



# Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD

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## Introduction

As of December 2021, 18.2 million have died globally from coronavirus disease 2019 (COVID-19) due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and millions more suffer from longer-term consequences (1). Morbidity and mortality from COVID-19 is higher in patients who are immunocompromised, including those with advanced CKD (stages 4 and 5) and those with kidney failure. Even after propensity-score matching for the higher comorbid disease burden, a higher risk for hospitalization (risk ratio, 1.6; 95% confidence interval, 1.3 to 1.9) and mortality (risk ratio, 1.3; 95% confidence interval, 1.3 to 2.0) in severe CKD was reported (2). Although case fatality rates for patients on dialysis have fallen in recent waves and with vaccination, they remain markedly higher than those in the general population (3).

While vaccines for COVID-19, particularly the mRNA vaccines, have reduced the severity and transmissibility of COVID-19, their effectiveness is attenuated in dialysis and transplant populations. Estimates of early antibody response in patients on dialysis were 89% relative to healthy controls, conferring incomplete protection that wanes over time (4). For kidney transplant recipients, antibody response was only 35% with small increments to repeat vaccination (4,5). For newer variants (such as omicron), higher antibody titers are required for viral neutralization, and vaccination alone will not provide sufficient protection against infection and severe outcomes in patients on dialysis and transplant patients (6).

Patients with advanced CKD, patients receiving dialysis, and kidney transplant recipients are frequently excluded from clinical trials evaluating new drugs. This phenomenon, coined “renalism,” recurred with COVID-19. A review of trial registries reported that 218 of 484 COVID-19 trials (45%) excluded patients with CKD (7). Studies evaluating nirmatrelvir/ritonavir have similarly excluded patients with advanced CKD, despite the relevance to this population. Nirmatrelvir/ritonavir, however, has pharmacology and toxicity data that can provide a basis for its use in advanced CKD (8).

## Nirmatrelvir/Ritonavir Efficacy

Nirmatrelvir is an orally administered antiviral agent inhibiting the SARS-CoV-2 3-chymotrypsin-like

cysteine protease enzyme (Mpro), also referred to as 3C-like protease or nsp5 protease, which renders the protein incapable of processing polyprotein precursors and prevents viral replication. The Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients (EPIC-HR) trial evaluated the safety and efficacy of nirmatrelvir plus ritonavir in nonhospitalized adults with mild-to-moderate COVID-19 at high risk for progression to severe disease (9). Nirmatrelvir/ritonavir was initiated at a dose of 300 mg of nirmatrelvir plus 100 mg of ritonavir every 12 hours for 5 days within 5 days of symptom onset. The incidence of COVID-19–related hospitalization or death by day 28 was 89% lower in the nirmatrelvir group than in the placebo group. There were 13 deaths, all in the placebo group. On this basis, nirmatrelvir/ritonavir 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. Patients with advanced CKD are at such high risk, but were excluded from this trial, and there are theoretical concerns about drug accumulation and safety in these patients. For these reasons, the product monograph states that it is “not recommended” for those with an eGFR of <30 ml/min per 1.73 m<sup>2</sup>.

## Pharmacology of Nirmatrelvir/Ritonavir

Nirmatrelvir is coadministered with a low dose (100 mg) of ritonavir, which acts as a pharmacokinetic enhancer. Ritonavir is a CYP3A4 inhibitor and enhances nirmatrelvir’s bioavailability, allowing required therapeutic concentrations to be achieved. In preclinical studies, the concentration threshold that correlated with efficacy was 181 nM (292 ng/ml) (8). Hence, the desired dose of nirmatrelvir is that which maintains a trough level above this, and led to the 300-mg dose chosen in the EPIC-HR trial. Nirmatrelvir has a molecular mass of 499.5 D, 35% is approximately excreted by the kidneys, and it is 70% protein bound. Ritonavir is mostly hepatically metabolized and is 99% protein bound. Thus, nirmatrelvir is expected to accumulate with decreasing kidney function. In a phase 2 study (C4671005) of eight patients with serious kidney

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<b>Patient population</b>	Unvaccinated or vaccinated CKD, dialysis, transplant recipients in the outpatient setting, with COVID-19 Presence of symptoms, with therapy initiation possible within 5 days of symptom onset
<b>Dose in CKD, eGFR &lt;30, not on dialysis</b>	300 mg nirmatrelvir + 100 mg ritonavir both on day 1 Then 150 mg nirmatrelvir + 100 mg ritonavir once a day for 4 more days
<b>Dose in dialysis</b>	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 <sup>a</sup>
<b>Important drug interactions<sup>b</sup></b>	Direct-acting oral anticoagulants (DOACs), warfarin, statins, calcium channel blockers (CCBs), alpha-adrenergic antagonists, hydromorphone, trazodone, calcineurin inhibitors, and anticonvulsants Pharmacist review advised
<b>Transplant considerations</b>	Hold or decrease calcineurin inhibitors for duration of nirmatrelvir/ritonavir therapy Restart at 48 to 72 hours post course completion at a lower dose Monitor drug levels closely to guide further adjustment
<b>Adverse effects</b>	Adverse events reported by more than 1% of the participants were dysgeusia, nausea, vomiting, headache, diarrhea, and fever. No dose dependent toxicity reported Specific adverse effects in CKD population are not yet known
<b>Further considerations</b>	The actual efficacy of nirmatrelvir/ritonavir in CKD, and the interaction with vaccination status and emerging variants, is yet unknown These dosing suggestions are based on pharmacology and should be reviewed once more data become available A discussion between the prescribing physician and the patient about the potential risks and benefits of the treatment, including alternative therapies, is essential prior to starting nirmatrelvir/ritonavir in advanced CKD

<sup>a</sup> The 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 is less than 40 kg.

<sup>b</sup> This list is not exhaustive and complete. Some agents (e.g., statins, in particular atorvastatin, simvastatin, lovastatin) could be held for the 5 days, while others (e.g., DOACs or CCBs) could be held or dose reduced in half as clinically appropriate; for others (hydromorphone), the analgesic effect may be reduced due to less conversion to active form of drug. See <https://www.covid19-druginteractions.org/checker> for more details.

#### Box 1. | Dosing guidance for nirmatrelvir/ritonavir in advanced CKD.

impairment (eGFR <30 ml/min per 1.73 m<sup>2</sup>, not on dialysis), the mean concentration at 24 hours was 694.2 ng/ml after a single dose of 100 mg nirmatrelvir (more than two times the required 292 ng/ml).

#### Adverse Effects of Nirmatrelvir/Ritonavir

From animal data, no adverse effects were observed at 1000 mg/kg per day, which correspond to an exposure approximately eight times higher than the recommended human dose (8). Nirmatrelvir-related adverse events after repeated dosing in monkeys at up to 600 mg/kg per day were limited to emesis, increased fibrinogen, and increased transaminases, which completely reversed within 2 weeks. In the EPIC-HR trial, serious adverse events were lower with nirmatrelvir/ritonavir (2%) compared with placebo (7%) (9). Adverse events reported by >1% of the participants were dysgeusia, nausea, vomiting, headache, diarrhea, and fever. In the phase 2 study with eGFR <30 ml/min per 1.73 m<sup>2</sup>, two of eight patients (25%) reported dysgeusia and dry mouth compared with none in the other arms with higher kidney function (8). Overall, nirmatrelvir/ritonavir

has a favorable safety profile, with no evidence of dose-dependent toxicity.

#### Rationale for Dosing in Patients with CKD and Those on Dialysis

A single dose of 100 mg nirmatrelvir inhibited Mpro enzymatic activity at 24 hours in patients with an eGFR of <30 ml/min per 1.73 m<sup>2</sup>. Hemodialysis will clear a clinically insignificant amount of nirmatrelvir, on the basis of what is known about its molecular size, protein binding, and volume of distribution. The safety profile of nirmatrelvir is favorable, with few serious adverse effects, and the animal data are not indicative of dose-dependent toxicity. Nirmatrelvir is currently formulated as a 150-mg tablet and dosed at 300 mg along with 100 mg ritonavir twice a day for patients with normal kidney function, and at 150 mg with 100 mg ritonavir twice a day in those with an eGFR of 30–60 ml/min per 1.73 m<sup>2</sup>. A dose of 300 mg nirmatrelvir (with 100 mg ritonavir) on day 1, followed by 150 mg nirmatrelvir (with 100 mg ritonavir) administered daily, given after hemodialysis on dialysis days, should provide

effective blood concentrations for enzyme inhibition (see Box 1). Minimal drug accumulation is expected on the basis of the short duration of therapy and single-dose pharmacokinetics. A lower dose of 150 mg every 48 hours could be considered for patients weighing <40 kg.

Drug interactions are important because ritonavir is a potent CYP3A4 inhibitor and an inducer of other cytochrome p450 enzymes. Commonly used drugs in patients with CKD with important drug interactions include statins, calcium channel blockers, and direct-acting oral anticoagulants (see Box 1). These interactions are not always a contraindication to therapy and are mitigated by temporarily suspending or reducing the doses of CYP3A4-metabolized drugs. Support from pharmacists will help identify appropriate, temporary changes in treatments.

A small case series using this modified lower dose of nirmatrelvir/ritonavir in 15 patients on dialysis who had COVID-19 reported rapid symptom resolution, with no safety signal, and highlighted the need to review drug interactions that were common in this population (P.A. Brown *et al.*, unpublished observations).

### Rationale for Dosing in Kidney Transplant Recipients

In patients with a kidney transplant, drug-drug interactions are an additional concern. The inhibition of drug metabolism due to ritonavir can result in extremely toxic levels (ten-fold higher) of calcineurin inhibitors (CNIs) and prolonged  $t_{1/2}$ . To a lesser extent, levels of mycophenolic acid and sirolimus may also be affected. Even with an eGFR of >30 ml/min per 1.73 m<sup>2</sup>, CNIs must be held or decreased, and close monitoring of CNI levels is required after therapy is complete to also avoid low CNI levels. The American Society of Transplantation also provided guidance on use of nirmatrelvir/ritonavir in kidney transplant recipients with an eGFR of >30 ml/min per 1.73 m<sup>2</sup> (see 10). Use in patients with an eGFR of <30 ml/min per 1.73 m<sup>2</sup> should be considered cautiously in consultation with experienced teams, including infectious disease and pharmacy. Although not discussed separately here, similar considerations should also apply to patients with CKD due to glomerulonephritis receiving these immunosuppressive drugs.

### Conclusion

The use of nirmatrelvir/ritonavir has been shown to be particularly effective in disarming SARS-CoV-2, especially in high-risk populations. Despite a relative dearth of data for the use and dosing of nirmatrelvir/ritonavir in patients with advanced CKD and those with a kidney transplant, these patients are at particularly high risk for COVID-19 morbidity and mortality and should not be excluded from therapy simply because of lack of data. We suggest patients with advanced CKD (eGFR <30 ml/min per 1.73 m<sup>2</sup>) and those receiving dialysis who contract COVID-19 be offered the low-dose nirmatrelvir/ritonavir regimens. This should be preceded by a discussion between the prescribing physician and the patient about the potential risks and benefits of the treatment, including alternative therapies. Special care must be taken with patients receiving immunosuppressive

therapies, especially those with a kidney transplant, because drug-drug interactions can seriously affect the  $t_{1/2}$ s of commonly used antirejection strategies.

### Disclosures

C. Argyropoulos reports receiving research funding from Akbia and Alkahest, having consultancy agreements with Baxter, Bayer, Otsuka, and Quanta, and serving in an advisory or leadership role for Baxter Healthcare, Bayer, Health Services Advisory Group, and Quanta. P. Blake reports serving on the editorial board of *American Journal of Nephrology*, receiving honoraria from Baxter Global, and serving as medical director of Ontario Renal Network (this is a paid role). K.S. Brimble reports serving as provincial lead of Ontario Renal Network. P.A. Brown reports having consultancy agreements with Amgen Canada, AstraZeneca Canada, and Otsuka Canada, receiving honoraria from AstraZeneca Canada and Otsuka Canada, and receiving research funding from Otsuka Canada. Z. Chagla reports serving on a speakers bureau for Gilead and Pfizer, receiving research funding from Gilead and Roche, and having consultancy agreements with Pfizer. S. Hiremath receives research salary support from the Department of Medicine, University of Ottawa; reports serving on the editorial boards of *American Journal of Hypertension*, *American Journal of Kidney Disease*, and *Canadian Journal of Cardiology*; and serving on the board of directors for NephJC (not-for-profit educational entity). D. Juurlink reports receiving payment for lectures and medicolegal opinions regarding the safety and effectiveness of analgesics, including opioids, and serving as a member of Physicians for Responsible Opioid Prescribing (a volunteer organization that seeks to reduce opioid-related harm through more cautious prescribing practices). M. McGuinty reports receiving research funding from VBI. All remaining authors have nothing to disclose.

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P. Blake, R. Cooper, S. Hiremath, S. Hoar, M. McGuinty, D. Treleaven, and M. Walsh conceptualized the study; S. Hiremath provided supervision; P. Blake, P.A. Brown, S. Hiremath, D. Juurlink, and M. McGuinty wrote the original draft; and C. Argyropoulos, P. Blake, K.S. Brimble, P.A. Brown, Z. Chagla, R. Cooper, S. Hiremath, S. Hoar, D. Juurlink, M. McGuinty, D. Treleaven, M. Walsh, and A. Yeung reviewed and edited the manuscript.

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