



Ontario Health
Ontario Renal Network

COVID-19 Supplemental Clinical Guidance #4: Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients With Advanced Chronic Kidney Disease and Patients on Dialysis with COVID- 19

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INTRODUCTION

Major planning directives related to the COVID-19 pandemic are coordinated through Ontario Health, the Ministry of Health, and Ontario Public Health.

On March 9th, 2020, the Ontario Renal Network (ORN), a part of Ontario Health (Cancer Care Ontario) (OH-CCO) circulated the Pandemic Planning Clinical Guideline for Patients with Chronic Kidney Disease, which provides recommendations for a systematic approach in determining priority for consultation and treatment of patients with chronic kidney disease in Ontario during the time of a pandemic. It is intended to augment provincial, regional, and organizational pandemic planning by providing clinical guidance specific to chronic kidney disease care.

The COVID-19 Supplemental Clinical Guidance for Patients with Chronic Kidney Disease (Supplemental Guidance) documents are intended as additional guidance specific to clinical care during the COVID-19 pandemic. Further updates may be released as the COVID-19 pandemic evolves and clinical evidence develops. The information provided herein is supplemental to that provided in sections of the Pandemic Planning Clinical Guideline and does not replace it.

Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients with Advanced Chronic Kidney Disease and Patients on Dialysis with COVID-19

The purpose of this document is to suggest the use of Nirmatrelvir/Ritonavir (Paxlovid) in patients with advanced chronic kidney disease (CKD) and patients on dialysis, taking into account the risks of COVID-19, the benefits of therapy, after dose adjustment and mitigating the drug interactions.

Key Highlights

1. Patients with advanced CKD (stages 4 and 5), including those on dialysis, and kidney transplant recipients, continue to have a very high case fatality rate from COVID-19 in Ontario. Current estimates with the Omicron variant are more than 100 times the rate in the general population (~6% v 0.03%), despite high levels of vaccination. Their risk of hospitalization and ICU admission is similarly very high.
2. Patients with CKD have a diminished immune response to vaccination compared to the general population with faster waning of antibody levels over time.
3. Present Wave 6 modeling suggests that the risk of contracting COVID-19 will rise substantially over the next few weeks in Ontario.
4. Paxlovid (nirmatrelvir/ritonavir) is currently the most effective therapy for reducing severe outcomes in COVID-19 infection but is “not recommended” for these vulnerable advanced CKD patients, and these patient groups have also been excluded in clinical trials.
5. The lack of recommendation is based on the absence of clinical trial information and the concern that the Nirmatrelvir component of Paxlovid will accumulate in advanced CKD. However, we argue that: (a) pharmacokinetic studies suggest that this risk can be attenuated by appropriate reduction

of Nirmatrelvir dose and (b) that there is no known dose-related toxicity with Nirmatrelvir, suggesting the benefits of treatment are maintained with minimal increase in unintended harm.

6. Further studies on the safety of Paxlovid in advanced CKD are not likely to be available in any relevant time frame so we need to act on present available information, however limited.
7. On the basis of the above risks of serious morbidity and mortality from COVID-19 infection in patients with advanced CKD, and the small estimated incremental risks from extending the use of Paxlovid to these patients, we suggest providing Paxlovid after discussing these aspects with the patient.

COVID-19 and Chronic Kidney Disease (CKD)

As of March 31, 2022, there have been 6.14 million deaths globally from Coronavirus disease (COVID-19) due to the Severe Acute Respiratory Syndrome Coronavirus -2 (SARS-CoV-2), of which 37,653 have occurred in Canada [1]. Additionally, there are other longer term consequences from COVID-19, including post critical illness syndromes, auto-immune diseases, cardiovascular disease, and other physical and neurocognitive sequelae [2–4]. These numbers are expected to grow over the next few years and will have a major impact on life expectancy and healthcare utilization.

The burden of morbidity and mortality of COVID-19 is higher in immunocompromised patients including those with advanced CKD (stages 4 and 5) and those with end stage kidney disease (ESKD), receiving dialysis. Hemodialysis patients cannot self-isolate, usually receiving their life-sustaining treatment three times a week in a congregate setting. Kidney transplant recipients are immunosuppressed and have other comorbid conditions making them more susceptible as well. Presently, about 3 million people receive dialysis worldwide, 23,708 of them in Canada, and 13,330 in Ontario [5,6]; [7]. Excluding Quebec, there are 18,052 kidney transplant recipients in Canada [CORR data, 2020].

In the first year after the declaration of the pandemic, in the United States alone, the year-over-year decline in the dialysis census was 1.6%, representing a deficit of 3.8%, relative to the forecasted increasing trend [8]. In Ontario over the first 5 months of the pandemic in 2020, 187 (1.5%) of 12,501 patients undergoing dialysis were diagnosed with SARS-CoV-2 infection. Of these, 117 (62.6%) were admitted to hospital and the case fatality rate was 28.3% [9]. These data predate the availability of vaccination. While case fatality rates for patients on dialysis have fallen in more recent waves in Ontario (18% in Wave 3 and 6% in Wave 5) and are 12% overall during the pandemic, they remain markedly higher than those in the general population [Internal ORN Data]; [10]. Patients with advanced CKD, who attend Multi-Care Kidney Clinics (MCKCs) in Ontario have an even higher mortality rate of 18% overall during the pandemic.

The vaccines for COVID-19 are remarkably effective. However, their effectiveness is lower in the dialysis and transplant populations [11]. The pooled estimate of early antibody formation in dialysis patients was 89% (95% confidence interval [CI] 85 to 91%) [12] relative to healthy controls, thus conferring incomplete protection which wanes over time [12–14]. For kidney transplant recipients, these figures are much lower at 8% (95% CI 5 – 15%) and 35% (95% CI 29 – 42%) with multiple dosing resulting in progressively smaller incremental antibody responses [15]. For newer variants (such as Omicron), which

require higher antibody titres for viral neutralization, a corollary is that vaccines alone will not be sufficient for protection against infection and disease in dialysis patients [16].

‘Renalism’ and CKD

Patients with CKD, especially those with glomerular filtration rate (GFR) < 30, patients on dialysis and kidney transplant recipients are frequently excluded from clinical trials, in particular those evaluating investigational drugs. Proposed explanations for this have included the high comorbidity burden and high complication rates with competing events, and in particular the concern with decreased renal clearance for newer drugs making dosing decisions difficult for a phase 3 trial. The consequence is that CKD patients are excluded initially at time of drug approval, and therapeutic nihilism occurs, whereby these patients are denied effective therapies until data emerges several years later on safety and efficacy [17,18]. This phenomenon has been termed ‘renalism’, and has unfortunately recurred with COVID-19. A rapid review of trial registries with COVID-19 reported that 218 of 484 trials (45%) had an exclusion based on CKD status which was often poorly defined (such as ‘kidney dysfunction’ without a GFR cutoff) [19].

Several therapeutic options have been investigated, and some have been approved for early treatment of COVID-19, notably remdesivir (Velkury, Gilead Inc.) and nirmatrelvir/ritonavir (Paxlovid, Pfizer Inc.). However, patients with low GFR have been excluded from all clinical trials of nirmatrelvir/ritonavir (Paxlovid), and theoretical concerns about drug dosing and safety have led to GFR < 30 being labeled as a contraindication in the product monograph.

Paxlovid Efficacy

Nirmatrelvir (PF-07321332) is an orally administered antiviral agent targeting the SARS-CoV-2 3-chymotrypsin-like cysteine protease enzyme (Mpro). Coadministration of nirmatrelvir with a low dose (100 mg) of ritonavir, a CYP3A4 inhibitor, enhances nirmatrelvir concentration, allowing required therapeutic concentrations to be achieved (see next section for details). The EPIC-HR trial (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) evaluated the safety and efficacy of nirmatrelvir plus ritonavir in non-hospitalized adults with mild-to-moderate COVID-19 at high risk for progression to severe disease [20].

The incidence of COVID-19-related hospitalization or death by day 28 was lower in the nirmatrelvir group than in the placebo group by 6.32 percentage points (95% confidence interval [CI], -9.04 to -3.59; $P < 0.001$; relative risk reduction, 89.1%). There were 13 deaths, all in the placebo group. Patients with CKD were excluded from this trial. The Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-SR) trial in 1140 patients at standard risk has finished enrolment with results expected in a few months.

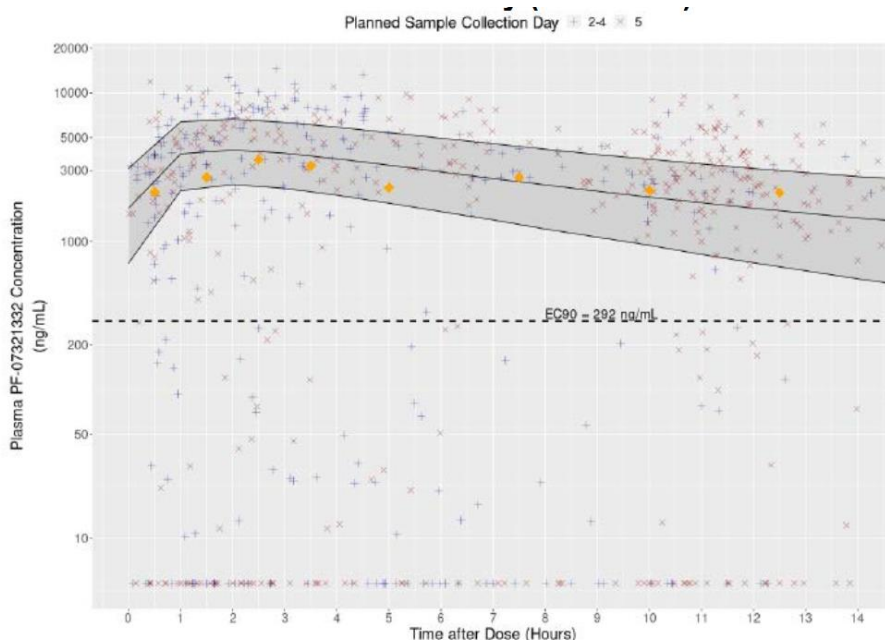
On this basis, Paxlovid is indicated for the treatment of mild-to-moderate COVID-19 (i.e. for outpatient treatment) in adults with positive SARS-CoV-2 viral testing, and who are at high risk for progression to

severe COVID-19, including hospitalization or death. It is not recommended for those with ‘serious renal impairment (eGFR < 30)’.

Paxlovid Pharmacology

Pharmacodynamics

Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease (Mpro), also referred to as 3C-like protease (3CLpro) or nsp5 protease. Inhibition of SARS-CoV-2 Mpro renders the protein incapable of processing polyprotein precursors which leads to the prevention of viral replication. Nirmatrelvir was shown to be an inhibitor of SARS-CoV-2 Mpro (at a $K_i=3.1$ nM, or $IC_{50}=19.2$ nM) in a biochemical enzymatic assay (*in vitro*) [21,22]. K_i refers to how well the drug inhibits the enzyme (lower values are indicative of greater inhibition) and IC_{50} to the concentration required to inhibit 50% of the enzyme over baseline (lower is better). Nirmatrelvir is a competitive inhibitor, and the EC_{50} (i.e. effective concentration) may be more important, which was measured at 3 times higher, i.e. 61.8 nM. However, in a study in mice, it was reported that EC_{90} correlated with efficacy, and this concentration was 181nM (292 ng/mL). Hence the desired dose of nirmatrelvir is that which maintains a trough level above the required EC_{90} concentration of 292 ng/mL. This was the basis of the use of the 300 mg dose in the EPIC-HR trial (see figure 1).



Symbols represent individual observations; Orange diamonds represent median of Day 5 observations binned by intervals (0, 1, 2, 3, 4, 6, 9, 11, 14 hours post-dose); Dashed horizontal line represents the target exposure EC_{90} . Excluded observations with time after dose >14 hours. EC_{90} = concentration required for 90% of maximum effect. Samples below limit of quantification are shown below the LLOQ of 10 ng/mL.

Figure 1: Study C4671005 Median and 90% prediction intervals (fifth and ninety fifth percentile) for nirmatrelvir concentration based on 1000 simulations (nirmatrelvir/ritonavir 300 mg/100 mg every 12 hours at steady-state) overlaid with observed data. Source (22)

Pharmacokinetics

Nirmatrelvir has a molecular weight of 499.5 Da, is about 35% renally excreted and is 70% protein bound. Ritonavir is mostly hepatically metabolized and is 99% protein bound. Hence it is expected that nirmatrelvir will accumulate with decreasing kidney function, while ritonavir will not. A small proportion of nirmatrelvir will be removed with dialysis as well.

Paxlovid Pharmacokinetic Data in CKD

Study C4671005 included 8 patients with serious renal impairment (defined as GFR < 30, not on dialysis). After a single dose of 100 mg nirmatrelvir, the overall concentration at 24 hours was 694.2 (42) ng/mL [geometric mean (coefficient of variation)], over 2 times the required 292 ng/mL (Table 1 and Figure 2).

Parameter (Unit) ^a	Normal Renal Function (N=10)	Mild Renal Impairment (N=8)	Moderate Renal Impairment (N=8)	Severe Renal Impairment (N=8)
N1, n	10, 10	8, 8	8, 6	8, 7
AUC _{inf} (ng.hr/mL)	14460 (20)	17910 (30)	27110 (27)	44040 (33)
AUC _{last} (ng.hr/mL)	14270 (20)	17770 (30)	26660 (21)	39420 (28)
C ₁₂ (ng/mL)	341.9 (35)	438.0 (30)	785.6 (33)	1213 (33)
C ₂₄ (ng/mL)	99.10 (35)	112.8 (55)	179.1 (108)	694.2 (42)
CL/F (L/hr)	6.913 (20)	5.581 (30)	3.689 (27)	2.270 (33)
C _{max} (ng/mL)	1600 (31)	2077 (29)	2210 (17)	2369 (38)
t _{1/2} (hr)	7.725 ± 1.8234	6.606 ± 1.5344	9.948 ± 3.4171	13.37 ± 3.3225
T _{max} (hr)	2.000 (1.00 - 4.00)	2.000 (1.00 - 3.00)	2.500 (1.00 - 6.00)	3.000 (1.00 - 6.05)
V _z /F (L)	74.95 (35)	51.95 (32)	50.34 (27)	42.73 (26)
Ae (mg)	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
Ae %	31.20 (45)	42.65 (23)	30.83 (56)	18.46 (50)
CL _r (L/hr)	2.180 (50)	2.395 (33)	1.154 (71)	0.4398 (73)

AUC_{inf} = area under the plasma concentration time curve from time zero to infinity; AUC_{last} = area under the plasma concentration time curve to the last measurable time point; C₁₂ = concentration at 12 hours; C₂₄ = concentration at 24 hours; CL/F = apparent oral clearance; CL_r = centred log ratio; C_{max} = maximum concentration; t_{1/2} = terminal elimination half life; T_{max} = time at maximum concentration; V_z/F = apparent volume of distribution.

N = Total number of participants in the cohort in the indicated population; N1 = Number of participants contributing to the summary statistics; n = Number of participants contributing to the summary statistics for t_{1/2}, AUC_{inf}, CL/F and V_z/F;

a. Geometric mean (geometric % coefficient of variation (CV)) for all: except Median (Range) for T_{max} and arithmetic mean ± standard deviation (SD) for t_{1/2}.

Table 1: Study C4671011 Descriptive summary of plasma and urine nirmatrelvir pharmacokinetic parameters (pharmacokinetic parameter analysis set). Source (22)

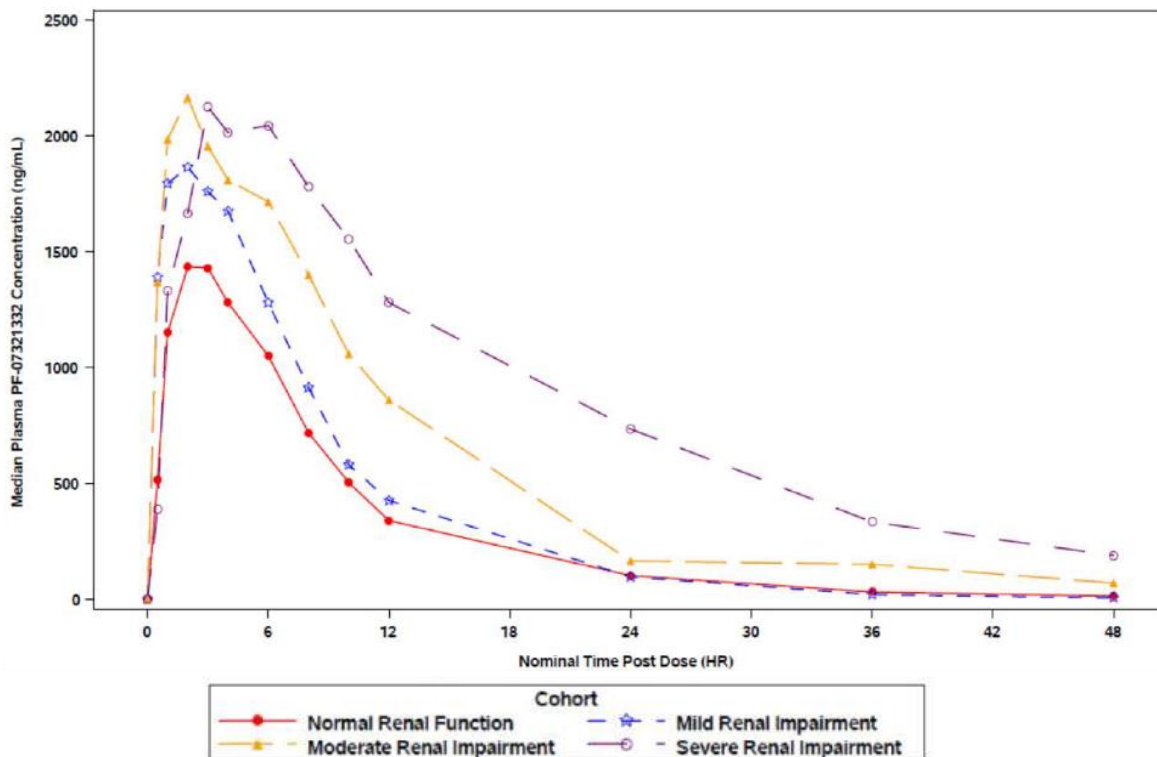


Figure 2: Study C4671011 Median plasma nirmatrelvir concentration time plot, following a single oral dose of nirmatrelvir/ritonavir, linear scale. HR = hour; PF-07321332 = drug development code for nirmatrelvir. The lower limit of quantification was 10 ng/mL.

Summary statistics were calculated by setting concentration values below the lower limit of qualification to zero. Source (22)

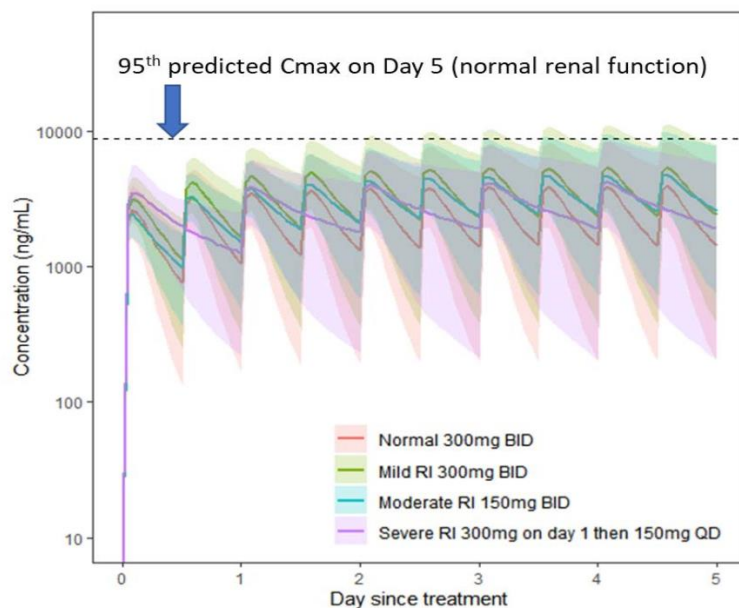
Paxlovid Adverse Effects

From animal data, no adverse effects were observed at 1000 mg/kg/day, which correspond to an exposure approximately 8 times higher than clinical exposures at the authorized human dose. Nirmatrelvir-related findings following repeat oral dosing in monkeys at up to 600 mg/kg/day were limited to emesis, increase in fibrinogen, as well as increases in ALT and AST levels. These findings completely reversed at the end of the 2-week recovery period. In the EPIC-HR trial, serious adverse events were lower with Paxlovid (1.6%) compared to placebo (6.6%). Adverse events reported by more than 1% of the participants were dysgeusia, nausea, vomiting, headache, diarrhea and fever. In study C 2/8 (25%) reported dysgeusia and dry mouth compared to none in the other arms with higher renal function. One patient did report several serious adverse events (SAEs), namely acute kidney injury, pulmonary edema, and pneumonia, which were likely related to COVID-19 infection rather than the medication. Overall, Paxlovid has a favorable safety profile, with no evidence of dose-dependent toxicity.

Rationale for Dosing of Paxlovid in CKD and Dialysis Patients

A single dose of nirmatrelvir 100 mg provided adequate concentration of drug to inhibit Mpro enzymatic activity at 24 hours, based on study C4671005 in non-dialysis CKD patients with GFR < 30. Similar concentrations would be seen in dialysis, and it is expected that there will be some clearance of nirmatrelvir with hemodialysis, given its molecular size, 70% protein binding and volume of distribution. The safety profile of nirmatrelvir is quite favorable, with few SAEs, with the animal data not indicative of a higher dose dependent toxicity. Nirmatrelvir is currently formulated as a 150 mg tablet and dosed at 300 mg with 100 mg ritonavir twice a day for patients with normal kidney function, and at 150 mgs with 100 mg ritonavir twice a day in those with eGFR 30-60. A dose of 300 mg (with 100 mg ritonavir) followed by 150 mg daily, administered after hemodialysis on days of dialysis is predicted to provide effective blood concentrations for enzyme inhibition (figure 3). Minimal drug accumulation is expected based on the short duration of therapy and single dose pharmacokinetics. A lower dose of 150 mg every 48 hours could be considered for patients less than 40 kgs.

Patients receiving peritoneal dialysis often have greater residual renal function compared to those receiving hemodialysis and may therefore have slightly higher endogenous clearance of nirmatrelvir. However, the dialytic removal with peritoneal dialysis will be lower compared with hemodialysis. Hence similar doses to those discussed above for hemodialysis are expected to achieve effective concentrations in these patients.



The color line and ribbon represent the median and 90% prediction interval respectively for each renal function category receiving the proposed dose

(Source: Reviewer's independent analysis)

Figure 3: From FDA guidance document, a reviewer's independent analysis based on modeling for achieved nirmatrelvir concentrations based on different kidney function Source (19)

Additional considerations of drug interactions are also important, since ritonavir is a potent CYP3A4 inhibitor. Commonly used drugs with important drug interactions in CKD and dialysis patients include direct acting oral anticoagulants, some statins, calcium channel blockers and alpha-adrenergic antagonists. These interactions however, are not a contraindication to therapy, and may be mitigated with support from clinicians and pharmacy and temporary suspension or dose reduction of these medications, depending on the clinical context (see table 3).

We suggest that patients with advanced CKD (eGFR < 30) and those on dialysis who contract COVID-19 be offered the low dose nirmatrelvir/ritonavir (Paxlovid) regimens. Since the current product monograph does not recommend the use of nirmatrelvir/ritonavir (Paxlovid) in these patients, this should be preceded by a discussion between the prescribing physician and the patient emphasizing that the potential benefits of the treatment substantially exceed the theoretical risks of toxicity.

Rationale for Dosing of Paxlovid in Kidney Transplant Recipients

In patients with a kidney transplant, drug-drug interactions are as much or more of a concern than the kidney function. The inhibition of drug metabolism due to ritonavir can result in extremely toxic levels (10-fold higher) of calcineurin inhibitors (CNIs), and prolonged half-life. To a lesser extent, levels of mycophenolic acid and sirolimus may also be affected (see table 3 for details). Hence even with eGFR > 30, CNIs must be held, and close monitoring of CNI levels is required even after the therapy is complete to decide on timing of restarting. Given this interaction, the use of nirmatrelvir/ritonavir (Paxlovid) in kidney transplant recipients with eGFR < 30 should be considered very cautiously. Though not discussed separately, similar considerations would also apply to patients with CKD due to glomerulonephritis receiving these immunosuppressive drugs.

Summary

Patients with advanced CKD (stages 4 and 5) and patients on dialysis who contract COVID-19, are at markedly higher risk of developing severe symptomatic disease and of dying. They have a lower and less sustained immune response to vaccination and need access to potentially lifesaving medications. Nirmatrelvir/ritonavir (Paxlovid) is a very effective therapy in the early management of high risk patients with symptomatic disease; however it is renally cleared and is currently not recommended for those with GFR < 30. On the basis of available data and pharmacological principles, an adjusted dose given at a lower frequency is proposed for use in people with GFR < 30 and in those on dialysis after appropriate evaluation and discussion of risks and benefits with the patient.

Current Recommendation		Proposed Dosing guidance	
<i>Kidney Function</i>	<i>Dosing schedule</i>	<i>Kidney Function</i>	<i>Dosing schedule</i>
GFR > 60	300 mg nirmatrelvir + 100 mg ritonavir both twice a day for 5 days	GFR > 60	300 mg nirmatrelvir + 100 mg ritonavir both twice a day for 5 days
GFR 30 - 60	150 mg nirmatrelvir + 100 mg ritonavir both twice a day for 5 days	GFR 30 - 60	150 mg nirmatrelvir + 100 mg ritonavir both twice a day for 5 days
GFR < 30	Do not use	GFR < 30	300 mg nirmatrelvir + 100 mg ritonavir both on day 1 then 150 mg nirmatrelvir + 100 mg ritonavir once a day for 4 more days
Dialysis	Do not use	Dialysis	300 mg nirmatrelvir + 100 mg ritonavir both on day 1 then 150 mg nirmatrelvir + 100 mg ritonavir once a day for 4 more days, to be dosed after dialysis ¹

Table 2: Proposed dosing guidance for Nirmatrelvir/Ritonavir in Chronic Kidney Disease

¹The dose should be reduced to 150 mg nirmatrelvir + 100 mg ritonavir on day 1 then 150 mg nirmatrelvir + 100 mg ritonavir every 48 hours for 2 more doses, to be given after dialysis if patient weight less than 40 kg

Drug name/class	Effect of Nirmatrelvir/Ritonavir	Possible action/mitigation
Calcium channel blockers	Metabolized by CYP3A4. Nirmatrelvir/ritonavir is predicted to increase exposure	Monitor blood pressure (BP); reduce dose or hold if necessary
Statins	Some statins (atorvastatin, simvastatin, lovastatin) are metabolized by CYP3A4 and concentrations are expected to increase due to inhibition of CYP3A4 by nirmatrelvir/ritonavir.	Hold statins for duration of nirmatrelvir/ritonavir therapy
Warfarin	Mixed effect; decreased R-warfarin levels may lead to reduced anticoagulation	Monitor international normalized ratio (INR) while on therapy
Direct Oral Anticoagulants (DOACs)	Concentrations of apixaban/rivaroxaban are expected to increase due to CYP3A4 and P-gp inhibition	Hold or reduce dose of DOACs during active treatment (5 days) based on indication
Clopidogrel	Clopidogrel is a prodrug and is converted to its active metabolite mostly via CYP 2C19, and CYPs 3A4, 2B6, and 1A2. May reduce the effect of clopidogrel (minor effect)	Avoid first 6 weeks – 3 months after stent placement; In these patients, consider use of prasugrel or alternate COVID-19 therapeutics
Hydromorphone	Hydromorphone is eliminated via glucuronidation, mainly by UGT2B7. Ritonavir induces glucuronidation and may result in reduced analgesic effect.	Warn of reduced analgesic effect, temporarily increase dose as needed
ARBs	Some ARBs ¹ are metabolized by via glucuronidation and oxidation (mainly CYP2C9). Nirmatrelvir/ritonavir could potentially decrease irbesartan exposure.	Drug interaction effect takes several days; no a priori dosage adjustment is recommended.
Indapamide	Indapamide is extensively metabolized by CYP450. Nirmatrelvir/ritonavir could potentially increase indapamide concentrations.	Monitor BP; reduce dose or hold if necessary
Labetolol	Labetalol is mainly glucuronidated by UGTs 1A1 and 2B7. Coadministration could potentially decrease labetalol exposure due to induction of UGT2B7 by ritonavir.	Drug interaction effect takes several days; no a priori dosage adjustment is recommended. Monitor BP; reduce dose or hold if necessary
Mycophenolate mofetil and mycophenolic acid	Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid (MPA). MPA undergoes glucuronidation; coadministration of inducers or inhibitors of glucuronidation, such as ritonavir, could alter mycophenolate levels.	The effect on MMF/MPA is expected to be minor over 5 days; additionally, these are often held during COVID-19 infection in transplant recipients.

Drug name/class	Effect of Nirmatrelvir/Ritonavir	Possible action/mitigation
Calcineurin Inhibitors (CNIs)	CNIs are metabolized by CYP3A4 and tacrolimus is also a substrate of P-gp. Coadministration with a ritonavir-boosted HIV protease inhibitor has been reported to profoundly increase CNI concentrations which rapidly reach toxic levels.	Hold CNIs; monitor levels and restart while monitoring levels after nirmatrelvir/ritonavir course completed ² .
Sirolimus	Coadministration may increase in sirolimus exposure > 10 fold is predicted in presence of nirmatrelvir/ritonavir.	Hold sirolimus; monitor levels and restart while monitoring levels after nirmatrelvir/ritonavir course completed ² .

Table 3: Important drug interactions for nirmatrelvir/ritonavir and commonly used drugs in kidney patients. This list is not exhaustive. For more consult <https://www.covid19-druginteractions.org/checker>

¹ *Not all ARBs may have this interaction, this has been reported for losartan, candesartan and irbesartan*

² *It is not clear when CNIs could be safely initiated as the enzyme inhibition may persist for a few days; monitor CNI levels closely to decide when these can be re-initiated.*

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APPENDIX A: Supplemental Guidance on Nirmatrelvir/Ritonavir Use in Patients With Severe Chronic Kidney Disease and Patients Dialysis with COVID-19 (2022)

The COVID-19 Supplemental Clinical Guidance for Patients with Chronic Kidney Disease on Nirmatrelvir/Ritonavir (Paxlovid) Use in Patients with Severe Chronic Kidney Disease and Patients on Dialysis with COVID-19 was developed by:

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