INESSS
LE SAVOIR PREND FORME

APRIL, 2021

COVID-19
USE OF REMDESIVIR

This clinical tool is intended mainly for clinicians. It is provided for information purposes only and should not replace the judgment of the clinician who performs the activities reserved under an act or a regulation. Its contents are based on a rapid and ongoing systematic review of the scientific literature available at the time of its creation and are supported by the knowledge and experience of Québec experts. Under the circumstances of such a public health emergency, INESSS continues to look for any new data that could cause it to revise 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 the symptoms and signs of coronavirus 2019 disease (COVID-19), see the table available here.

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 non-invasive ventilation (NIV) **OR** high-flow (O_2++)	Moderate	4 or 5
7. Hospitalized; Intubation **AND** mechanical ventilation, $pO_2/FiO_2 \geq 150$ or $SpO_2/FiO_2 \geq 200$ 8. Hospitalized; mechanical ventilation, pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) **OR** vasopressors 9. Hospitalized; mechanical ventilation, pO_2/FiO_2 <150 **AND** vasopressors **OR** dialysis OR ECMO 10. Dead	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 patient is hospitalized for isolation only (oxygen therapy or medical care not required), classify him or her as ambulatory patient.

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

REMDESIVIR

- Santé Canada is authorizing, with certain conditions, the use of remdesivir for the treatment of COVID-19 in adults and adolescents 12 years of age and older weighing at least 40 kg who have pneumonia requiring oxygen therapy.
- Remdesivir (or GS-5734) is an adenosine analogue. It generates a nucleoside metabolite that can be incorporated into viral RNA and inhibit the replication of susceptible RNA viruses.
- It was originally developed to inhibit Ebola virus replication. It possesses antiviral activity against SARS-CoV, MERS-CoV and the respiratory syncytial virus (RSV), among others.
- *In vitro* studies show that remdesivir exerts strong inhibitory activity on SARS-CoV-2 replication.
- This antiviral has no immunomodulating effect.

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 THE INITIATION OF REMDESIVIR THERAPY

Test	Before initiation	After initiation
Alanine aminotransferase (ALT)	✓	Daily
Other liver function tests (e.g., alkaline phosphatase [AP] and conjugated bilirubin)	–	PRN[1]
Creatinine clearance *(calculation of the estimated glomerular filtration rate [eGFR])*	✓	Daily
International normalized ratio (INR)	–	PRN[1]

1. Unless required by the patient's condition, it is preferable to limit the frequency of certain tests that are normally ordered, to reduce the exposure risk for the health professionals who draw the blood and to rationalize the use of personal protective equipment and medical equipment.

Québec

TREATMENT PRINCIPLES

- Based on the current state of knowledge, the use of remdesivir may lead to clinical improvement and promote a speedier recovery in certain patients, depending on their score on the clinical progression scale at the time of treatment initiation. However, the extent of the benefits is relatively modest with no clearly demonstrated effect on mortality or progression to mechanical ventilation.

A graphic representation of the current scientific data is available here.

- It is important to accurately determine the score, the stage of the disease, and the time since symptom onset before administering the treatment, in order to optimize the therapeutic window.
- Initiation of treatment with a systemic corticosteroid is strongly suggested in people with COVID-19 who require low-flow oxygen therapy, highflow oxygen therapy, invasive or non-invasive mechanical ventilation, ECMO, or the use of a vasopressor or ionotrope. For positions on the use of systemic corticosteroids, see the corresponding clinical tool.
- A treatment with tocilizumab, in combination with standard of care including dexamethasone or equivalent corticosteroid, could be initiated in people with COVID-19 who require low-flow oxygen therapy in the presence of systemic inflammation, and strongly suggested in people with COVID-19 who require highflow oxygen therapy, invasive or non-invasive mechanical ventilation, ECMO, or the use of a vasopressor or ionotrope. For positions on the use of tocilizumab, see the corresponding clinical tool.
- 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/en/covid-19.

CLINICAL POSITIONS

IMPORTANT CONSIDERATIONS

Given the many uncertainties associated with the current state of knowledge on COVID-19 and therapeutics, participation in research efforts is important to document the effects of different drugs. Thus, when the context allows it, registration for a clinical trial should be considered.

STAGE	Mild	Moderate O_2 +		Severe to critical O_2 ++	O_2 +++
Score at initiation of remdesivir[1]	1-2-3	4	5	6	7-8-9
≥ 12 years **AND** ≥ 40 kg		Consider enrolment in a clinical trial	Consider dexamethasone and tocilizumab in presence of systemic inflammation OR enrolment in a clinical trial	Consider dexamethasone and tocilizumab OR enrolment in a clinical trial	Consider dexamethasone and tocilizumab
< 12 years **OR** ≥ 12 years **AND** < 40 kg					
Pregnancy / breastfeeding					

1. Not registered as exceptional medication on the « Liste – Établissements »

Could be considered on a case-by-case basis for this population in addition to standard of care, especially if 10 days or less separate initiation and treatment and when other therapeutic options potentially more efficiency cannot be administrated. There is uncertainty over the clinical benefits relative to the stage of infection and the inflammatory status. Clinical trial enrolment should be considered. Level of scientific evidence regarding efficacy: insufficient to low

Use is not recommended for this population, given the scientific uncertainty over the potential benefits relative to the stage of infection or because other therapeutic options could be more beneficial. Clinical trial enrolment could be considered. Level of scientific evidence regarding efficacy: insufficient

Populations excluded from studies. Could be considered on a case-by-case basis for this population if the benefits outweigh the risks. Clinical trial enrolment could be considered. Level of scientific evidence regarding efficacy and safety: insufficient

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

CONDITIONS OF USE

REMDESIVIR			
Population	**Dosage**	**Duration of treatment**	**Infusion**
12 years or older **AND** 40 kg or more as per the recommendations above ! *The optimal time for initiating remdesivir is not known.*	200 mg IV once daily on Day 1, then 100 mg IV once daily starting on Day 2 ! *Do not administer intramuscularly (IM).* ! *No dose adjustment is proposed for geriatric patients.*	5 days[1]	Maximum volume: 250 ml Solution: 0.9% NaCl Infusion time[2]: 30-120 min ! *During infusion, do not administer remdesivir simultaneously with other drugs.* ! *Administer remdesivir the same day it is prepared.*

1. If there is no improvement after 5 days, the treatment may be continued up to a maximum of 10 days, according to clinical judgment and considering the issues with the drug's availability.
2. Opt for a slow infusion to reduce the risk of adverse effects or extravasation of the drug.

INFORMATION ABOUT THE DRUG

Contraindications	• A history of allergy to remdesivir or any of the ingredients of the formulation (including the nonmedicinal ingredients) or to a component of the container. • ALT ≥ 5 times the upper limit of normal (ULN) • eGFR < 30 ml/min
Precautions	• eGFR < 50 ml/min (the preparation contains sulfobutyl ether-ß-cyclodextrin sodium, which can accumulate in the kidneys of patients with reduced renal function.) • Exercise vigilance if the patient is taking drugs that reduce renal function
Most common adverse effects	• Adverse effects associated with the infusion (e.g., nausea, vomiting, hypotension, tachycardia) • Elevated ALT • Acute kidney damage
Drug interactions	• Remdesivir is mainly and rapidly excreted in the urine (74%) and feces (18%), which limits its interaction with P450 cytochromes (CYP). • Remdesivir is a substrate for CYP 2C8, 2D6 and 3A4 *in vitro*, but it appears that it is mostly metabolized by hydrolases. • No human studies have examined interactions between remdesivir and other drugs. • The concomitant administration of remdesivir and chloroquine or hydroxychloroquine is not recommended.

DISCONTINUATION CRITERIA

➔ Remdesivir therapy should be stopped in the following situations:

- ALT at 5 times the ULN or more.
  ! *The treatment may be restarted when the ALT falls below 5 times the ULN (taken from product monograph).*
- An increase in the ALT accompanied by an increase in the conjugated bilirubin, AP or INR or the occurrence of symptoms of hepatic inflammation.
- Signs of kidney damage with an eGFR of less than 30 ml/min.
- The occurrence of another major adverse effect (e.g., signs and symptoms of a drug allergy).
- At discharge from hospital.

MAIN REFERENCES

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