

Drug Interactions With a Short Course of Nirmatrelvir and Ritonavir: Prescribers and Patients Beware

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The COVID-19 pandemic has taught us to expect the unexpected. Each advance has been met with a new setback, such as vaccine hesitancy, long COVID, and vaccine-tolerant mutations. Since the start of the pandemic, oral outpatient treatment has been a goal, even with little or no supporting clinical data (eg, hydroxychloroquine, ivermectin). Thus, there is great public interest regarding the recent Emergency Use Authorizations granted by the US Food and Drug Administration for 2 oral products for the treatment of mild to moderate COVID-19, Pfizer's combination product, composed of nirmatrelvir 250 mg and ritonavir 100 mg (N + R),^{1,2} and Merck's molnupiravir³—both administered over 5 days. While N + R appears to have greater efficacy than molnupiravir, there has been little discussion regarding the unintended consequences of widespread distribution of a ritonavir-containing product.

Ritonavir was initially developed as a viral protease inhibitor intended for the treatment of HIV infection. However, ritonavir was coincidentally found to be an inhibitor of a number of human cytochrome P450 (CYP) enzymes^{4,5} (Table 1) — in particular, the CYP3A enzymes, of which ritonavir is a highly potent inhibitor.^{4,5} CYP3A is present in human liver as well as gastrointestinal enteric mucosal cells, and CYP3A (collectively referring to CYP3A4 and CYP3A5 isoforms) is the most important and abundant human drug-metabolizing enzyme.⁶ Ritonavir is now recognized as the most potent of the clinically available CYP3A inhibitors.^{7,8} Today, ritonavir is primarily administered for its pharmacokinetic “boosting” effect, not for its antiviral properties.⁹ Ritonavir primarily inhibits first-pass metabolism by the small intestine and liver, thereby increasing plasma concentrations of drugs that are partly or entirely metabolized by CYP3A.^{7,8} In addition, it is an inducer and inhibitor of P-glycoprotein.^{10,11} This boosting strategy is used in combination with multiple antiviral products for the

treatment of HIV or hepatitis C infection. Likewise, the coformulation of N + R enables maintenance of effective antiviral concentrations of nirmatrelvir over a full 24-hour period with twice-daily dosing.¹

The Emergency Use Authorization is based on the results of a 3000-patient randomized placebo-controlled trial (EPIC-HR; NCT04960202), which demonstrated an 89% reduction in the rate of hospitalization or death with a 5-day course.² We do not dispute these results, but note that the trial was conducted in a population that may not be fully representative of patients likely to be diagnosed with symptomatic COVID-19. For example, the trial excluded patients on any medication that is highly dependent on CYP3A for clearance, as well as those who had been previously vaccinated. Since ≈60% of all medications are partially or completely metabolized by CYP3A,⁶ many patients on chronic medications for conditions that predispose to severe COVID-19 infection (eg, hypertension, obesity, cancer, respiratory illness, diabetes) were excluded.

While the reports of the EPIC-HR trial suggest no significant safety concerns, which does not imply that N + R is safe in a broader population, particularly

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Table 1. In Vitro IC₅₀ Values for Ritonavir as Inhibitor of Activity of Human CYP Isoforms

CYP isoform	Index Substrate	Ritonavir IC ₅₀ (μM)
CYP1A2	Phenacetin	>150
CYP2B6	Bupropion	16.2
CYP2C9	Flurbiprofen	12.6
CYP2C19	S-mephenytoin	18.0
CYP2D6	Dextromethorphan	6.6
CYP2E1	Chlorzoxazone	>250
CYP3A	Triazolam	0.015

CYP, cytochrome P450; IC₅₀, 50% inhibitory concentration. Conversion of molar to mass units for ritonavir concentration: 1 μM = 0.72 μg/mL. Data entries adapted in part from references 4 and 5.

among patients who may have low health literacy, psychiatric illnesses, or substance abuse disorders. Appropriately, there are clear warnings in the Pfizer Fact Sheet for Health Providers,¹ with a table of >50 potential concomitant drugs requiring potential dose adjustment (and additional recommendations have been published by NIH¹²). The Fact Sheet also indicates that N + R is contraindicated in combination with 27 other drugs, as well as 1 herbal product (St. John's wort). Notably, the Fact Sheet does not include any warnings regarding the risks of taking N + R in combination with the many illicit drugs that are potentiated by ritonavir. The Fact Sheet also states, "Drugs listed in Table 1 are a guide and not considered a comprehensive list of all possible drugs that may interact with PAXLOVID. The health care provider should consult appropriate references for comprehensive information."

Despite extensive previous experience with ritonavir boosting for chronic infections, there is little or no prior experience in treating an acute illness with a drug product that incorporates such boosting. When prescribed for treating HIV, ritonavir is administered chronically, whereas for hepatitis C, ritonavir is generally administered for 8 weeks. The opportunity to anticipate and prevent drug interactions is much greater with elective initiation of chronic therapy as opposed to the urgent institution of treatment for COVID-19. Furthermore, patients seeking emergency or urgent care for COVID-19 may not recall all of their current medications, and may also receive prescription medications from more than 1 pharmacy. For example, patients on oral anticancer drugs (eg, see Table 1 of Fact Sheet) usually receive drugs from a specialty pharmacy.

Patients may also fail to disclose all medications they are receiving due to fear of being stigmatized (eg, erectile dysfunction, major psychiatric illness). Furthermore, patients may not read or comply with the patient information for a new drug that is only to be administered for a short course, especially if they are fearful, and feel they have no alternative.

Providers may also lack the time or understanding of drug metabolism and drug interactions to optimally counsel patients. While pharmacists could play an important role in this context, patients often decline to receive counseling from a pharmacist when filling a prescription. And in some areas, patients may receive N + R by home delivery, a less-than-ideal setting for patients to receive appropriate counseling regarding concomitant medications, although telephone counseling would generally be available. Furthermore, there would be no counseling available for desperate patients who might obtain N + R from a friend or relative who did not complete their prescribed 5-day course.

But even assuming that the patient provides a complete medication history to the provider, there will be uncertainty with respect to the optimal dosage or dosing regimen for many CYP3A substrates, since there are currently no reliable studies using a 5-day course of ritonavir. While a provider may be motivated to reduce or hold the dosage of ≥1 other drugs, the exact dose reduction may be unknown. It may also be difficult to reduce the dosage of some drugs, if that would require obtaining a new prescription for a decreased strength (eg, many oral anticancer agents). Furthermore, a provider seeing a patient in an emergency or urgent care setting may be uncomfortable recommending discontinuation or dosage modification for a drug prescribed by another provider.

The duration of the effect of ritonavir boosting after discontinuation of a 5-day course of 100 mg twice daily is also of concern. Ritonavir inhibits CYP3A via both reversible and irreversible mechanisms, and thus recovery from inhibition after ritonavir is discontinued is dependent in part on regeneration of CYP3A4. As such, the effects will persist, at least partially, for several days after stopping ritonavir.¹³ Prescribers will have to make difficult choices in the absence of data, where there will be risks of both overdosing and underdosing, resulting in toxicity and treatment failure, respectively.

While we think it is important to publicize the risks of this important new drug product, we do not have any clear short-term solutions. There should be consideration of temporarily discontinuing all interacting drugs, although the safety of doing so needs to be considered carefully for each patient, and for each interacting drug. For some drugs, a dose adjustment should be considered rather than temporary discontinuation. A number of resources are available on the Internet, but the complexities of making a temporary adjustment of the dose of a narrow therapeutic index drug are likely to pose great challenges for most prescribers. The NIH guidelines note that "clinicians should consider consulting an expert (eg, a pharmacist, HIV specialist, and/or the patient's specialist provider[s], if applicable), ..." although the average patient will not have access to an

HIV specialist, and subspecialists (eg, oncologists) may not have sufficient expertise in clinical pharmacology to make confident recommendations. It is also unclear to us as to the appropriate recommendations for any drug with a narrow therapeutic index, as the duration of ritonavir's inhibitor effects is somewhat uncertain, given the novelty of a 5-day ritonavir course.

We hope that the Food and Drug Administration requires a sufficient set of drug interaction studies, including careful evaluation of the required washout period after completion of the 5-day course. Such studies should evaluate multiple different representative CYP3A substrates, as the required washout period may be substrate specific. Generating these data will aid providers in the longer term.

In the interim, providers who choose to prescribe N + R will need to fully understand the implications of initiating a 5-day course of ritonavir. And patients will need to fully understand the risks of taking any drugs (whether or not prescribed) in this context. However, given that many patients who will be seeking N + R have already declined medical recommendations for vaccination, it is likely that some patients will also choose to ignore the warnings regarding the risks of certain concomitant drugs, which include ivermectin,¹⁴ as well as many recreational drugs.¹⁵

Conflicts of Interest

M.J.R. reports personal fees from Apotex, Aptevco, Arvinas Operations, Ayala Pharma, bluebird bio, Credit Suisse, Eagle Pharmaceuticals, EMD Serono, Emerson Lake Safety, EQRx, Sandoz, Actavis, Aurobindo, Dr. Reddy's Laboratories, Mylan, Hetero Labs, Breckenridge Pharmaceutical, Teva, Mereo, T3 Pharmaceuticals, Shilpa, Accord, MSN, Natco, Pneuma Respiratory, Genentech, and Virology Education V.V., outside the submitted work; a pending patent application for low-dose tocilizumab for COVID-19; and leadership roles (director and treasurer) in the Optimal Cancer Care Alliance. D.J.G. has served as a scientific advisor to Emerald Lake Safety LLC, Newport Beach, CA.

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