Nirmatrelvir/Ritonavir (Paxlovid®)

What is it?

- **The combination of two medications, nirmatrelvir and ritonavir, taken together to treat individuals with non-severe COVID-19.**
- **Nirmatrelvir is a SARS-CoV-2 protease inhibitor that works to disrupt viral replication. Ritonavir acts as a "pharmacokinetic booster" to inhibit nirmatrelvir hepatic metabolism and optimize nirmatrelvir plasma concentrations and dosing profile.**

On January 17, 2022 nirmatrelvir/ritonavir was **authorized for use by Health Canada via a Notice of Compliance with Terms and Conditions**. The recommended treatment course of nirmatrelvir/ritonavir is 300 mg/100 mg po BID x 5 days.

Health Canada Indication:	**Treatment of mild-to-moderate COVID-19 in adults with a positive COVID-19 test result, and who are at high risk* for progression to severe COVID-19, including hospitalization or death.**

***High risk criteria** may include:

- Older age (i.e., 60 years of age and older)
- Obesity or being overweight (i.e., BMI >25 kg/m^2)
- Current cigarette smoking
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- Active cancer
- Chronic lung disease (i.e., chronic obstructive pulmonary disease, asthma [moderate-to-severe], interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (i.e., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (i.e., genetic or metabolic syndromes and severe congenital anomalies)
- Medical-related technological dependence not related to COVID-19 (i.e., tracheostomy, gastrostomy, or positive pressure ventilation)

Note: Other medical conditions or factors (e.g., race or ethnicity) may also place individual patients at high risk for progression to severe COVID-19 and may be considered on a case-by-case basis.

Evidence:

- Support comes from EPIC-HR, a Phase 2/3 RCT that enrolled 2246, unvaccinated, non-hospitalized adults ≥ 18 years of age with COVID-19 who were at high-risk* for disease progression, between July 16 and December 9, 2021. Those eligable had no prior history of COVID-19 infection and an oxygen saturation of >92% on room air. Patients were randomized **within 5 days of symptom onset and positive SARS-CoV-2 test** to receive either 1) nirmatrelvir/ritonavir 300 mg/100mg po BID x 5 days or 2) placebo po BID x 5 days.[1-2] Key results are below.
- Data released from the manufacturer for EPIC-SR, a Phase 2/3 RCT including those at standard risk for developing severe COVID-19, suggests no difference in time to symptom alleviation, hospitalization, or death.[3]
- Several observational retrospective cohort studies demonstrate benefit of nirmatrelvir/ritonavir during circulation of the Omicron variant in mainly vaccinated, non-hospitalized adults with COVID-19 at high risk* for progression.[4-5] In one study, those ≥ 65 years of age had lower rates of hospitalization (HR 0.27, 95% CI 0.05-0.82) and death (HR 0.21, 95% CI 0.05-0.82), and no evidence of benefit was found in those 40-64 years old.[6]
- A retrospective analysis in Hong Kong demonstrated lower all-cause mortality in 40776 adults (mainly >65 years old) hospitalized with mild-moderate COVID-19 (HR 0.32, 95% CI 0.23-0.45), between February and April, 2022.[7]
- There is a lack of evidence to suggest COVID-19 rebound between days 2 to 8 after initial recovery warrants additional treatment with nirmatrelvir/ritonavir[8-9], or that susceptibilities of Omicron to nirmatrelvir/ritonavir are reduced.[10]

EPIC-HR: double-blind, multicenter RCT, intention to treat analysis[2]

- **Fewer COVID-19-related hospitalizations and deaths by day 28:** 0.77% (8/1039) in nirmatrelvir/ritonavir group vs 6.31% (66/1046) in placebo; Absolute risk reduction (ARR) -5.62% (95% CI -7.21 to –4.03), p<0.001
  - 0 deaths in nirmatrlvir/ritonavir group vs 12 deaths in placebo
  - In those treated ≤ 3 days after symptom onset: 0.72% (5/697) vs 6.45% (44/682), ARR 5.81% (95% CI -7.78 to -3.84), p<0.001
- **Adverse events:** 22.6% in nirmatrelvir/ritonavir group vs 23.9% in placebo. Mainly dysgeusia (5.6% vs 0.3%) and diarrhea (3.1% vs 1.6%)

Number needed to treat (NNT): For every 17 COVID-19 outpatients who receive a 5-day course of nirmatrelvir/ritonavir, one fewer COVID-19-related hospitalization or death will occur by day 28 days versus placebo.

The Infectious Diseases Society of America (IDSA): suggests using nirmatrelvir/ritonavir within 5 days of symptom onset in ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease.[11]

Practical Considerations

- **Many clinically significant drug-drug interactions exist through the impact of ritonavir on hepatic cytochrome P450 enzymes. Pharmacist assessment and management is crucial.**
- **Requires dose adjustment for impaired renal function (eGFR ≥ 30 to < 60 mL/min). Currently not recommended if eGFR < 30 mL/min.**
- **Supplied pre-packaged as a box containing 5 daily blister cards (reflecting standard dosing with a morning and an evening dose of 2x nirmatrelvir 150 mg tablets and 1x ritonavir 100 mg tablet).**

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