INESSS
LE SAVOIR PREND FORME

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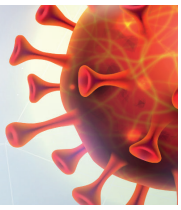
NIRMATRELVIR / RITONAVIR (PAXLOVID™)

Analysis of the EPIC-HR study and preliminary clinical position



This dissemination tool is intended primarily for clinicians for use outside hospitals. It is provided for information purposes only and should not replace the judgment of the clinician who performs activities reserved under an act or a regulation. Its contents are based on a rapid, ongoing review of the scientific literature available when it was being developed and unpublished confidential data provided by the manufacturer, and it is supported by the knowledge and experience of Québec clinicians and experts who contributed to the discussion. In the circumstances of such a public health emergency, INESSS continues to look 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.

IMPORTANT CONSIDERATIONS

- INESSS bases its preliminary clinical position mainly on information provided by the manufacturer as part of the approval process. To date, no article has been published in a peer-reviewed journal.
- The EPIC-HR clinical trial was conducted in an unvaccinated adult population with no history of SARS-CoV-2 infection and infected with the Delta variant.
- The current situation in Québec is different. The population is strongly vaccinated and therefore generally well protected against hospitalizations, and the Omicron variant, which is more contagious but less virulent than the Delta variant, is widely dominant. Thus, the magnitude of the expected benefits in the current context is necessarily smaller than that reported in the EPIC-HR study.
- In response to a request from the Ministère de la Santé et des Services sociaux regarding the marketing of this novel antiviral in the therapeutic arsenal against COVID-19, and in the context of anticipated supply issues, INESSS conducted a prioritization exercise aimed at identifying the populations most at risk for an unfavourable course who might receive it.
- The preliminary position developed takes into account the analysis of the available non-public data, the current epidemiological context, recommendations from other organizations, Health Canada's assessment, and consultations with clinicians, experts, ethicists and members of the general public. For further details, see highlights.
- This preliminary position does not necessarily reflect the views of all those consulted. INESSS assumes sole responsibility for the form and final contents of this tool at the time of its publication. INESSS will update this position as new evidence becomes available.
- INESSS wishes to point out that, regardless of the risk of shortages and possible temporary supply issues, every effort should be made to have patients participate in research projects if the context so permits, particularly in academic settings.

NIRMATRELVIR / RITONAVIR (PAXLOVID™)

- PAXLOVID™ is an antiviral consisting of nirmatrelvir and ritonavir.
- Nirmatrelvir, a novel antiviral, is a specific SARS-CoV-2 3CL protease inhibitor with antiviral activity that inhibits the virus's replication.
- Ritonavir, a human immunodeficiency virus (HIV) protease inhibitor, is used in Paxlovid™ as a pharmacological enhancer, exploiting its potent inhibitory activity against CYP3A4. Ritonavir therefore slows the metabolism and elimination of nirmatrelvir, thereby optimizing its plasma concentrations and duration of action.
- The results of a Phase I study did not raise any safety or tolerability concerns and confirmed that the co-administration of ritonavir significantly increases nirmatrelvir plasma concentrations. The IC_{90} for neutralizing SARS-CoV-2 *in vitro* is much lower than for other coronaviruses, which increases confidence in the plausibility of significant antiviral activity against SARS-CoV-2.
- The preliminary data suggest that nirmatrelvir retains its *in vitro* antiviral activity against variants of concern, including Omicron

Québec

WHAT DO THE SCIENTIFIC DATA SAY AT THIS TIME?

- The EPIC-HR clinical trial, a randomized, double-blind, multicentre, controlled Phase II/III trial conducted primarily in the United States. It was conducted in individuals:
  - Who were unvaccinated and who did not have a history of documented SARS-CoV-2 infection
  - 98% of whom were infected with the Delta variant, with nucleic acid amplification test (NAAT) or antigen test confirmation
  - Who had been symptomatic for 5 days or less with mild to moderate symptoms (not requiring oxygen)
  - Who were not hospitalized at the time of recruitment
  - Who were at high risk for developing life-threatening of COVID-19 complications (hospitalization or death)
  - Whose main characteristics were as follows:

Median age 46 years (18-88); age 60 years and older (21.6%); obesity with body mass index (BMI) > 30: 36.8%; obesity ≥ 35: 12.6%, BMI > 40 (5.2%); smokers (39.0%); hypertension (32.9%); diabetes (12.2%); chronic lung disease (4.6%); cardiovascular disorder (4.1%). Chronic renal impairment, cancer and immunosuppression were conditions very poorly represented in the trial, with less than 1% each.

Parameters	EPIC-HR (N = 2 246)
PRIMARY OUTCOME	
 or 	**Symptoms ≤ 3 days** 89% relative risk reduction in hospitalizations (≥ 24 hrs) or deaths (through Day 28), with a possible reduction of between 72% and 96%, based on the 95% confidence interval (CI). Absolute risk reduction: 5.8% (**0.7%** in the treatment group vs. **6.5%** in the placebo group). Number needed to treat[1] to prevent one hospitalization (≥ 24 hrs) or death (through Day 28) more than the placebo group: 18 (baseline risk of hospitalization or death in the placebo group = 6.5%)
SECONDARY OUTCOME	
 or 	**Symptoms ≤ 5 days** 88% relative risk reduction in hospitalizations (≥ 24 hrs) or deaths (through Day 28), with a possible reduction of between 75% and 94%, based on the 95% confidence interval (CI). Absolute risk reduction: 5.5% (**0.8%** in the treatment group vs. **6.3%** in the placebo group). Number needed to treat[1] to prevent one hospitalization (≥ 24 hrs) or death (through Day 28) more than the placebo group: 19 (baseline risk of hospitalization or death in the placebo group = 6.3%)
	**Symptoms ≤ 3 days** Risk reduction (absolute) in deaths through Day 28 (**0 deaths vs. 9 deaths, or 0 % vs. 1.3 %**) **Symptoms ≤ 5 days** Risk reduction (absolute) in deaths through Day 28 (**0 deaths vs. 12 deaths, or 0 % vs. 1.1 %**)

1. The number needed to treat (NNT) to prevent one event was calculated by INESSS using the following formula from Furukawa et al., 2002: NNT = 1/(PEER x (1-RR)), where PEER = patient expected event rate.

SAFETY IN STUDY POPULATION

Most frequent adverse effects:

- Dysgeusia (**6% vs. < 1%** in the placebo group)
- Diarrhea (**3% vs. 2%** in the placebo group)
- Hypertension (**1% vs. < 1%** in the placebo group)
- Myalgia (**1% vs. < 1%** in the placebo group)

Frequency of occurrence of serious adverse events: **1.6 % vs. 6.6 %** in the treatment group and placebo group, respectively,

Favorable profile in the absence of absolute contraindications or significant drug interactions

EPIC-SR

The final results of the subgroup analyses of the EPIC-SR study, which concern vaccinated participants at high risk for developing COVID-19 complications and which are currently in progress, should indicate whether or not vaccinated individuals are likely to benefit from this antiviral treatment.

PRELIMINARY CLINICAL POSITION

INESSS considers that in the current context involving supply issues, this treatment should be offered on a priority basis to individuals at very high risk for an unfavourable course, regardless of their vaccination status, namely:

- Immunocompromised, non-hospitalized adults who have been symptomatic for 5 days or less with a SARS-CoV-2 infection confirmed by NAAT or a rapid antigen test;
- Who have no contraindications due to their health or concomitant medication;
- And who do not have access to sotrovimab, which remains the treatment of choice, supplies and access permitting.

Depending on residual availability and the anticipated increase in supplies, access to the nirmatrelvir/ritonavir combination may eventually be extended to other inadequately vaccinated or protected populations at high risk for COVID-19 complications. This decision will have to be based on the clinician's judgment, in consultation with the parties in the health and social services facilities who are responsible for identifying individuals to be treated on a priority basis.

Individuals are considered immunocompromised if they have a condition (e.g., uncontrolled HIV or AIDS, transplant, certain active cancers [e.g., hematologic], an autoimmune disease, hypogammaglobulinemia) OR are receiving a treatment that is compromising their cellular or humoral immunity, regardless of their vaccination status.

The following is a non-exhaustive and evolving list of such immunosuppressive treatments:

- Antirejection therapies in transplant recipients (e.g., tacrolimus, cyclosporin, sirolimus and everolimus)
- Antimetabolites (e.g., methotrexate, mycophenolate mofetil and azathioprine)
- Proteosome inhibitors
- Bruton tyrosine kinase inhibitors and certain other antineoplastics (e.g., cladribine and 5-FU)
- Immunotherapy targeting B or T cell activation or differentiation (e.g., ocrelizumab, rituximab, ofatumumab, alemtuzumab, obinutuzumab, blinatumomab, daratumumab, basiliximab, and antithymocyte globulin)
- Janus kinase inhibitors (e.g., baricitinib, tofacitinib, upadacitinib and ruxolitinib)
- Immunosuppressants (e.g., high-dose corticosteroids [e.g., prednisone, more than 20 mg daily, or its equivalent])

The following individuals are not considered immunocompromised and at very high risk for an unfavourable course: those taking an immunomodulator (e.g., hydroxychloroquine) OR a biotherapy directed against a specific inflammatory mediator or its receptor (such as TNFα, IL-1, IL-6, IL-17/23 or integrins) used as monotherapy OR a corticosteroid therapy considered nonimmunosuppressive.

⚠ WARNING

The risk of developing COVID complications is greater in individuals with:

- Advanced age
- Multiple comorbidities
- One or more of the health conditions associated with a high risk of uncontrolled complications

The decision to initiate treatment with the nirmatrelvir/ritonavir combination should be based on a risk-benefit-assessment and the feasibility of monitoring and managing drug interactions (skills, available resources).

A clinician who is considering prescribing the nirmatrelvir/ritonavir combination should be aware of the limitations of the currently available scientific data. Indeed, the external validity of the EPIC-HR study is compromised by a certain number of elements. The study was conducted in unvaccinated individuals infected primarily with the Delta variant (98% Delta, no Omicron). In addition, 21.6% of the EPIC-HR study participants were over the age of 60 years, and the most represented risk factors were high blood pressure, obesity and active smoking. Immunocompromised patients accounted for less than 1% of the participants. Together, these factors limit the generalizability of the results to inadequately vaccinated or protected individuals who are older or who have a higher comorbidity burden. Therefore, the clinician will need to stay abreast of advances in scientific knowledge and exercise caution regarding drug interactions by working with a pharmacist as needed.

To make an informed decision, it will be important to explain the advantages and drawbacks (e.g., adverse effects and possible drug interactions) of this novel antiviral to the patient or their caregiver.

WHO SHOULD NOT RECEIVE NIRMATRELVIR/RITONAVIR

Individuals with a history of serious hypersensitivity reactions (toxic epidermal necrolysis or Stevens-Johnson syndrome) to any of the formulation's ingredients.

Individuals receiving drugs whose concomitant use with a potent CYP3A4 inhibitor is absolutely contraindicated (unless the drug can be temporarily discontinued without harm to the patient) OR receiving a potent CYP3A4 inducer (list not exhaustive)

- Alpha-1 adrenergic antagonists: *alfuzosin*
- Aldosterone antagonists: *eplerenone*
- Endothelin receptor antagonists: *bosentan*
- Antiplatelet agents: *ticagrelor*
- Antianginals: *ranolazine*
- Antiarrhythmics: *amiodarone, dronedarone, flecainide, ivabradine, propafenone, quinidine*
- Antibiotics: *fusidic acid*
- Anticancer drugs: *apalutamide, neratnib, venetoclax*
- Anticoagulants: *rivaroxaban*
- Anticonvulsants: *carbamazepine, phenytoin, phenobarbital*
- Azole antifungals: *voriconazole*
- Anti-gout medications: *colchicine*
- Antimycobacterials: *rifampin*
- Antipsychotics: *lurasidone, pimozide, clozapine*
- Antivirals: *glecaprevir/pibrentasvir*
- Others: *flibanserin, St. John's wort*
- Long-acting beta-2 agonists: *salmeterol*
- Rye ergot derivatives: *dihydroergotamine, ergonovine*
- HMG-CoA reductase inhibitors: *lovastatin, simvastatin*
- PDE5 inhibitors: *sildenafil (pulmonary hypertension), vardenafil (erectile dysfunction)*
- Triglyceride transfer protein inhibitor: *lomitapide*
- Sedatives/hypnotics: *triazolam, midazolam*

Individuals receiving drugs whose elimination is highly CYP3A4-dependent and elevated levels of which may be associated with serious consequences

Treatment with Paxlovid™ should not be initiated in Individuals receiving drugs whose elimination is highly CYP3A4-dependent and elevated levels of which may be associated with serious consequences if close monitoring of the plasma levels or adverse effects (even if a dose adjustment has been made) is not feasible during treatment. The assessment may involve the use of usual pharmaceutical information sources, such as Micromedex, Lexicomp, the HIV/HCV treatment guide (**https://www.guidetherapeutiquevih.com/**) or the University of Liverpool's "COVID-19 Drug Interactions" (**https://www.covid19-druginteractions.org/**)

Severe chronic (Cl_{cr} < 30 ml/min) or end-stage (hemodialysis) renal impairment

Severe liver failure (Child-Pugh Class C and cirrhosis)

Pregnant women

Individuals under 18 years of age

TREATMENT ALTERNATIVE

For these conditions, availability permitting, other treatments should be considered, such as sotrovimab.

TREATMENT PRINCIPLES

CONDITIONS OF USE

ADULTS		
Drug[1]	**Dosage[2]**	**Duration of treatment**
Nirmatrelvir	300 mg BID PO For patients with moderate renal impairment ($30 \text{ ml/min} \leq Cl_{Cr} < 60 \text{ ml/min}$) 150 mg BID PO	5 days
Ritonavir	100 mg BID PO	

1. Consult the product monograph and the usual or more specific drug interaction analysis tools (e.g., Liverpool COVID-19 Interactions [https://www.covid19-druginteractions.org/] or https://www.guidetherapeutiquevih.com).

2. No adjustment required in patients with mild to moderate hepatic failure or in patients receiving ritonavir or cobistat for the treatment of HIV or HCV treatment.

DISCONTINUATION CRITERIA

- Treatment with the antiviral combination nirmatrelvir/ritonavir should be discontinued in the following situation:
  - If the patient experiences an allergic reaction or a serious adverse effect.

MAIN REFERENCES

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