Early Outpatient COVID-19 Treatment

January 27, 2022

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Presenter Disclosure: LB

- Industry:
  - AbbVie
  - Gilead
  - Merck
  - BMS
  - ViiV
  - Eli Lilly

- Academic:
  - Affiliation with Dalhousie University and Nova Scotia Health Authority

- Therapeutics:
  - Canadian Therapeutics Taskforce
  - AMMI Canada COVID Therapeutic Practice Point Writing Group
  - Contributor, PHAC Considerations for nirmatrelvir/ritonavir use in the context of limited supply

- Advocacy:
  - HCV and HIV advocacy groups
  - COVID related science communications
  - COVID testing

Presenter Disclosure: TR

- Presenter's Name: Tasha Ramsey
- I have relationships with commercial interests:
  - Advisory Board/Speakers Bureau: Not applicable
  - Funding (Grants/Honoraria): Pharmacy Examining Board of Canada
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  - Speaker/Consulting Fees: Canadian Society of Hospital Pharmacists, Pharmacy Examining Board of Canada, Pharmacy Association of Nova Scotia, Pharmacists' Association of Newfoundland and Labrador
  - Other:
    - Nova Scotia Health and Dalhousie University employee
    - Immunize Canada National Coalition member
    - Nova Scotia COVID Network member
    - Nova Scotia COVID-19 Vaccine Expert Panel member
    - Nova Scotia COVID-19 Therapeutics and Prophylactics Advisory Group co-chair
- Speaking Fees for current program:
  - I have received no speaker's fee for this learning activity

Disclaimer

- COVID-19 medication evidence is rapidly evolving
- Information is based on federal and provincial recommendations and the best available **evidence as of January 27, 2022**
- Will refer to **manufacturers/brand names** of medications
- **Some COVID-19 therapy discussed is off-label**

  (e.g.: budesonide)

COVID-19
Game Changers?

CBC | MENU | Beijing 2022

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Health Canada approves Pfizer's COVID-19 antiviral treatment

Paxlovid reduces rate of hospitalization and death among high-risk COVID-19 patients, Pfizer says

John Paul Tasker · CBC News · Posted: Jan 17, 2022 9:20 AM ET | Last Updated: January 18

The product has been hailed as a pandemic "game changer" by some doctors because it could reduce hospitalizations and deaths among COVID-19 patients.

Experts say an effective pill that's easy to self-administer at home could relieve some of the pressure on the health care system and change the trajectory of the pandemic. Existing therapeutics approved for use in Canada — such as monoclonal antibodies and remdesivir — must be administered intravenously in a hospital setting.

Paxlovid is meant to be taken as 30 pills over five days. Patients take three pills at a time: two of nirmatrelvir and one of ritonavir.

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HEALTH

Sotrovimab COVID-19 drug: A look at how it's being used to combat Omicron in Canada

By Saba Aziz · Global News

Posted January 2, 2022 5:09 pm · Updated January 2, 2022 5:45 pm

Objectives

By the end of this presentation, participants should be able to:

1. Describe the stages of COVID-19 infection and the role of therapeutics for outpatients
2. List therapeutic options recommended for the treatment of outpatients with COVID-19
3. Discuss early outpatient COVID-19 case management in a time of limited drug supply

Outline

1. Inhaled budesonide
2. Sotrovimab
3. Nirmatrelvir/ritonavir
4. Eligibility/prioritization considerations
5. Cases

Role in therapy
Mechanism of action
Individual medication overview
Process

NS Health COVID-19 Medication Recommendations

Recommendation	Medication	Notes
Routine Care	Casirivimab/ imdevimab	Use on a case-by-case basis in individuals with non-severe symptomatic COVID-19, confirmed by a positive COVID-19 test, who are at high risk for progression to severe disease. To be ordered by a designated prescriber while in a prioritization phase.
	Dexamethasone	If symptoms for 5 or more days: use for individuals with SpO2 less than or equal to 94% on room air or supplemental oxygen, or mechanical ventilation (including ECMO). If less than 5 days since symptom onset, consult infectious diseases.
	Inhaled Budesonide	Use on a case-by-case basis in individuals with mild symptomatic COVID-19 (do not require: new or additional supplemental oxygen, intravenous fluids, or physiological support) within 14 days of symptom onset.
	Nirmatrelvir/ ritonavir	Use on a case-by-case basis in individuals with non-severe symptomatic COVID-19, confirmed by a positive COVID-19 test, who are at high risk for progression to severe disease. To be ordered by a designated prescriber while in a prioritization phase.
	Sotrovimab	Use on a case-by-case basis in individuals with non-severe symptomatic COVID-19, confirmed by a positive COVID-19 test, who are at high risk for progression to severe disease. To be ordered by a designated prescriber while in a prioritization phase.
Research	Baricitinib	Use in the context of pragmatic research (e.g.: the CO-VIC study) in patients with moderate-severe symptomatic COVID-19.
	Remdesivir	Use in the context of pragmatic research (e.g.: the CO-VIC study) in hospitalized patients with symptomatic COVID-19.
	Sarilumab	Use on a case-by-case basis in the context of pragmatic research (e.g.: the CO-VIC study) in patients with moderate to severe symptomatic COVID-19.
	Tocilizumab	Use in the context of pragmatic research (e.g.: the CO-VIC study) in hospitalized patients with severe COVID-19, SpO2 less than or equal to 92% on room air or supplemental oxygen, and systemic inflammation (e.g.: CRP >75 mg/L) in addition to standard of care.
Do NOT Recommend	Bamlanivimab, Colchicine, Fluvoxamine, Ivermectin	

NS Health COVID-19 Medication Recommendations

NON-SEVERE COVID-19 TREATMENT

i.e. SpO2 ≥ 94% and not requiring oxygen

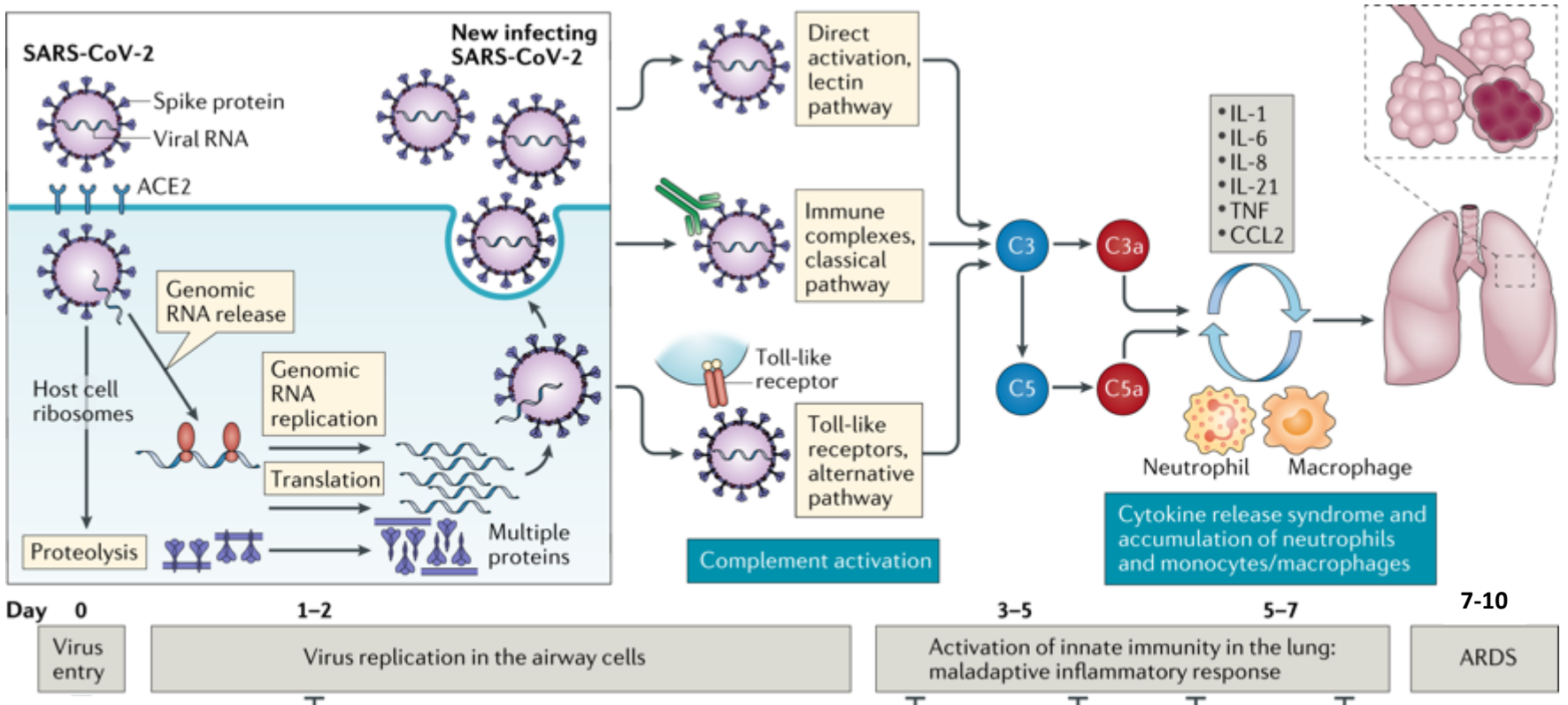
Symptoms	Therapeutics
Asymptomatic	• No COVID-directed therapy indicated; monitor for symptoms and changes in clinical status
Mild symptoms i.e. sore throat, cough, headache, weakness, diarrhea, fever, etc. PPO Known or Suspected COVID−19 Patient Admission Orders − ADULT (click link)	Consider: • **Budesonide dry powder inhaler (inhaled corticosteroid)** ◦ 800 mcg inh BID x 14 days or until symptom recovery ◦ Initiate within 14 days of symptom onset ◦ Do NOT substitute with nebules, alternative inhaled corticosteroids, or oral/ IV corticosteroids • **Sotrovimab (anti-SARS-CoV-2 monoclonal antibody)** ◦ Initiate within 7 days of symptom onset if meets **eligibility criteria** (click link) ◦ Email COVIDTreatment@nshealth.ca to reach a designated prescriber • **Nirmatrelvir/ritonavir (oral antiviral)** ◦ Initiate within 5 days of symptom onset if meets **eligibility criteria** (click link) ◦ Email COVIDTreatment@nshealth.ca to reach a designated prescriber **Thromboprophylaxis** If no separate indication for anticoagulation (e.g.: known clot, a.fib.) **Outpatients**: • No VTE prophylaxis indicated **Inpatients**: • Standard VTE prophylaxis (i.e.: dalteparin 5000 units subcut daily)

Disclaimer: Evidence is evolving quickly and recommendations are subject to change. This document provides general guidance and is not a substitute for clinical judgement in individual patient cases.

Last updated: January 20, 2022

Non-severe COVID-19 Treatment Overview

Mechanism of Action



Antiviral: nirmatrelvir/ritonavir, remdesivir
Neutralizing monoclonal antibodies: casirivimab/imdevimab, bamlanivimab, sotrovimab

Immunomodulatory: baricitinib, dexamethasone, budesonide, sarilumab, tocilizumab

https://www.nature.com/articles/s41577-020-0320-7/figures/1

1. Inhaled Budesonide

Inhaled Budesonide

Dose/Route/ Frequency	Budesonide 800 mcg inhaled twice daily for 14 days (or until symptom recovery) Note: nebulizing medications = AGMP. Turbuhaler is recommended.
Crushing Information	Not applicable
Renal adjustment	Not applicable
Adverse Effects	Oral thrush (up to 5%), hoarseness, throat irritation (up to 5%) Rinsing mouth after inhaler use may reduce risk, limit systemic absorption
PK	Moderate CYP3A4 inducer
Canadian Availability	Available, not approved for COVID-19

PRINCIPLE and STOIC

Evidence:

- Key support comes from the primary analysis of the **PRINCIPLE** trial[2] which involved 2350 adult outpatients with confirmed COVID-19 and symptom onset within the past 14 days and who were at high risk for complications, i.e. either advanced age ≥ 65 years or ≥ 50 years with comorbidities (CVD, HTN, asthma/lung disease, DM, hepatic impairment, stoke or neurological problems, weakened immune system, obesity/BMI ≥ 35 kg/m^2). Patients (mean age 64.2 years [SD 7.6], 81% with comorbidities, median 6 days since symptom onset), were randomized to receive either 1) budesonide dry powder inhaler 800 mcg inh BID x 14 days + usual care (n = 787) or 2) usual care alone (n = 1069). The trial was stopped early when pre-specified superiority criteria were met:

PRINCIPLE: multi-centre, open-label RCT based out of primary care centres in the UK (enrolled April 2020-March 2021)

- **Quicker time to self-reported recovery [median days (95% Bayesian credible interval)]**
  - 11.8 days (10.0 – 14.1) budesonide recipients versus 14.7 days (12.3 – 18.0) usual care recipients; HR 1.21 (1.08 – 1.36), probability of superiority >0.999*
- **No difference in composite of hospital admission or death at 28 days [absolute rate (95% Bayesian credible interval)]**
  - 6.8% (4.1 – 10.2) budesonide recipients versus 8.8% (5.5 – 12.7) usual care recipients; OR 0.75 (0.55 – 1.03), probability of superiority 0.963*
- **Serious adverse events (SAEs):**
  - Recorded in 2 budesonide recipients (hospitalization for lower limb fracture, alcohol-induced pancreatitis) and 4 usual care recipients (hospitalization for cholelithiasis, atrial fibrillation, heart valve surgery, and appendicitis)

*Threshold for superiority pre-specified at 0.99

- The **STOIC** trial[3], a phase 2 open-label RCT, investigated the role of inhaled budesonide versus usual care alone for reducing urgent care visits (emergency department assessments or hospitalization) in adult outpatients with early, mild COVID-19 (n = 146). In this overall young and healthy population (median age 45, 5% diabetes, 9% cardiovascular disease, mean BMI 26-27 kg/m^2), there were statistically significantly fewer urgent care visits in budesonide recipients [2/73 (3%)] versus usual care [11/73 (15%)]; difference in proportion 0.123 (95% CI 0.033 – 0.213); p = 0.009.

Practical Considerations

Tip: consider inhaled budesonide use for individuals with respiratory symptoms

- NS Health formulary drug without restrictions
- Seniors/Family pharmacare benefit
- Turbuhaler requires forceful inhalation
- Do not recommend:
  - Substitution with other inhaled corticosteroids (others have not been shown to have a benefit)
  - Substitution with PO or IV corticosteroids (dexamethasone systemically administered early in disease course is associated with harm)
  - Nebules, nebules are an aerosol generating medical procedures (AGMP)

Order

13. **Medications**

Inhaled Corticosteroid

Indications:

- Consider for patients with mild symptoms of COVID–19 (e.g. do not require new or additional supplemental oxygen, intravenous fluids, or physiological support) within 14 days of symptom onset.

❑ Budesonide dry powder inhaler 800 mcg inh bid x 14 days or until symptom recovery
Do NOT substitute with nebules, alternative inhaled corticosteroids, or oral / IV corticosteroids.

Systemic Corticosteroid

Indications:

- SpO2 less than or equal to 94 % on room air or supplemental oxygen OR
- Mechanical ventilation (including ECMO)

❑ Dexamethasone 6 mg po/ng/IV daily x 10 days or until hospital discharge (whichever is sooner)
(If less than 5 days since symptom onset, consider ID consult prior to initiating dexamethasone)

- If pregnant, see Corticosteroid Treatment for Pregnant COVID–19 Patient order set (NS_OSCOVIDCT)

COVID Admission Orders

2. Sotrovimab

Sotrovimab

Dose/Route/ Frequency	Sotrovimab 500 mg IV x 1 dose
Crushing Information	Not applicable
Renal adjustment	No adjustment recommended
Adverse Effects	Injection site reaction, hypersensitivity, diarrhea, pruritis, skin rash, chills, dizziness
PK	No known interactions
Canadian Availability	Available (July 30, 2021, authorized under interim order for COVID-19) Indication: Treatment of mild to moderate COVID-19, confirmed by direct SARS-CoV-2 viral testing, in adults and adolescents (aged 12 years and older weighing at least 40 kg) who are at high risk for progression to hospitalization and/or death.

COMET-ICE

Evidence: key support comes from **COMET-ICE, a Phase 3, multi-centre, double-blinded RCT[2,3] with results released in pre-print form**. It reports on 1057 adults (≥ 18 years of age) with lab-confirmed mild to moderate COVID-19, no previous vaccination against SARS-CoV-2, ≥ 1 COVID-associated symptom with onset ≤ 5 days prior, and who had at least one **high-risk factor** for progression to severe disease.

- **High risk factors** included: age 55 or older, diabetes requiring medication, obesity (BMI > 30 kg/m^2), chronic kidney disease (eGFR below 60 mL/min/1.73 m^2), heart failure (NYHA class II or higher), COPD, or moderate to severe asthma.

Patients were randomized to receive 1) sotrovimab 500 mg or 2) matching placebo as a single IV infusion. The trial was stopped early due to efficacy findings at the time of a planned interim analysis.

COMET-ICE: Preprint Results

- **Lower rate of composite all-cause hospitalizations > 24 hours and deaths by day 29:**
  - 1% (6/528) sotrovimab vs 6% (30/529) placebo; RRR 79% (95% CI 50 – 91%), p < 0.001
- **Less progression to severe (requiring supplemental O2) or critical (requiring mechanical ventilation) disease:**
  - 1% (7/528) sotrovimab vs 5% (28/529) placebo;RRR 74% (95% CI 41 – 88%), p = 0.002
- **Serious adverse events (SAEs):**
  - Occurred in 2% (11/523) of sotrovimab recipients vs 6% (32/526) of placebo recipients (no statistical comparison provided).

Number needed to treat (NNT):
For every 20 COVID-19 outpatients who receive sotrovimab, 1 fewer all-cause hospitalization or death will occur by day 29 versus placebo.

Sotrovimab Healthcare Professional Overview

Distribution

Federal Government

Distributes supply free of charge to provinces and territories through an allocation process determined by the Public Health Agency of Canada

Provincial Drug Distribution Program (PDDP)

Receives allocation for Nova Scotia

Hospital Distribution

PDDP distributes supply to designated hospitals

Administration

Outpatients meeting eligibility and prioritization criteria are:

- prescribed therapy by designated prescriber and
- referred to a designated hospital to receive infusion

Sotrovimab Eligibility

- Encourage patients to complete report and support form either online or via 811 to be considered for sotrovimab

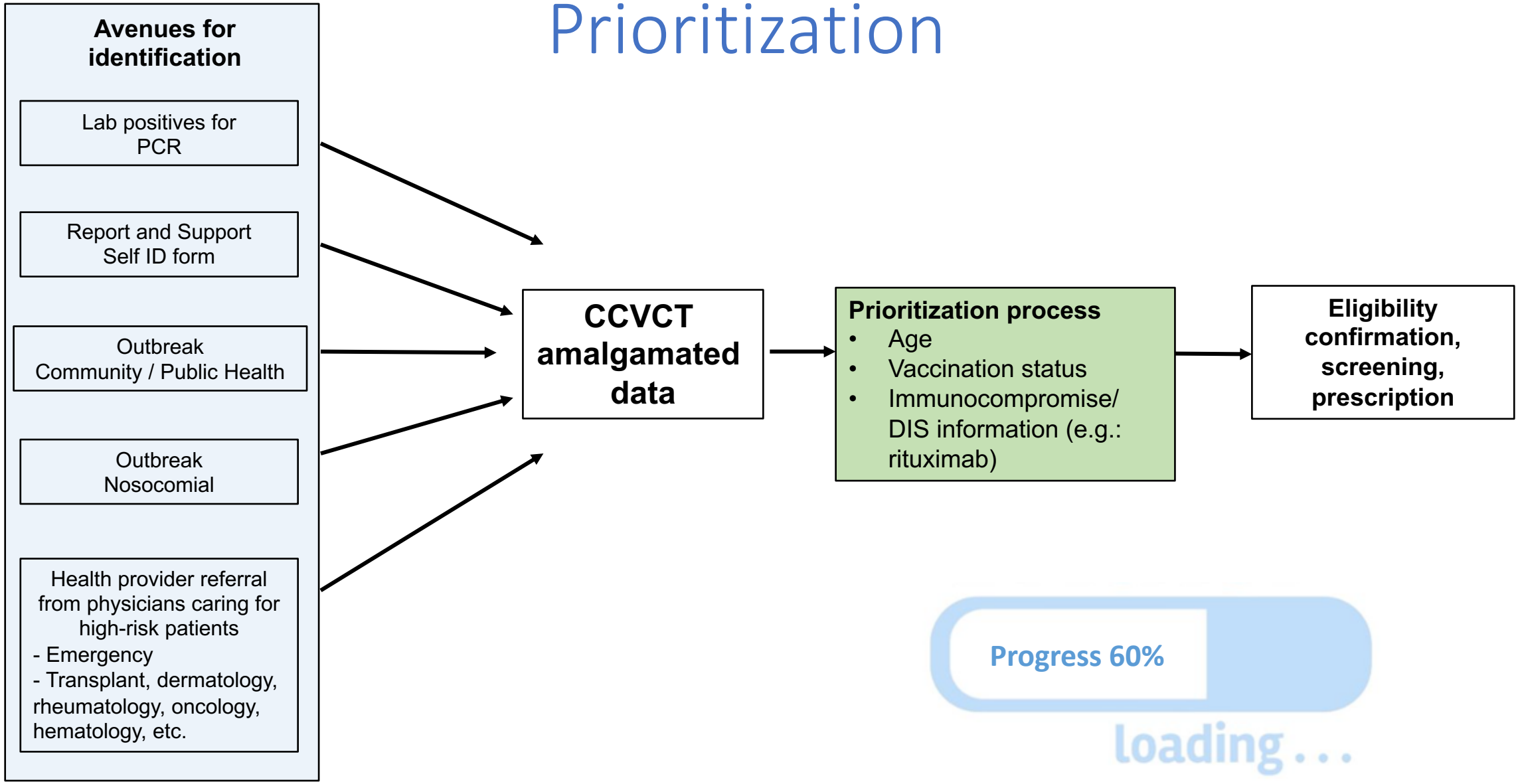
Some individuals who meet ALL criteria may be candidates for therapy. If ALL boxes are checked, refer patient to COVIDTreatment@nshealth.ca

- ☐ Age ≥ 12 years and weight ≥ 40 kg
- ☐ Positive SARS-CoV-2 (PCR) test (or rapid antigen test while prevalence high)
- ☐ Symptom onset within previous 7 days
- ☐ Non-severe COVID-19 symptoms (e.g.: no SOB at rest, oxygen sats ≥ 94%)
- ☐ Patient NOT sufficiently vaccinated against COVID-19
  - Insufficient vaccination includes immunocompetent patients who received ≤1 dose or are < 2 weeks post 2nd dose OR
  - Moderately-severely immunocompromised* patients who received < 3 doses or are < 2 weeks post 3rd dose OR
  - Immunocompromised* and not expected to mount an adequate immune response to COVID-19, regardless of vaccine status (e.g.: post-HSCT or taking rituximab) OR
  - ≥ 80 years, vaccinated with primary series and < 2 weeks post booster
- ☐ ≥ 1 high risk factor for progression
  - Age ≥ 55 years
  - Diabetes requiring medication
  - Obesity (BMI >30 kg/m2)
  - CKD (eGFR < 60 mL/min/1.73 m2)
  - Congestive heart failure (NYHA class II or higher)
  - COPD (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnea on physical exertion)
  - Moderate to severe asthma (requires an inhaled steroid to control symptoms or has been prescribed a course of oral steroids in the past year)
  - Self-identifies as moderately to severely immunocompromised*

Monoclonal Antibody Eligibility Criteria Checklist

Monoclonal Antibody Quick Link Resources

Prioritization



3. Nirmatrelvir/ritonavir (Paxlovid®)

Nirmatrelvir/ritonavir (Paxlovid®)

- Other names: Paxlovid®, PF-07321332 and ritonavir
  - **Nirmatrelvir** SARS-CoV-2 protease inhibitor AND
  - **Ritonavir** (low-dose) protease inhibitor that acts as a “pharmacokinetic booster” to inhibit hepatic metabolism of nirmatrelvir and optimize dosing profile

Nirmatrelvir/ritonavir (Paxlovid®)

Dose/Route/ Frequency	nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days with or without food
Crushing Information	Do not crush
Renal adjustment	eGFR ≥ 30 to < 60 mL/min: nirmatrelvir 150 mg (1 x 150 mg tablet) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days eGFR < 30 mL/min: not recommended
Adverse Effects	Change in sense of taste (6/100) Diarrhea (3/100) High blood pressure (1/100) Muscle aches (1/100) Hepatotoxicity
PK	nirmatrelvir (with ritonavir) and ritonavir: t1/2: 6 days MANY drug-drug interactions. Ritonavir inhibitor of CYP 3A4 (strong), CYP 2D6 (weak), MRP2, P-glycoprotein/ABCB1;and also induces CYP 1A2 (weak), CYP 2B6 (moderate), CYP2C19 (weak), CYP 2C9 (weak), UGT1A1
Canadian Availability	Authorized with terms and conditions by Health Canada- January 17, 2022

EPIC-HR

Evidence: key support comes from the **Phase 2/3 RCT EPIC-HR, with interim data released from the manufacturer.**[1,2] The analysis cited in the Canadian product monograph[1] reports on 774 non-hospitalized adults ≥ 18 years of age with COVID-19 and oxygen saturation > 92% on room air, who were un-vaccinated and with no prior history of COVID-19 infection, and who had at least 1 high risk factor* for severe disease. 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. Key results:

EPIC-HR: double-blind, multicenter RCT (unpublished interim analysis from manufacturer)[1]

- **Fewer COVID-19-related hospitalizations and deaths by day 28:**
  - 0.8% (3/389) nirmatrelvir/ritonavir recipients vs 7.0% (27/385) placebo recipients; Absolute reduction relative to placebo -6.32% (95% CI -10.61% to -2.02%)
- **Adverse events (no statistical comparison provided):**
  Events that occurred at a greater frequency in the nirmatrelvir/ritonavir arm than the placebo arm and at a rate of 1% or more:
  - Dysgeusia in 5.6% nirmatrelvir/ritonavir recipients vs 0.3% in placebo recipients
  - Headache in 1.4% nirmatrelvir/ritonavir recipients vs 1.3% in placebo recipients
  - Diarrhea in 3.1% nirmatrelvir/ritonavir recipients vs 1.6% in placebo recipients
  - Vomiting in 1.1% nirmatrelvir/ritonavir recipients vs 0.8% in placebo recipients

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.

Distribution

Federal Government

Distributes supply free of charge to provinces and territories through an allocation process determined by the Public Health Agency of Canada

Provincial Drug Distribution Program (PDDP)

Receives allocation for Nova Scotia

Pharmacy and Hospital Distribution

PDDP distributes supply to designated community pharmacies and hospitals

Dispense

Outpatients meeting eligibility and prioritization criteria are:

- prescribed therapy by designated prescriber and
- referred to a designated pharmacy to obtain supply via delivery or pick-up by non-isolating friend/family

Nirmatrelvir/ritonavir Eligibility

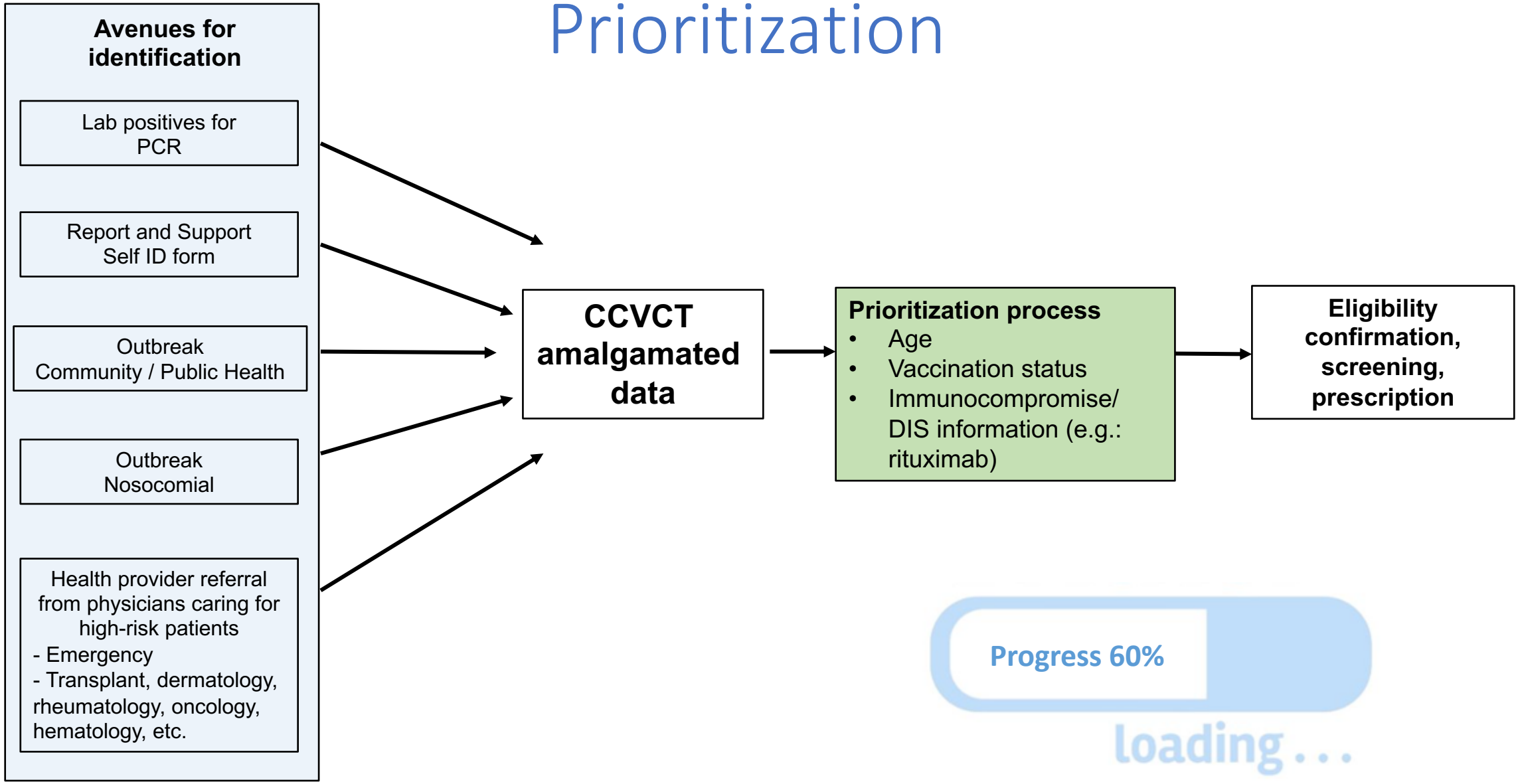
- Encourage patients to complete report and support form either online or via 811 to be considered for nirmatrelvir/ritonavir (Paxlovid)

Some individuals who meet ALL criteria may be candidates for therapy.
If ALL boxes are checked, refer patient to COVIDTreatment@nshealth.ca

- ☐ Age ≥ 18 years
- ☐ Positive SARS-CoV-2 (PCR) test (or rapid antigen test while prevalence high)
- ☐ Symptom onset within previous 5 days
- ☐ Non-severe COVID-19 symptoms (e.g.: no SOB at rest, oxygen sats ≥ 94%)
- ☐ Patient is NOT sufficiently vaccinated against COVID-19
  - Insufficient vaccination includes immunocompetent patients who received ≤ 1 dose or are < 2 weeks post 2nd dose OR
  - Moderately-severely immunocompromised* patients who received < 3 doses or are < 2 weeks post 3rd dose OR
  - Immunocompromised* and not expected to mount an adequate immune response to COVID-19, regardless of vaccine status (e.g.: post-HSCT or taking rituximab) OR
  - ≥ 80 years, vaccinated with primary series and < 2 weeks post booster
- ☐ ≥ 1 high risk factor for progression
  - Older age (i.e., ≥ 60 years)
  - Obesity or being overweight
  - Chronic kidney disease
  - Diabetes
  - Immunosuppressive disease or immunosuppressive treatment
  - Cardiovascular disease or hypertension
  - Chronic lung disease (i.e., COPD , moderate-severe asthma, interstitial lung disease, cystic fibrosis, and pulmonary hypertension)
  - Sickle cell disease
  - Neurodevelopmental disorders (i.e., cerebral palsy, Trisomy 21) or other conditions that confer medical complexity
  - Active cancer
  - Medical-related technological dependence not related to COVID-19 (i.e., tracheostomy, gastrostomy, or positive pressure ventilation)

Eligibility Criteria

Prioritization



Prioritization

- Expression of Interest: COVID Network Therapeutics Prioritization Advisory Group
  - Application deadline: no later than Friday, January 28, 2022

Prescription

- Designated prescribers available via COVIDTreatment@nshealth.ca

nova scotia health

ORDER SET

Oral Antiviral for COVID-19

Patient: _____ Allergies _____

HCN: _____ DOB: _____

To be completed for outpatient prescriptions:
Community Pharmacy Name: _____ Fax Number: _____
Designated Pick-up Person: _____

Items preceded by a **bullet** (•) are active orders. Items preceded by a **checkbox** (□) are only to be carried out if checked

1. **Criteria for Use**
   - Treatment of non-severe, symptomatic COVID-19 in adults with a positive COVID-19 test, and who are at high risk for progression to severe COVID-19.
   - Not recommended in severe renal impairment (eGFR less than 30 mL/min/1.73m^2), severe hepatic impairment (Child Pugh C), pregnancy, or breastfeeding.

   ☐ Patient meets criteria for use

2. **Renal Function Assessment** (select one)
   ☐ eGFR _____ mL/min/1.73m^2
   ☐ No known renal impairment AND eGFR not available

3. **Oral Antiviral Therapy (nirmatrelvir and ritonavir - Paxlovid®)**
   Select one of the following based on renal function:

   eGFR equal to or greater than 60 mL/min/1.73m^2:
   ☐ Nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days

   eGFR 30 to 59 mL/min/1.73m^2:
   ☐ Nirmatrelvir 150 mg (1 x 150 mg tablet) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days
   - Dispensing pharmacy to alter packaging to remove 1 nirmatrelvir tablet from each dosing interval in daily blister card

4. **Drug Interaction Assessment**
   - Assess all prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins for drug interactions with nirmatrelvir and ritonavir

   _____

   _____

   _____

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Designated Prescriber's Signature _____ Date _____ Time _____

Designated Prescriber's Name _____ Reg. No. _____
Print

Assessment Protocol

Nirmatrelvir and Ritonavir (Paxlovid®) Pharmacist Assessment Protocol

Client Information		
Name: _____ Preferred Name/Alias: _____ HCN: _____ Street Address: _____ City/Town: _____ Province: _____ Postal Code: _____ Phone Number: _____ Date of Birth: _____ Age: _____ Gender: □Male □Female □Gender X □Undifferentiated		
Eligibility	Criteria (hyperlinked for information only, pharmacist not required to confirm eligibility)	
Medical History	Allergies, medical conditions, and medications* are updated on patient record	□Yes
	Is patient pregnant or breastfeeding?	□Yes - STOP □No
	Chronic kidney disease with eGFR < 30 mL/min?	□Yes- STOP □No
	Severe hepatic impairment (Child Pugh C)?	□Yes - STOP □No
Drug Interaction Review	Recommend using University of Liverpool COVID DI Checker (hyperlinked) to screen for drug interactions in addition to pharmacy dispensing software **Select one of the following:** □ No clinically significant interactions with nirmatrelvir/ritonavir (Paxlovid®) and patient's current medications* identified □ Clinically significant interactions with nirmatrelvir/ritonavir (Paxlovid®) and patient's current medications* identified that require monitoring and/or intervention Details: _____ □ Nirmatrelvir/ritonavir (Paxlovid®) CONTRAINDICATED due to interactions with the patient's current medications* Details: _____	
Assessment	**Select one of the following:** □ The patient is eligible for nirmatrelvir and ritonavir (Paxlovid®) Medical history and drug interaction screen do not indicate nirmatrelvir and ritonavir (Paxlovid®) contraindications □ Patient does not qualify for antiviral therapy due to: _____ □ Patient referred to Physician or Nurse Practitioner for assessment due to: _____	

Prescription	Confirm prescription is **one of the following regimens** and **ordered by a designated prescriber** □ eGFR ≥ 60 mL/min: nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days Dispensed as Paxlovid® x 1 box (5 day treatment course) □ eGFR ≥ 30 to < 60 mL/min: nirmatrelvir 150 mg (1 x 150 mg tablet) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days Dispensed as Paxlovid® x 1 box (5 day treatment course) Dispensing pharmacy to alter packaging to remove 1 nirmatrelvir tablet from each dosing interval in daily blister card
Patient Education/ Follow-up	Patient education sheet reviewed. English (hyperlinked), French (hyperlinked). Self-monitoring for efficacy and toxicity discussed: **Efficacy monitoring** • If COVID-19 signs or symptoms improving, or symptoms are stable, ensure completion of therapy • If COVID-19 signs or symptoms not improving and require support from another healthcare provider for management refer to MD/NP/811 •If COVID-19 progression to severe symptoms such as: difficulty breathing, severe chest pain, loss of consciousness, or feelings of confusion refer to ED or call 911 immediately **Toxicity monitoring** • Side effects including: • Change in sense of taste • Diarrhea • High blood pressure (if patient able to monitor at home) • Muscle aches • Hepatotoxicity: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain □ Faxed notification to primary care provider regarding: _____ Optional: Follow-up date (3 days recommended): _____ (Set reminder in software)

* **Medications/therapy** that require assessment include prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins administered by mouth, injection, eye drops, inhalers, creams, and nasal sprays, etc.

Assessment Protocol

Eligibility	Criteria (hyperlinked for information only, pharmacist not required to confirm eligibility)	
Medical History	Allergies, medical conditions, and medications* are updated on patient record	□Yes
	Age < 18 years?	□Yes - STOP □No
	Is patient pregnant or breastfeeding?	□Yes - STOP □No
	Chronic kidney disease with eGFR < 30 mL/min?	□Yes- STOP □No
	Severe hepatic impairment (Child Pugh C)?	□Yes - STOP □No

Assessment Protocol

Eligibility	
Drug Interaction Review	Recommend using University of Liverpool COVID DI Checker (hyperlinked) to screen for drug interactions in addition to pharmacy dispensing software **Select one of the following:** □ No clinically significant interactions with nirmatrelvir/ritonavir (Paxlovid®) and patient's current medications* identified □ Clinically significant interactions with nirmatrelvir/ritonavir (Paxlovid®) and patient's current medications* identified that require monitoring and/or intervention Details: _____ □ Nirmatrelvir/ritonavir (Paxlovid®) CONTRAINDICATED due to interactions with the patient's current medications* Details: _____ * **Medications/therapy** that require assessment include prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins administered by mouth, injection, eye drops, inhalers, creams, and nasal sprays, etc.

Drug Interactions

- MANY interactions
  - Ritonavir is inhibitor of CYP 3A4 (strong), CYP 2D6 (weak), MRP2, P-glycoprotein/ABCB1;and also induces CYP 1A2 (weak), CYP 2B6 (moderate), CYP2C19 (weak), CYP 2C9 (weak), UGT1A1

- Assess prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins
  - Includes products taken by mouth, injection, eye drops, inhalers, creams, and nasal sprays

- Recommend using University of Liverpool COVID DI Checker to screen for drug interactions in addition to pharmacy dispensing software

Drug Interactions

Twitter: **Kirsteen Hill** @kndhill

Drug Interactions

A Few Examples, Always Check for DIs

- Corticosteroids
  - Unlike PIs used ongoing for HIV, short duration nirmatrelvir/ritonavir with non-systemic (e.g.: inhaled) and low dose systemic corticosteroids (e.g.: dexamethasone for COVID) may be considered
- Statins
  - Given short duration of nirmatrelvir/ritonavir, statin should be stopped. Restart 3 days after the last dose of nirmatrelvir/ritonavir.
- Hormonal Contraception
  - Use alternative contraceptive method or an additional barrier method of contraception during treatment with nirmatrelvir/ritonavir, and until one menstrual cycle after stopping nirmatrelvir/ritonavir
- Transplant medication
  - Increased exposure (transplant medication toxicity risk) + decreased mycophenolate exposure
- Anticoagulants and antiplatelet
  - Apixaban, rivaroxaban, ticagrelor: co-administration contraindicated
  - Others, except ASA, require adjustment/assessment
- Anticonvulsants
  - Carbamazepine, phenobarbital, phenytoin: co-administration contraindicated
  - Others require require adjustment/assessment
- Psychotropics:
  - Lurasidone: co-administration contraindicated
  - Clozapine/quetiapine (and more): require require adjustment/assessment
- Colchicine:
  - Co-administration contraindicated in the setting of renal/hepatic impairment
- + calcium channel blockers, antiarrhythmics, and MANY more…. stay tuned for DI guidance document

Assessment Protocol

Prescription	Confirm prescription is **one of the following regimens** and **ordered by a designated prescriber** ☐ eGFR ≥ 60 mL/min: nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days Dispensed as Paxlovid® x 1 box (5 day treatment course) ☐ eGFR ≥ 30 to < 60 mL/min: nirmatrelvir 150 mg (1 x 150 mg tablet) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days Dispensed as Paxlovid® x 1 box (5 day treatment course) Dispensing pharmacy to alter packaging to remove 1 nirmatrelvir tablet from each dosing interval in daily blister card

Prescription

ORDER SET

Oral Antiviral for COVID-19

Patient: _____ Allergies _____

HCN: _____ DOB: _____

To be completed for outpatient prescriptions:
Community Pharmacy Name: _____ Fax Number: _____
Designated Pick-up Person: _____

Items preceded by a **bullet** (•) are active orders. Items preceded by a **checkbox** (□) are only to be carried out if checked

1. **Criteria for Use**
   - Treatment of non-severe, symptomatic COVID-19 in adults with a positive COVID-19 test, and who are at high risk for progression to severe COVID-19.
   - Not recommended in severe renal impairment (eGFR less than 30 mL/min/1.73m^2), severe hepatic impairment (Child Pugh C), pregnancy, or breastfeeding.

   ☐ Patient meets criteria for use

2. **Renal Function Assessment** (select one)
   ☐ eGFR _____ mL/min/1.73m^2
   ☐ No known renal impairment AND eGFR not available

3. **Oral Antiviral Therapy (nirmatrelvir and ritonavir - Paxlovid®)**
   Select one of the following based on renal function:

   eGFR equal to or greater than 60 mL/min/1.73m^2:
   ☐ Nirmatrelvir 300 mg (2 x 150 mg tablets) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days

   eGFR 30 to 59 mL/min/1.73m^2:
   ☐ Nirmatrelvir 150 mg (1 x 150 mg tablet) and ritonavir 100 mg (1 x 100 mg tablet) po bid x 5 days
   - Dispensing pharmacy to alter packaging to remove 1 nirmatrelvir tablet from each dosing interval in daily blister card

4. **Drug Interaction Assessment**
   - Assess all prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins for drug interactions with nirmatrelvir and ritonavir

   _____

   _____

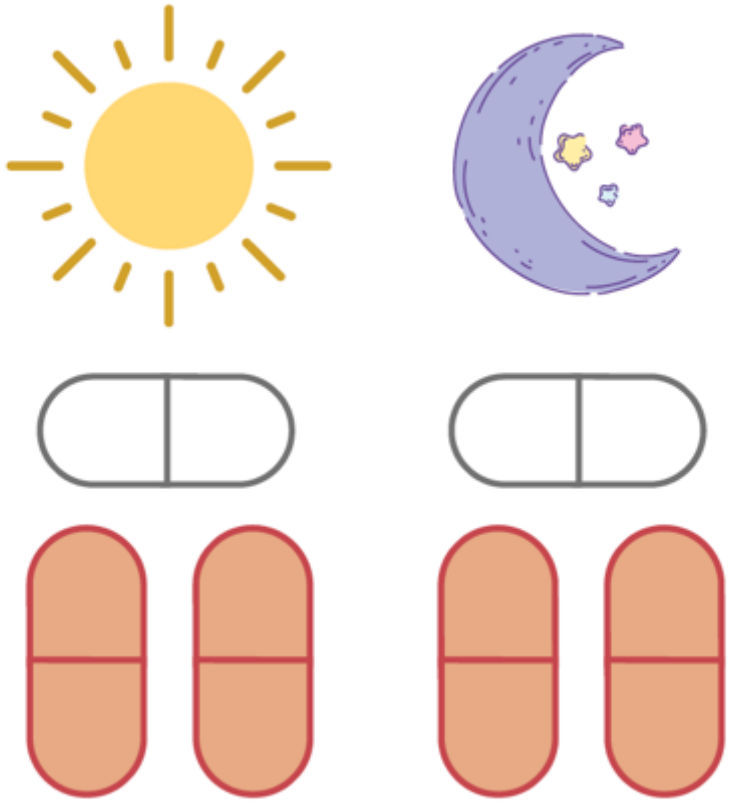
   _____

Printed copies of this document are considered uncontrolled and valid only for the day printed.

Designated Prescriber's Signature _____ Date _____ Time _____

Designated Prescriber's Name _____ Reg. No. _____
Print

Administration



nirmatrelvir 300 mg (**2** x 150 mg tablets)

AND

ritonavir 100 mg (**1** x 100 mg tablet)

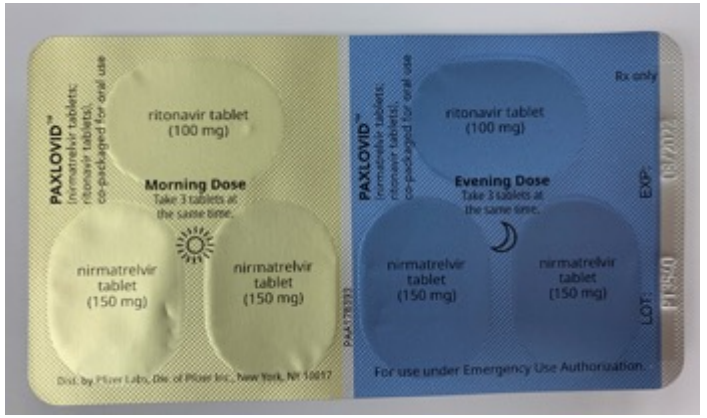
po bid x 5 days with or without food

Swallow whole and do not break/chew/crush

Supplied

- Box containing 5 daily-dose blister cards, each containing
  - 4 x nirmatrelvir 150 mg tablets and
  - 2 x ritonavir 100 mg tablets

- For renal impairment, alter daily blister cards to ensure they receive the correct dose. Remove 1 nirmatrelvir tablet from each dosing interval in daily blister card.



Assessment Protocol

Patient Education/ Follow-up	Patient education sheet reviewed. English (hyperlinked), French (hyperlinked). Self-monitoring for efficacy and toxicity discussed: **Efficacy monitoring** • If COVID-19 signs or symptoms improving, or symptoms are stable, ensure completion of therapy • If COVID-19 signs or symptoms not improving and require support from another healthcare provider for management refer to MD/NP/811 •If COVID-19 progression to severe symptoms such as: difficulty breathing, severe chest pain, loss of consciousness, or feelings of confusion refer to ED or call 911 immediately **Toxicity monitoring** • Side effects including: • Change in sense of taste • Diarrhea • High blood pressure (if patient able to monitor at home) • Muscle aches • Hepatotoxicity: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain □ Faxed notification to primary care provider regarding: _____ Optional: Follow-up date (3 days recommended): _____ (Set reminder in software)

Nirmatrelvir and Ritonavir (Paxlovid®)

What is nirmatrelvir and ritonavir (Paxlovid®)?

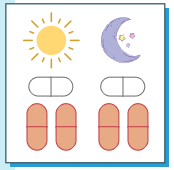
- A combination of two medications, nirmatrelvir and ritonavir, taken together to treat individuals with mild to moderate symptoms of COVID-19.
- Nirmatrelvir is an antiviral that prevents the virus that causes COVID-19 from multiplying. Ritonavir helps nirmatrelvir work in the body.
- Health Canada has approved nirmatrelvir and ritonavir (Paxlovid®) for COVID-19 with a "Notice of Compliance with Terms and Conditions." This means safety and effectiveness information will continue to be monitored as the medications are used more.

How may nirmatrelvir and ritonavir (Paxlovid®) be helpful for COVID-19?

- In people with mild or moderate symptoms of COVID-19, taking nirmatrelvir and ritonavir (Paxlovid®) may reduce the risk the infection will worsen to become severe and require hospitalization or progress to death.

Who may benefit from nirmatrelvir and ritonavir (Paxlovid®)?

- Adults at high risk for getting very sick (for example, the elderly, those without vaccination, or with certain underlying medical conditions or immunosuppression) may benefit from treatment. Nirmatrelvir and ritonavir (Paxlovid®) is only useful in the early stages of infection (within 5 days of feeling ill and within 5 days of a positive COVID-19 test).
- Nirmatrelvir and ritonavir (Paxlovid®) may not be appropriate for those with liver or kidney disease, other serious illnesses, or if you are pregnant or planning on becoming pregnant. **Many prescription medications, over-the-counter products, traditional medicines, natural health products, and vitamins interact with Nirmatrelvir and ritonavir (Paxlovid®) and cannot be taken together (see next page).**



How do I take nirmatrelvir and ritonavir (Paxlovid®)?

- Take 2 nirmatrelvir (pink) tablets and 1 ritonavir (white) tablet by mouth in the morning and in the evening.
  - For individuals with kidney disease, the dose may be different.
- Swallow the tablets whole. Do not crush, chew, or break the tablets. Tablets may be taken with or without food.
- If you miss a dose and it is within 8 hours of the time it is usually taken, take the dose as soon as you remember. If it has been more than 8 hours, skip the dose and take your next dose at your regular time.

What are the possible side effects?

- A change in your sense of taste (about 6 out of 100 people may experience this)
- Diarrhea (about 3 out of 100 people may experience this)
- High blood pressure (about 1 out of 100 people may experience this)
- Muscle aches (about 1 out of 100 people may experience this)

- Liver problems are also possible. **Tell your healthcare provider right away if you have any of these signs or symptoms of liver problems: loss of appetite, yellowing of your skin and the whites of eyes (jaundice), dark-colored urine, pale colored stools and itchy skin, stomach area (abdominal) pain.**

- Since nirmatrelvir and ritonavir (Paxlovid®) are relatively new, not all possible side effects are known. Some may be serious. If you have concerns, reach out to your healthcare provider.

What should I do if my COVID-19 symptoms get worse?

- For minor changes in your symptoms, call 811 or your primary healthcare provider to discuss questions or concerns.
- **Call 911 immediately** if you experience any severe symptoms such as: **difficulty breathing, severe chest pain, loss of consciousness, or feelings of confusion.**

Updated:January 18, 2022

Patient Education

[Nirmatrelvir/ritonavir (Paxlovid) (English)]

General Tips

Acetaminophen, Ibuprofen

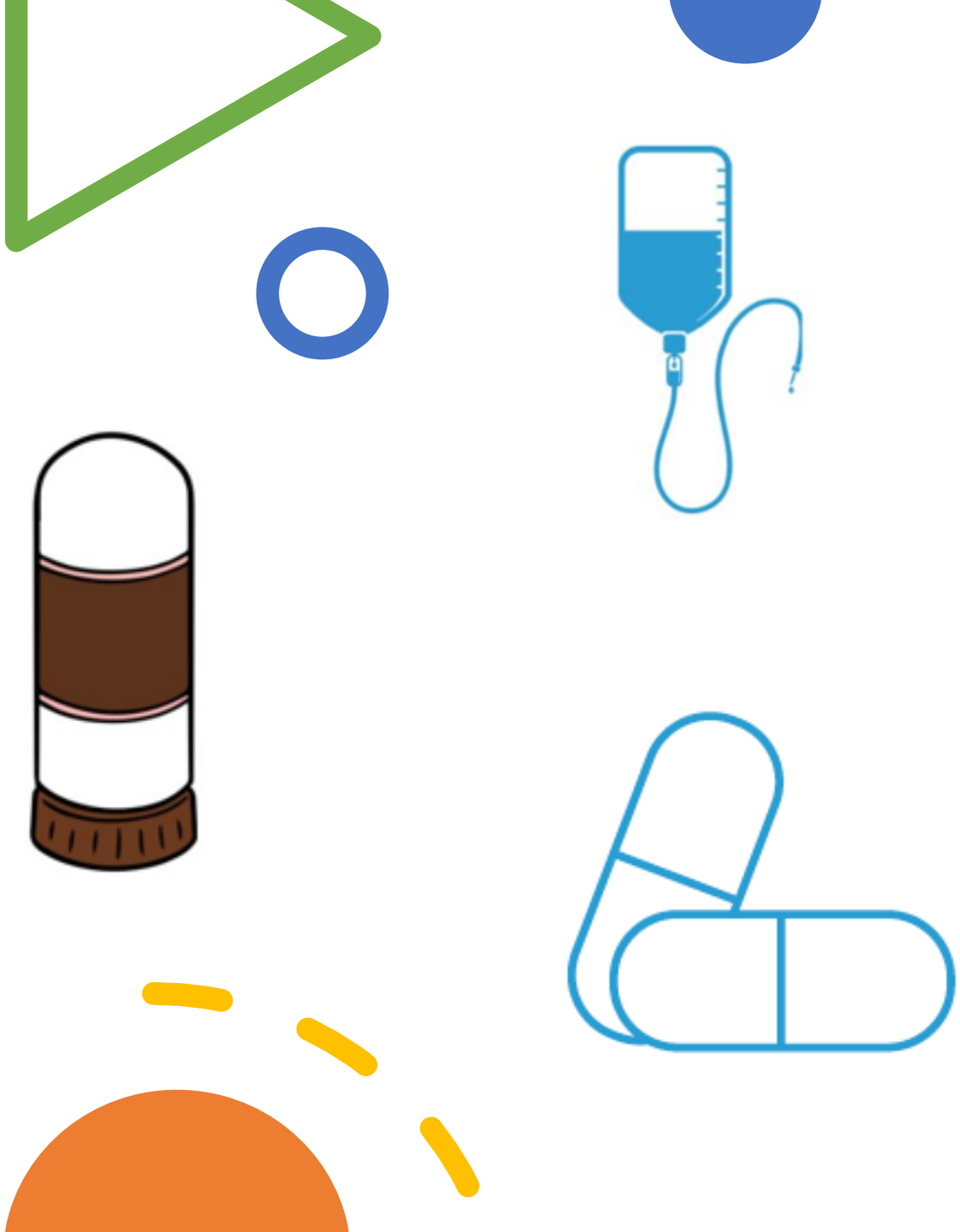
- No COVID-related reason to avoid acetaminophen or ibuprofen
- Early on in the pandemic, theoretical concern that ibuprofen (and NSAIDs) may worsen symptoms of COVID-19
  - A letter to the editor in the Lancet Respiratory Medicine hypothesized ibuprofen may upregulate ACEII and, because ACEII is used for viral entry, this could theoretically cause more severe COVID-19 disease
  - No data was provided to support the hypothesis
- Letter took off on social media. However, no high-quality literature to support this claim. Health Canada released a safety alert in March 2020 stating there is no need to avoid ibuprofen and no evidence to support worsening of symptoms.

Immunization Considerations Post Infection

- Immunize as soon as eligible, once no longer infectious or symptomatic with COVID-19 according to current guidance for recovery
  - Ensure no longer infectious to not infect others and ensure no longer symptomatic to not complicate vaccine side effect monitoring
- Encourage patient to wait if they receive a neutralizing monoclonal antibody (e.g.: sotrovimab)
  - Target spike protein (vaccine antigen) and may interfere with vaccine response
  - **Wait 90 days** after neutralizing monoclonal antibodies to receive COVID vaccination

Take Away Points

- Inhaled budesonide, sotrovimab, nirmatrelvir/ritonavir:
  - Options for outpatients with non-severe COVID-19
  - **Limited supply**
  - Sotrovimab, nirmatrelvir/ritonavir
    - Evidence supports use in a defined population (within 5-7 days of symptom onset, risk factors for progression to severe disease, not sufficiently vaccinated)
    - Ordered by designated prescriber
    - Subject to eligibility criteria and prioritization



Acknowledgments

- Emma Reid
- Thomas Parker

Questions?

Pharmacy One-pagers

- Inhaled Budesonide
- Nirmatrelvir/ritonavir
- Sotrovimab

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**. This ensures ongoing efficacy and safety monitoring occurs as use continues. The recommended treatment course of nirmatrelvir/ritonavir is 300 mg/100 mg po BID x 5 days.[1]

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/m²)
- Current smoker
- Chronic kidney disease
- Diabetes
- Immunosuppressive disease or treatment
- Cardiovascular disease (including congenital heart disease) or hypertension
- 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)
- Active cancer
- Medical-related technological dependence not related to COVID-19 (i.e., tracheostomy, gastrostomy, or positive pressure ventilation)

Note that 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: key support comes from the **Phase 2/3 RCT EPIC-HR, with interim data released from the manufacturer**.[1,2] The analysis cited in the Canadian product monograph[1] reports on 774 non-hospitalized adults ≥ 18 years of age with COVID-19 and oxygen saturation > 92% on room air, who were un-vaccinated and with no prior history of COVID-19 infection, and who had at least 1 high risk factor* for severe disease. 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. Key results:

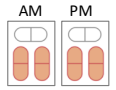
EPIC-HR: double-blind, multicenter RCT (unpublished interim analysis from manufacturer)[1]

- **Fewer COVID-19-related hospitalizations and deaths by day 28:**
  - 0.8% (3/389) nirmatrelvir/ritonavir recipients vs 7.0% (27/385) placebo recipients; Absolute reduction relative to placebo -6.32% (95% CI -10.61% to -2.02%)
- **Adverse events (no statistical comparison provided):**
  Events that occurred at a greater frequency in the nirmatrelvir/ritonavir arm than the placebo arm and at a rate of 1% or more:
  - Dysgeusia in 5.6% nirmatrelvir/ritonavir recipients vs 0.3% in placebo recipients
  - Headache in 1.4% nirmatrelvir/ritonavir recipients vs 1.3% in placebo recipients
  - Diarrhea in 3.1% nirmatrelvir/ritonavir recipients vs 1.6% in placebo recipients
  - Vomiting in 1.1% nirmatrelvir/ritonavir recipients vs 0.8% in placebo recipients

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 in ambulatory patients (or those hospitalized for reasons other than COVID-19) with mild to moderate COVID-19 at high risk for progression to severe disease, initiated within 5 days of symptom onset with consideration for drug interactions and renal function.[3]

Practical Considerations



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

Prepared by: COVID-19 Clinical Pharmacy Working Group
Last Update: January 2022 contact: emmak.reid@nshealth.ca

COVID Hub: COVID-19 Medication Resources

Patient Education

- Neutralizing monoclonal antibodies (English)
- Neutralizing monoclonal antibodies (French)
- Nirmatrelvir/ritonavir (Paxlovid) (English)
- Nirmatrelvir/ritonavir (Paxlovid) (French)

Nirmatrelvir and Ritonavir (Paxlovid®)

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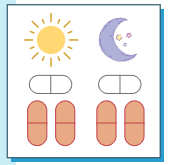

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Updated:January 18, 2022

Nirmatrelvir/ritonavir Resources

- NS Health COVID-19 Medication Recommendations
- Non-severe COVID-19 Treatment Overview
- Healthcare Professional Overview
- MSSU Summary
- Patient Information Sheet English
- Patient Information Sheet French
- Eligibility Criteria