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► To cite this version:

Florian Lemaitre, Matthieu Grégoire, Caroline Monchaud, Stéphane Bouchet, Béatrice Saint-Salvi, et al.. Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT). *Therapies*, 2022, 77 (5), pp.509-521. 10.1016/j.therap.2022.03.005 . hal-03690324

HAL Id: hal-03690324

<https://hal.science/hal-03690324>

Submitted on 16 Jun 2022

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THERAPIES

HEADING: Therapeutic drug monitoring//Pharmacokinetics

Management of drug-drug interactions with nirmatrelvir/ritonavir in patients treated for Covid-19: Guidelines from the French Society of Pharmacology and Therapeutics (SFPT)

Guidelines for nirmatrelvir/ritonavir DDI

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Received 14 March 2022; Accepted 17 March 2022

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Summary

Objectives.- Nirmatrelvir in association with ritonavir (PAXLOVID™, Pfizer) is an antiviral agent targeting the 3-chymotrypsin-like cysteine protease enzyme (3C-like protease or Mpro) which is a key enzyme of the viral cycle of the SARS-CoV-2. This combination with a well-known pharmacokinetic enhancer leads to a high risk for drug-drug interactions in a polymedicated elected population for treatment. The aim of this work was to provide recommendations on behalf of the national French society of pharmacology (French Society of Pharmacology and Therapeutics; SFPT), by suggesting optimal and pragmatic therapeutic strategies if nirmatrelvir/ritonavir is to be given together with drugs commonly used, in order to ensure secured physicians' prescription.

Methods.- Six clinical pharmacologists search the scientific literature to provide a first draft of recommendations. Thereafter, twelve other clinical pharmacologists verified the recommendations and proposed modifications. The final draft was then validated by all 18 participants.

Results.- Five distinct recommendations were issued: i) contra-indications, ii) " PAXLOVID™ not recommended with the comedication", iii) " PAXLOVID™ possible whether the comedication is discontinued", iv) "PAXLOVID™ possible only after an expert advice" and v) " PAXLOVID™ possible without modification of the associated treatment". The final document comprises recommendations for 171 drugs/therapeutic classes aiming to secure prescription. In complex situations, clinicians are advised to contact their pharmacology department to obtain specific recommendations on the management of drug-drug interactions with nirmatrelvir/ritonavir.

Conclusion.- These recommendations intend to be a help for clinicians willing to prescribe nirmatrelvir/ritonavir and to prevent drug-drug interactions leading to adverse drug reactions or loss of efficacy. They constitute a guideline for primary care situations. Of course, some complex situations may require expert advices and here, again, clinical pharmacologists are at the forefront in providing therapeutic advice.

KEYWORDS

Paxlovid; Antiviral; Ritonavir; Drug monitoring; Pharmacokinetics; Pharmacodynamics

Abbreviations

ANSM: Agence nationale de sécurité des médicaments et des produits de santé

BCRP: breast cancer resistance protein

COVID-19: severe coronavirus disease 2019

CYP3A4: cytochrome P450 3A4 isoenzyme

DDI: drug-drug interactions

Pgp: P-glycoprotein

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SFPT: French Society of Pharmacology and Therapeutics

SmPC: summary of products characteristics

UGTs: UDP-glucuronyl transferases

Introduction

Up to recently, no antiviral treatment was available for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, particularly during the early phase of infection (i.e the viremic phase) in order to prevent the progression to severe pneumonia (i.e the inflammatory phase). Nirmatrelvir in association with ritonavir (PAXLOVID™, Pfizer) is an antiviral agent targeting the 3-chymotrypsin-like cysteine protease enzyme (3C-like protease or M^{pro}) which is a key enzyme of the viral cycle of the SARS-CoV-2 [1]. The drug pharmacological mechanism prevents the 11 cleavages performed by M^{pro} on the polyprotein produced by the virus and then blocks its replication cycle. Nirmatrelvir has shown a good efficacy in preclinical models (cellular human bronchial epithelial cells Calu-3 and in murine models) with effective concentrations achievable in patients [2,3]. In a randomized controlled trial including symptomatic, unvaccinated, non-hospitalized adults at high risk for progression to severe coronavirus disease 2019 (COVID-19), nirmatrelvir reduced the incidence of COVID-19 related hospitalization or death by 89.1% at day-28. Notably, there was no death in the experimental arm while 13 patients died in the placebo arm [4]. Nirmatrelvir appears, therefore, as a first line option for the treatment of at-risk patients of severe COVID-19 such as elderly patients and those with chronic disease. However, as already observed with HIV-protease inhibitors, nirmatrelvir displays a short half-life, which could result in suboptimal drug exposure and difficulties in achieving efficacy threshold. Indeed, nirmatrelvir is also a substrate of cytochrome P450 3A4 isoenzyme (CYP3A4) and is extensively metabolized through this pathway, which contributes to the important inter-individual pharmacokinetic variability. To circumvent this limitation, nirmatrelvir is combined with ritonavir, a well-known pharmacokinetic enhancer for its potent CYP3A4 inhibiting properties. The approved drug dosage is 300 mg of nirmatrelvir (in two 150 mg tablets) to be administered in combination with ritonavir 100 mg twice daily within 3 to 5 days following the first COVID-19 symptoms and during five consecutive days.

The main concern in case of a broad use of nirmatrelvir is the impact of ritonavir on the clearance of numerous co-administered drugs, which can result in major drug-drug interactions

(DDI) leading to potential adverse drug reactions [5]. While numerous studies on ritonavir combined with HIV protease inhibitors are available for, data regarding DDI with nirmatrelvir/ritonavir association are scarce. In this context, the expert opinion of clinical pharmacologists is crucial for a safe use of this drug, which is expected to be prescribed by general practitioners to the at-risk, polymedicated patients.

The aim of this work was to provide recommendations on behalf of the national French society of pharmacology (French Society of Pharmacology and Therapeutics; SFPT), by suggesting optimal and pragmatic therapeutic strategies if nirmatrelvir/ritonavir is to be given together with drugs commonly used, in order to ensure secured physicians' prescription.

Methods

Six clinical pharmacologists, called in the paper the specialists in clinical pharmacology, were in charge of analyzing documents related to potential DDI for drugs expected to be combined with nirmatrelvir/ritonavir in patients. These specialists in clinical pharmacology reviewed the scientific literature on DDI studies between substrates and ritonavir or, whether no study was available with ritonavir, with ketoconazole, an equipotent CYP3A4 inhibitor. These documents were extracted from the Medline database, the summary of products characteristics (SmPC) of the various drugs of interest (see references) and the national handbook for DDI (*Thesaurus des interactions médicamenteuses*) edited by the French national regulatory agency (Agence Nationale de Sécurité du Médicament, ANSM) [6]. The SmPC of the drug PAXLOVID™ was also used to provide recommendations [7]. The specialists in clinical pharmacology based their recommendations on inhibitory and inducing properties of ritonavir depending on the metabolic and safety profile of the target drugs. Five situations were identified, for which the specialists in clinical pharmacology's recommendations were formulated as follows: i) contra-indications, which was strictly reported in the document whenever mentioned in the PAXLOVID™ SmPC or in the national handbook for DDI, even if some of them may have been challenged by recent reassuring data, ii) "PAXLOVID™ not recommended with the comedication", iii) "PAXLOVID™ possible whether the comedication is discontinued", iv) "PAXLOVID™ possible only after an expert advice" and v) "PAXLOVID™ possible without modification of the associated treatment".

After finalizing a first draft, these recommendations were submitted to a panel of 12 other clinical pharmacologists, namely the proofreaders, who verified them and proposed modifications. The final draft was then validated by all 18 participants.

Results

As already stated, the specialists in clinical pharmacology identified several situations for DDI with nirmatrelvir/ritonavir. The most frequent situations were: co-administration of drugs which are not substrates of CYP, or those for which the metabolic pathway was minimally affected by ritonavir, and those with large therapeutic index. For these drugs no major adverse drug reaction is expected during the 5-day nirmatrelvir/ritonavir treatment course, therefore the recommendation was: "PAXLOVID™ possible without modification of the associated treatment". In the case of drugs contra-indicated in the SmPC of PAXLOVID™ or in the French national handbook for DDI, the recommendation was: " PAXLOVID™ contra-indicated with the comedication". area contra-indication is mentioned mainly for: i) drugs for which a large variation in exposure is expected when associated with nirmatrelvir/ritonavir (usually over a 5-fold increase of the area under the curve of the drug), ii) drugs for which an increase in exposure may lead to serious adverse drug reactions, including life-threatening reactions even during as short a period as 5 days (the typical example being colchicine), iii) drugs for which a pharmacodynamic potentiation of adverse drug reaction with serious consequences is expected and, iv) drugs known as potent CYP3A4 inducers potentially leading to a decrease in nirmatrelvir, with a risk of antiviral treatment failure (the typical case is rifampicin but carbamazepine is concerned as well). For drugs not strictly contra-indicated in the regulatory documents (SmPC or the French national handbook for DDI), but having a high risk of accumulation, the recommendation was: " PAXLOVID™ not recommended with the comedication". Associated with PAXLOVID™, these drugs may show large variations in exposure, potentially leading to concentration-related severe adverse event. Therefore, the specialists in clinical pharmacology considered that the combination may put the patient at risk for toxicity and general practitioners had to be warned about this. Alternatives COVID-19 treatments should be proposed in these situations. Some drugs can be safely discontinued during the antiviral treatment without causing harm to patients. For these drugs, the clinical pharmacologists' recommendation was: " PAXLOVID™ possible whether the comedication is discontinued". The typical case is HMG-CoA reductase inhibitors, i.e statins. The discontinuation of this pharmacological class can be safely proposed during the treatment with nirmatrelvir/ritonavir to avoid myopathy and potential rhabdomyolysis. Finally, the specialists in clinical pharmacology evidenced a fifth case. The recommendation in that situation was: "PAXLOVID™ possible only after an expert advice" for drugs which have to be pursued during the nirmatrelvir/ritonavir treatment and the exposure of

which would be largely changed by the inhibiting or inducing action of ritonavir. Discontinuing these drugs would be harmful for patients and cannot be considered. For these drugs, a dosage adjustment is, then, required and a clinical pharmacologist expert advice must be sought. The typical examples are immunosuppressive drugs, substrates of both CYP3A4 and P-glycoprotein. Their titration should be reduced (up to 40-time factor for tacrolimus) and therapeutic drug monitoring appears paramount to manage inter-patient variability during this DDI.

The final document comprises recommendations for 171 drugs/therapeutic classes aiming to secure prescription (Table 1) [5,7–28]. In complex situations, clinicians are advised to contact their pharmacology department to obtain specific recommendations on the management of DDI with nirmatrelvir/ritonavir.

Discussion

Nirmatrelvir combined with ritonavir is a first line option for the oral treatment of patients developing a COVID-19 infection with a subsequent risk of severe disease. Despite its seducing efficacy, the drug has some limitations due to safety. Among them, data in severe renal or hepatic failure and on the high risk of DDI related to ritonavir are lacking. Given this concern on DDI and in cases where the combination of the PAXLOVID™ with commonly prescribed drugs is impossible, other pharmacological options are available taking into account the viral ecology. Sotrovimab is a monoclonal antibody neutralizing SARS-CoV-2 and has shown a 85% decrease in hospitalization and death in infected patients [29]. This drug can also be proposed in patients at-risk of severe disease infected by susceptible virus strains. Another alternative is remdesivir, a nucleotide inhibitor of the viral RNA-dependent RNA polymerase, which has been reported to decrease the death and hospitalization rates of 87% [30]. However, while they do not carry the DDI risk, none of these drugs can be administered in both inpatients and outpatients. For patients in who nirmatrelvir/ritonavir is considered the best option, the recommendations of the French Society of Pharmacology and Therapeutics aim at guiding the clinicians' prescription to alleviate the risk of adverse drug reaction due to DDI. This risk is mainly subsequent to the use of ritonavir as a pharmacokinetic booster, already used in the field of HIV and HVC treatments. Ritonavir is well known as a potent CYP3A4 inhibitor but it is also expected to inhibit CYP2C9, CYP2D6, breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp) [31]. DDI studies showed that the magnitude of these latter interactions may be lower than expected. For example, ritonavir only leads to a 60% increase of desipramine, a reference substrate of CYP2D6 [32]. Limited interaction is

therefore expected with most neuropsychiatric drugs. When associated with dabigatran, a reference substrate for intestinal P-gp, at the dose of 100 mg, ritonavir has few effects on the anticoagulant exposure [33]. However, P-gp renal inhibition might be a bit more pronounced, as digoxin exposure may increase from 30 to 80% according to different studies. Ritonavir is also expected to induce CYP1A2, CYP2B6, CYP2C19 and UDP-glucuronyl transferases (UGTs) [31]. CYP2C19 induction may lead to significant decrease in drug exposure as highlighted by the data on voriconazole [34].

The induction of UGT may be different according to isoenzymes. Indeed, if a lower exposure in lamotrigine, which is metabolized by UGT1A4, is expected, a much lower impact has been described on mycophenolic acid, a drug metabolized by UGT1A9 and 2B7 [20,35].

Interestingly, contra-indications in the SmPC of ritonavir have been extensively maintained in SmPC of PAXLOVID™. Ritonavir was approved in 1996 and many DDI studies have been conducted since then, shedding a light on its pharmacokinetics [25]. Hence, some contra-indications seem quite conservative, and may result from the speed with which the dossier was urgently compiled for the rolling review. For example, the association of PAXLOVID™ with clozapine which is mainly metabolized by the CYP1A2 is contra-indicated even though minimal interaction is expected. Another example is amiodarone, metabolized into an equipotent metabolite, for which no major clinical impact is therefore expected when associated with ritonavir [36]. Nevertheless, as contra-indications in SmPCs are enforceable, we chose to strictly report these contra-indications in our recommendations.

Conclusion

As specialists of both pharmacokinetics and adverse drug reactions evaluation, clinical pharmacologists are at the very heart of professional expertise to help clinicians with the prescription of drugs in a context of DDI. These recommendations intend to be a help for clinicians willing to prescribe nirmatrelvir/ritonavir and to prevent DDI leading to adverse drug reactions or loss of efficacy. They constitute a guideline for primary care situations. Of course, some complex situations may require expert advices and here, again, clinical pharmacologists are at the forefront in providing therapeutic advice.

Disclosure of interest

Authors have no competing interest to declare

References

- [1] Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J*2014;281:4085-96.
- [2] Li P, Wang Y, Lavrijsen M, Lamers MM, de Vries AC, Rottier RJ, et al. SARS-CoV-2 Omicron variant is highly sensitive to molnupiravir, nirmatrelvir, and the combination. *Cell Res* 2022;32:322-4.
- [3] Owen DR, Allerton CMN, Anderson AS, Aschenbrenner L, Avery M, Berritt S, et al. An oral SARS-CoV-2 Mpro inhibitor clinical candidate for the treatment of COVID-19. *Science* 2021;374:1586-93.
- [4] Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med*. 16 févr 2022; doi: 10.1056/NEJMoa2118542. Sous presse.
- [5] Lemaitre F, Solas C, Grégoire M, Lagarce L, Elens L, Polard E, et al. Potential drug-drug interactions associated with drugs currently proposed for COVID-19 treatment in patients receiving other treatments. *Fundam Clin Pharmacol* 2020;34:530-47.
- [6] Agence Nationale de Sécurité du Médicament. Thesaurus des interactions médicamenteuses. 2020. <https://ansm.sante.fr/documents/reference/thesaurus-des-interactions-medicamenteuses-1>. [Accessed 18 March 2022].
- [7] EMA. Paxlovid, Summary of products characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf [Accessed 18 March 2022 (44 pp.)]
- [8] Ancrenaz V, Daali Y, Fontana P, Besson M, Samer C, Dayer P, et al. Impact of genetic polymorphisms and drug-drug interactions on clopidogrel and prasugrel response variability. *Curr Drug Metab* 2010;11:667-77.
- [9] Itkonen MK, Tornio A, Lapatto-Reiniluoto O, Neuvonen M, Neuvonen PJ, Niemi M, et al. Clopidogrel increases dasabuvir exposure with or without ritonavir, and ritonavir inhibits the bioactivation of clopidogrel. *Clin Pharmacol Ther* 2019;105:219-28.

- [10] Badri P, Dutta S, Coakley E, Cohen D, Ding B, Podsadecki T, et al. Pharmacokinetics and dose recommendations for cyclosporine and tacrolimus when coadministered with ABT-450, ombitasvir, and dasabuvir. *Am J Transplant* 2015;15:1313-22.
- [11] Badri PS, Parikh A, Coakley EP, Ding B, Awni WM, Dutta S, et al. Pharmacokinetics of tacrolimus and cyclosporine in liver transplant recipients receiving 3 direct-acting antivirals as treatment for hepatitis C infection. *Ther Drug Monit* 2016;38:640-5.
- [12] Niu W, Li S, Jin S, Lin X, Zhang M, Cai W, et al. Investigating the interaction between nifedipine- and ritonavir-containing antiviral regimens: A physiologically based pharmacokinetic/pharmacodynamic analysis. *Br J Clin Pharmacol* 2021;87:2790-806.
- [13] Grimm SW, Richtand NM, Winter HR, Stams KR, Reece SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol* 2006;61:58-69.
- [14] Greenblatt DJ, von Moltke LL, Harmatz JS, Durol AL, Daily JP, Graf JA, et al. Differential impairment of triazolam and zolpidem clearance by ritonavir. *J Acquir Immune Defic Syndr* 2000;24:129-36.
- [15] Greenblatt DJ, von Moltke LL, Harmatz JS, Durol AL, Daily JP, Graf JA, et al. Alprazolam-ritonavir interaction: implications for product labeling. *Clin Pharmacol Ther* 2000;67:335-41.
- [16] Schmitt C, Hofmann C, Riek M, Patel A, Zwanziger E. Effect of saquinavir-ritonavir on cytochrome P450 3A4 activity in healthy volunteers using midazolam as a probe. *Pharmacotherapy* 2009;29:1175-81.
- [17] Johnson FM, Agrawal S, Burris H, Rosen L, Dhillon N, Hong D, et al. Phase 1 pharmacokinetic and drug-interaction study of dasatinib in patients with advanced solid tumors. *Cancer* 2010;116:1582-91.
- [18] Freise KJ, Hu B, Salem AH. Impact of ritonavir dose and schedule on CYP3A inhibition and venetoclax clinical pharmacokinetics. *Eur J Clin Pharmacol* 2018;74:413-21.

- [19] Elens L, Langman L, Hesselink D, Bergan S, Moes D, Molinaro M, et al. Pharmacologic treatment of transplant recipients infected with SARS-CoV-2: considerations regarding therapeutic drug monitoring and drug-drug interactions. *Ther Drug Monit* 2020; 42:360-8.
- [20] Lemaitre F, Ben Ali Z, Tron C, Jezequel C, Boglione-Kerrien C, Verdier M, et al. Managing drug-drug interaction between ombitasvir, paritaprevir/ritonavir, dasabuvir, and mycophenolate mofetil. *Ther Drug Monit* 2017;39:305-7.
- [21] de Jong J, Skee D, Murphy J, Sukbuntherng J, Hellemans P, Smit J, et al. Effect of CYP3A perpetrators on ibrutinib exposure in healthy participants. *Pharmacol Res Perspect* 2015;3(4):e00156.
- [22] Wind S, Giessmann T, Jungnik A, Brand T, Marzin K, Bertulis J, et al. Pharmacokinetic drug interactions of afatinib with rifampicin and ritonavir. *Clin Drug Investig* 2014;34:173-82.
- [23] Dingemans J, van Giersbergen PLM, Patat A, Nilsson PN. Mutual pharmacokinetic interactions between bosentan and lopinavir/ritonavir in healthy participants. *Antivir Ther* 2010;15:157-63.
- [24] Sekar V, Lefebvre E, De Marez T, De Pauw M, De Paepe E, Vangeneugden T, et al. Effect of repeated doses of darunavir plus low-dose ritonavir on the pharmacokinetics of sildenafil in healthy male subjects: phase I randomized, open-label, two-way crossover study. *Clin Drug Investig* 2008;28:479-85.
- [25] EMA. Ritonavir summary of product characteristics. 2022. https://www.ema.europa.eu/en/documents/product-information/norvir-epar-product-information_en.pdf. [Accessed 18 March 2022 (109 pp.)]
- [26] King JR, Menon RM. Ombitasvir/paritaprevir/ritonavir and dasabuvir: drug interactions with antiretroviral agents and drugs for substance abuse. *Clin Pharmacol Drug Dev* 2017;6:201-5.
- [27] Olkkola KT, Palkama VJ, Neuvonen PJ. Ritonavir's role in reducing fentanyl clearance and prolonging its half-life. *Anesthesiology* 1999;91:681-5.
- [28] Ouellet D, Hsu A, Qian J, Locke CS, Eason CJ, Cavanaugh JH, et al. Effect of ritonavir on the pharmacokinetics of ethinyl oestradiol in healthy female volunteers. *Br J Clin Pharmacol* 1998;46:111-6.

- [29] Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Falci DR, et al. Early treatment for COVID-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N Engl J Med* 2021;385:1941-50.
- [30] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N Engl J Med* 2022;386:305-15.
- [31] Cattaneo D, Cossu MV, Rizzardini G. Pharmacokinetic drug evaluation of ritonavir (versus cobicistat) as adjunctive therapy in the treatment of HIV. *Expert Opin Drug Metab Toxicol* 2019;15:927-35.
- [32] von Moltke LL, Greenblatt DJ, Duan SX, Daily JP, Harmatz JS, Shader RI. Inhibition of desipramine hydroxylation (Cytochrome P450-2D6) in vitro by quinidine and by viral protease inhibitors: relation to drug interactions in vivo. *J Pharm Sci* 1998;87:1184-9.
- [33] Kumar P, Gordon LA, Brooks KM, George JM, Kellogg A, McManus M, et al. Differential influence of the antiretroviral pharmacokinetic enhancers ritonavir and cobicistat on intestinal P-glycoprotein transport and the pharmacokinetic/pharmacodynamic disposition of dabigatran. *Antimicrob Agents Chemother* 2017;61:e01201-17.
- [34] Liu P, Foster G, Gandelman K, LaBadie RR, Allison MJ, Gutierrez MJ, et al. Steady-state pharmacokinetic and safety profiles of voriconazole and ritonavir in healthy male subjects. *Antimicrob Agents Chemother* 2007;51:3617-26.
- [35] van der Lee MJ, Dawood L, ter Hofstede HJM, de Graaff-Teulen MJA, van Ewijk-Beneken Kolmer EWJ, Caliskan-Yassen N, et al. Lopinavir/ritonavir reduces lamotrigine plasma concentrations in healthy subjects. *Clin Pharmacol Ther* 2006;80:159-68.
- [36] Ghovanloo M-R, Abdelsayed M, Ruben PC. Effects of amiodarone and N-desethylamiodarone on cardiac voltage-gated sodium channels. *Front Pharmacol* 2016;7:39.

#NAME?	Nature and magnitude of the effect	Therapeutic strategy	
<i>Anti-platelet agents</i>			
Aspirin	No interaction expected	Paxlovid possible without modification	
Prasugrel	45% decrease in prasugrel AUC but clinical effect is expected to be maintained	Paxlovid possible without modification of the associated treatment	In ca
Clopidogrel	Decrease in anti-platelet effect reported but clinical effect is expected to be maintained	Paxlovid possible without modification of the associated treatment	In ca
Ticagrelor	Increase in ticagrelor exposure and increase in bleeding risk	Paxlovid contra-indicated with	
<i>Anticoagulants</i>			
Acenocoumarol, Warfarin	Weak interaction expected	Paxlovid possible without modification of the associated treatment	IN
Apixaban	Increase in apixaban exposure and increase in bleeding risk	Paxlovid not recommended with	
Dabigatran	Weak interaction expected when simultaneously administered with ritonavir. No change in pharmacodynamic parameters expected.	Paxlovid possible without modification of the associated treatment ; caut	
Rivaroxaban	Increase in rivaroxaban exposure (AUC and Cmax increased by 153% and 53%, respectively) with increase in bleeding risk.	Paxlovid not recommended with	
<i>Drugs for angina and heart failure</i>			
Ivabradine, Eplerenone	Risk of heart rhythm disorders	Paxlovid contra-indicated with	
<i>Antiarrhythmic agents</i>			
Amiodarone, Flecainide, Dronedarone, Propafenone, Quinidine	Risk of cardiac arrhythmias	Paxlovid contra-indicated with	
Digoxine	Digoxine AUC increase expected between 30 and 80%	Paxlovid possible whether the com	

<i>Antihypertensive drugs</i>		
IEC/ARA2/Diurétiques	No interaction expected	Paxlovid possible without modification
Calcium channel blockers - except for Lercanidipine, Verapamil, Diltiazem	Weak interaction expected	Paxlovid possible without modification
Lercanidipine, Verapamil, Diltiazem	Higher interaction expected than for other calcium channel blockers	Paxlovid possible whether the com
Beta-blockers -(Atenolol, Propranolol, Nebivolol, Carvedilol, Timolol - except for Bisoprolol)	Weak interaction expected for propranolol, nebivolol, carvedilol, timolol and for atémolol (which is renally excreted)	Paxlovid possible without modification
Bisoprolol	Higher interaction expected	Paxlovid not recommended wi
<i>Lipid agents</i>		
HMG-CoA reductase inhibitors	Particularly high interaction magnitude expected for simvastatin and lovastatin	Paxlovid possible whether the comedication is discontinued
Lomitapide	Increase of AUC by a factor 27 expected	Paxlovid contra-indicated wi
<i>Antipsychotics</i>		
Clozapine	Possible QTc prolongation	Paxlovid contra-indicated wi
Quétiapine	Quetiapine AUC is increased by a factor 6.5	Paxlovid contra-indicated wi
<i>Antidepressants</i>		
ISRS/IRSNa/Mirtazapine/Mianserine	Weak interaction expected (10-50%)	Paxlovid possible without modification
Tricycliques/IMAO		Paxlovid not recommended wi
<i>Benzodiazepines and related drugs</i>		
Midazolam oral, Diazepam, Clorazepate, Estazolam	Increase in benzodiazepine exposure by a 10 to 25 factor. Risk of respiratory failure.	Paxlovid contra-indicated wi
Alprazolam	Increase in benzodiazepine exposure by a 2 to 3 factor. Risk of respiratory failure.	Paxlovid not recommended wi
Zolpidem, Zopiclone	Weak interaction expected	Paxlovid possible without modification
<i>Anticonvulsivants</i>		
Carbamazepine	Risk of antiviral treatment failure.	Paxlovid contra-indicated wi
Phenobarbital	Risk of antiviral treatment failure.	Paxlovid contra-indicated wi

Phenytoin	Risk of antiviral treatment failure.	Paxlovid contra-indicated with	
Valproate	Weak interaction expected	Paxlovid possible without modification	
Lamotrigine	Possible decrease in lamotrigine concentrations but weak magnitude expected.	Paxlovid possible without modification	
Levetiracetam	No interaction expected	Paxlovid possible without modification	
<i>Immunosuppressive drugs</i>			
Tacrolimus	Increase in tacrolimus exposure by a 40 factor.	Paxlovid possible only after an expert advice	Adm Adm usua Nir restart with t
Ciclosporine	Increase in ciclosporine exposure by a 8 factor.	Paxlovid possible only after an expert advice	A Nirma 6 th trea
Everolimus	Increase in everolimus exposure by a 15 factor.	Paxlovid possible only after an expert advice	Adm day ind
Sirolimus	Increase in sirolimus exposure by a 11 factor.	Paxlovid possible only after an expert advice	Adm day ind
Mycophenolic acid	Weak interaction expected. Possible decrease in mycophenolic acid exposure.	Paxlovid possible only after an expert advice	Whet

Prednisone	Weak interaction expected. Possible increase in prednisone exposure.	Paxlovid possible only after an expert advice	Prednisone
<i>Anticancer drugs</i>			
Cytotoxic drugs	According to the substrates, an important interaction can occur. Vincristin, Vinblastin: risk of neutropenia and neurotoxicity.	Paxlovid possible whether the comedication is discontinued, cytotoxic and treatment.	
For the following kinase inhibitors: Abemaciclib, Axitinib, Bosutinib, Cobimetinib, Crizotinib, Encorafenib, Erlotinib, Gefitinib, Ibrutinib, Nilotinib, Olaparib, Palbociclib, Pazopanib, Sunitinib...) except for the drug below	Increase in kinase inhibitors, which may be important for some substrates.	Paxlovid possible whether the comedication is discontinued	Therapeutic advice
Venetoclax	Risk of tumor syndrome lysis	Paxlovid contra-indicated with	
Afatinib, Alectinib, Binimetinib, Cabozantinib, Imatinib, Osimertinib, Sorafenib, Trametinib	Weak exposure increase (AUCs increase from 26 to 40%)	Paxlovid possible without modification	
Tamoxifen	Weak interaction expected	Paxlovid possible without modification	
Apalutamide, Enzalutamide	Risk of antiviral treatment failure.	Paxlovid not recommended with	
<i>Pneumology drugs</i>			
Beta-2 agonists	Exposure increase but weak clinical effect expected	Paxlovid possible without modification	
Inhaled corticosteroids	Exposure increase but weak clinical effect expected	Paxlovid possible without modification	
Sildenafil, Tadalafil, Vardenafil, Avanafil	Large increase in substrates' exposure	Paxlovid contra-indicated with	
Bosentan	Increase in bosentan exposure by a 5 factor.	Paxlovid not recommended with	
<i>Non opiates analgesics and antiinflammatory drugs</i>			
Aspirin, Acetaminophen, Ibuprofen, Diclofenac, Naproxen, Ketoprofen	No interaction expected	Paxlovid possible without modification	
Colchicin	Risk of colchicin accumulation and toxicity	Paxlovid contra-indicated with	

<i>Opiates</i>		
Codeine, Tramadol, Buprenorphine	Weak interaction expected	Paxlovid possible without modification
Fentanyl	Possible increase in fentanyl exposure with risk of respiratory failure	Paxlovid not recommended with
Methadone	Possible decrease in methadone exposure	Paxlovid possible without modification
Morphine	Possible increase in morphine glucuronide metabolites	Paxlovid possible without modification
Oxycodone	Increase in oxycodone exposure by 90%	Paxlovid contra-indicated with
<i>Antibacterial agents</i>		
Aminoglycosides	No interaction expected	Paxlovid possible without modification
Beta-lactams	No interaction expected	Paxlovid possible without modification
Fluoroquinolones	No interaction expected	Paxlovid possible without modification
Fosfomicin	No interaction expected	Paxlovid possible without modification
Glycopeptides	No interaction expected	Paxlovid possible without modification
Oxazolidinones	No interaction expected	Paxlovid possible without modification
Polymyxines	No interaction expected	Paxlovid possible without modification
Sulfamides	No interaction expected	Paxlovid possible without modification
Tetracyclines	No interaction expected	Paxlovid possible without modification
Macrolides - except Erythromycin	Increase in macrolides exposure (clarithromycin)	Paxlovid possible without modification of the associated treatment
Erythromycin	Possible increase in erythromycin exposure and risk of cardiac arrhythmia	Paxlovid not recommended with
<i>Antituberculous agents</i>		
Isoniazid, Ethambutol, Pyrazinamide	No interaction expected	Paxlovid possible without modification
Rifampicin	Large decrease in Nirmatrelvir/ritonavir exposure	Paxlovid contra-indicated with

Rifabutin	Possible decrease in Nirmatrelvir/ritonavir exposure. Increase of rifabutin exposure by a 4 fold factor	Paxlovid not recommended with	
<i>Antifungal agents</i>			
Echinocandins	No interaction expected	Paxlovid possible without modification of the associated treatment	
Fluconazole, Isavuconazole, Itraconazole, Posaconazole	Moderate increase in Nirmatrelvir/Ritonavir exposure (up to 39% with itraconazole)	Paxlovid possible without modification of the associated treatment	
Voriconazole	Decrease in voriconazole exposure (decrease of AUC of 39%). Mild increase in Nirmatrelvir/ritonavir exposure expected.	Paxlovid not recommended with	
<i>Antiretrovirals</i>			
Boosted protease inhibitors (Darunavir/r, Atazanavir/r, Lopinavir/r)	Increase in protease inhibitors exposure	Paxlovid possible without modification of the associated treatment	Adverse
Integrase strand inhibitors (Raltegravir, Dolutegravir, Bictegravir, Cabotegravir)	Weak interaction expected	Paxlovid possible without modification of the associated treatment	
Nevirapine, Efavirenz, Etravirine	Possible decrease in Nirmatrelvir/ritonavir exposure. No decrease in substrates exposure is expected/	Paxlovid not recommended with	
Doravirine	Increase in doravirine exposure by a 3.5 factor.	Paxlovid possible without modification of the associated treatment	
Rilpivirine	Possible increase in rilpivirine exposure and possible risk of QTc prolongation.	Paxlovid possible without modification of the associated treatment	In
Maraviroc	Increase in maraviroc exposure	Paxlovid not recommended with	
Tenofovir	An increase in tenofovir exposure is expected	Paxlovid possible without modification of the associated treatment	
Nucleoside reverse transcriptase inhibitors (Abacavir, Emtricitabine, Lamivudine)	No interaction expected	Paxlovid possible without modification of the associated treatment	
<i>Hepatitis C direct acting antiviral</i>			
Sofosbuvir/ Velpatasvir	No interaction expected	Paxlovid possible without modification of the associated treatment	

Glecaprevir/Pibrentasvir	Large increase in glecaprévir/pibrentasvir exposure expected. Increase in liver enzymes due to glecaprevir accumulation.	Paxlovid not recommended with this combination.
Voxaliprevir	Increase in voxaliprevir exposure, possible liver enzymes increase.	Paxlovid not recommended with this combination.