, with a reduction that could be in the range of 4% to 69%, based on the 95% confidence interval (CI), p=0.03. Absolute risk reduction: 19% 44% reduction in the adjusted hazard ratio for **mortality (by day 60)**, with a reduction that could be in the range of 3% to 67%, based on the 95% confidence interval (CI), p=0.0027. Absolute risk reduction: 17%

SAFETY IN THE STUDY POPULATION

Safety profile: possible secondary infections

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