Treatment of COVID-19 with PAXLOVID
(nirmatrelvir [PF-07321332], ritonavir)

Note:

This information has been compiled by CPhA's Pharmacist Editors to provide information about Paxlovid (nirmatrelvir/ritonavir) until a Health Canada—approved monograph is available.

Key Points:

- Nirmatrelvir/ritonavir (nirmatrelvir [PF-07321332], ritonavir) is an oral treatment for COVID-19 that is taken at home upon onset of symptoms to help prevent hospitalization and death.
- The U.S. Food and Drug Administration issued an emergency use authorization (EUA) for nirmatrelvir/ritonavir for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and pediatric patients (≥12 years of age and ≥40 kg) with positive results of direct SARS-CoV-2 testing and who are at high risk for progression to severe COVID-19, including hospitalization or death (December 22, 2021).
- Health Canada is currently reviewing nirmatrelvir/ritonavir (submitted December 2021 by Pfizer Canada; will be reviewed under expedited timelines due to its relevance to the ongoing COVID-19 pandemic).
- Nirmatrelvir has shown consistent in vitro antiviral activity against the previously identified variants of concerns (i.e., Alpha, Beta, Delta, Gamma, Lambda and Mu); in vitro data confirm that nirmatrelvir is a potent inhibitor of the Omicron 3CL protease.

Background:

- Nirmatrelvir is an orally administered antiviral that inhibits 3CL protease; it was specifically designed for SARS-CoV-2.
- Coadministration with a low dose of ritonavir helps slow the metabolism of nirmatrelvir.
- In preclinical studies, nirmatrelvir did not demonstrate evidence of mutagenic DNA interactions.
- Recommended dose: 300 mg (2 x 150 mg tablets) of nirmatrelvir with 100 mg (1 x 100 mg tablet) of ritonavir every 12 hours for 5 days. Treatment should be initiated as soon as possible after diagnosis of COVID-19 and within 5 days of symptom onset.
- Side effects in clinical trials were mostly mild and included impaired sense of taste, diarrhea, high blood pressure and muscle aches.
- Availability: 1 box contains 5 blister packs of four 150 mg nirmatrelvir tablets copackaged with two 100 mg ritonavir tablet, providing all required doses for a full 5-day treatment course.

Clinical Studies:

The **EPIC** (**E**valuation of **P**rotease **I**nhibition for **C**OVID-19) Phase 2/3 development program for nirmatrelvir/ritonavir consists of 3 clinical trials:

EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients, July 2021, *completed**)
**At the recommendation of an independent data monitoring committee and in consultation with the U.S. FDA, Pfizer ceased enrolment into the study due to the efficacy demonstrated in the preliminary results.*

- To evaluate efficacy and safety in patients with COVID-19 who are at high risk of progressing to severe illness
- Randomized, double-blind, placebo-controlled trial; the trial was stopped at 75% enrolment of planned 3000 patients; 1219 patients included in scheduled interim analysis, 2246 patients in final analysis
- Primary outcome: proportion of participants with COVID-19-related hospitalization or death from any cause (timeframe: Day 1 through Day 28)
- Secondary outcomes:
    - incidence of adverse events (AEs) and serious adverse events (SAEs) of nirmatrelvir/ritonavir relative to placebo
    - incidence of treatment-emergent adverse events (TEAEs) of nirmatrelvir/ritonavir relative to placebo
    - duration of each targeted COVID-19 sign/symptom
    - severity of each targeted COVID-19 sign/symptom
    - proportion of participants with death (all cause)
    - determine the pharmacokinetics (PK) in plasma and whole blood of nirmatrelvir in nonhospitalized symptomatic adult participants with COVID 19 who are at increased risk of progression to severe disease
    - viral titers measured by reverse transcription polymerase chain reaction (RT-PCR) in nasal swabs
    - number of COVID-19-related medical visits other than hospitalization
    - number of days in hospital and intensive care unit for the treatment of COVID-19

EFFICACY:

- Interim analysis (n=1219)
    - patients treated within 3 days of symptom onset:
        - 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared with placebo (primary endpoint)
        - 3/389 nirmatrelvir/ritonavir patients hospitalized with no deaths vs. 27/385 placebo patients hospitalized with 7 subsequent deaths; (p <0.0001)
    - patients treated within 5 days of symptom onset:
        - 85% reduction in risk of COVID-19-related hospitalization or death from any cause compared with placebo
        - 1.0% of nirmatrelvir/ritonavir patients were hospitalized through Day 28 (6/607 hospitalized, with no deaths), compared with 6.7% of placebo patients (41/612 hospitalized with 10 subsequent deaths); (p <0.0001)

    - overall study population:
        - 0 deaths in nirmatrelvir/ritonavir patients vs. 10 deaths in placebo patients (1.6%)
- Final analysis (n=2246)
    - patients treated within 3 days of symptom onset:
        - 89% reduction in risk of COVID-19-related hospitalization or death from any cause compared with placebo (primary endpoint)
        - hospitalization to Day 28: nirmatrelvir/ritonavir 0.7% (5/697) vs. placebo 6.5% (44/682) (p <0.0001)
    - patients treated within 5 days of symptom onset:
        - 88% reduction in risk of COVID-19-related hospitalization or death from any cause compared with placebo
        - hospitalization to Day 28: nirmatrelvir/ritonavir 0.8% (8/1039) vs. placebo 6.3% (66/1046) (p <0.0001)
    - overall study population:
        - 0 deaths in nirmatrelvir/ritonavir patients vs. 12 deaths in placebo patients (1.2%)
    - Day 5: 10-fold decrease in viral load relative to placebo (n = 499)

SAFETY:

- Treatment-emergent adverse events: nirmatrelvir/ritonavir 23% vs. placebo 24%; most were mild in intensity
- Side effects included impaired sense of taste, diarrhea, high blood pressure and muscle aches
- Serious adverse events: nirmatrelvir/ritonavir 1.6% vs. placebo 6.6%
- Discontinuation of drug due to adverse events: nirmatrelvir/ritonavir 2.1% vs. placebo 4.2%

EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients, August 2021, *ongoing**)

**The data were reviewed by an independent data monitoring committee (DMC) and, based on the totality of the data available, the DMC recommended that the trial continue.*

- To evaluate efficacy and safety in patients with a confirmed diagnosis of SARS-CoV-2 infection who are at standard risk (i.e., low risk of hospitalization or death)
- Includes a cohort of vaccinated patients who have an acute breakthrough symptomatic COVID-19 infection and who have risk factors for severe illness
- Randomized, double-blind, placebo-controlled trial of 1140 patients
- Primary outcome: time to sustained alleviation of all targeted COVID-19 signs/symptoms (time frame: baseline through Day 28)
- Secondary outcomes:
    - percentage of participants who experience adverse events (AE)
    - percentage of participants who experience an AE or serious adverse events (SAE) that leads to study discontinuation
    - proportion of participants with severe signs/symptoms attributed to COVID-19

- time to sustained resolution of all targeted COVID-19 signs/symptoms
- duration of each targeted COVID-19 sign/symptom
- proportion of participants progressing to a worsening status in 1 or more COVID 19 signs/symptoms
- proportion of participants with a resting peripheral oxygen saturation ≥95%
- number of COVID-19-related medical visits
- number of days in hospital and intensive care unit (ICU) stay in participants with COVID-19-related hospitalization
- proportion of participants with COVID-19-related hospitalization or death from any cause
- proportion of participants with death (all cause)
- minimal concentration of nirmatrelvir
- viral titers measured via reverse transcription polymerase chain reaction (RT-PCR) in nasal swabs
- time to sustained alleviation of all targeted COVID-19 signs/symptoms

EFFICACY:

- Interim analysis (n=673)
  - primary endpoint not met (self-reported, sustained alleviation of all symptoms for 4 consecutive days compared with placebo)
  - 70% reduction in risk of COVID-19-related hospitalization or death from any cause compared with placebo (secondary endpoint)
  - hospitalization: nirmatrelvir/ritonavir 0.6% (2/333) vs. placebo 2.4% (8/329)
  - Day 5: 10-fold decrease in viral load relative to placebo
- Follow-on analysis (n=854)
  - Hospitalization: nirmatrelvir/ritonavir 0.7% (3/428) vs. placebo 2.4% (10/426)

SAFETY:

- Treatment-emergent adverse events: nirmatrelvir/ritonavir 22% vs. placebo 21%; most were mild in intensity
- Serious adverse events: nirmatrelvir/ritonavir 1.4% vs. placebo 1.9%
- Discontinuation of drug due to adverse events: nirmatrelvir/ritonavir 2.1% vs. placebo 1.2%

EPIC-PEP (Evaluation of Protease Inhibition for COVID-19 in Post-Exposure Prophylaxis, September 2021, *ongoing*)

- To evaluate efficacy and safety as postexposure prophylaxis for adult household contacts of a patient with COVID-19
- Randomized, double-blind, double-dummy, placebo-controlled trial of 2634 patients
- Primary outcome: proportion of participants who have a negative reverse transcription polymerase chain reaction (RT-PCR) result at baseline who develop a symptomatic, RT-PCR confirmed SARS-CoV-2 infection (timeframe: Day 1 to Day 14)
- Secondary outcomes:
  - percentage of participants who experience adverse events

- efficacy in preventing symptomatic COVID-19 in participants who have a negative RT-PCR result at baseline and are at increased risk of severe COVID-19 illness
- prevention of SARS CoV-2 infection in participants by RT-PCR status at enrolment
- prevention of SARS CoV-2 infection in participants who have a negative RT-PCR result at baseline
- compare the duration of COVID-19-related signs and symptoms in participants who have a negative RT-PCR result at baseline
- compare the severity of COVID-19-related signs and symptoms in participants who have a negative RT-PCR result at baseline
- minimal concentration (Ctrough) of nirmatrelvir
- all-cause mortality in participants who have a negative RT-PCR result at baseline
- viral titers measured via RT-PCR in nasal swabs in participants who have a negative RT-PCR result at baseline
- number of days of hospital and intensive care unit stay in participants with COVID-19-related hospitalization who have a negative RT-PCR result at baseline

References:

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Prepared: December 22, 2021.

Revised: January 5, 2022.