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Interactions listed in the Paxlovid fact sheet, classified according to risks, pharmacological groups, and consequences

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Article history

Received: 30 June 2022; Accepted: 7 July 2022; Published: 13 July 2022

ABSTRACT

Paxlovid (nirmatrelvir plus ritonavir) is a new oral antiviral therapeutic for the treatment of COVID-19. Nirmatrelvir is an inhibitor of SARS-CoV-2 main protease, while ritonavir is used as a CYP3A inhibitor in low doses to slow the metabolism of nirmatrelvir, thus enhancing their therapeutic effect. The isoenzyme CYP3A4 is responsible for at least part of the oxidative metabolism of approximately 60% of available medications and ritonavir is therefore a significant source of drug interactions. We describe here the drugs that are contraindicated or should be used with or without precautions when Paxlovid (nirmaltrevir plus ritonavir) should be administered according to each fact sheet in force at the Spanish Agency for Medicines and Health Products.

Keywords: Paxlovid, Nirmatrelvir / ritonavir, Drug interactions, COVID-19, SARS-CoV-2

Interacciones recogidas en la ficha técnica de Paxlovid, clasificadas según los riesgos, grupos farmacológicos y consecuencias

RESUMEN

Paxlovid (nirmatrelvir más ritonavir) es un nuevo tratamiento antiviral oral para la COVID-19. Nirmatrelvir es un inhibidor de la principal proteasa del SARS-CoV-2, mientras que ritonavir es usado como un inhibidor de la CYP3A a baja dosis para reducir el metabolismo de nirmatrelvir, potenciando así su efecto terapéutico. La isoenzima CYP3A4 es responsable de al menos una parte del metabolismo oxidativo de aproximada-

mente el 60% de los medicamentos disponibles, por lo que el ritonavir es una fuente importante de interacciones farmacológicas. Describimos los fármacos cuyo uso está contraindicado o deben utilizarse con precauciones o sin ella cuando debe administrarse Paxlovid (nirmaltrevir más ritonavir), de acuerdo con cada ficha técnica vigente en la Agencia Española de Medicamentos y Productos Sanitarios

Palabras clave: Paxlovid, Nirmatrelvir / ritonavir, Interacciones medicamentosas, COVID-19, SARS-CoV-2

INTRODUCTION

The following table describes the drugs that are contraindicated or should be used with or without precautions when Paxlovid (nirmatrelvir plus ritonavir) should be administered. The information has been compiled directly from each Fact Sheet (FS) in force at the Spanish Agency for Medicines and Health Products.

The table (Table 1) has been constructed as follows:

- In the rows the drugs have been grouped using the ATC classification (Anatomical Therapeutic Chemical classification).
- The first column corresponds to the pharmacological group
- The second column, titled Fact Sheet, gathers the contraindications and use with precautions that are included in the Paxlovid FS.
- The third column, entitled alternatives, includes drugs whose use is possible with or without precautions, in patients treated with Paxlovid, as alternatives to those mentioned in the antiviral FS
- To reduce the final size of the text, a system of coding the type of interaction, its consequences and the action guideline has been used (see below).

As a general principle this document is intended as an aid to the management of Paxlovid in relation to the drugs that

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Table 1	Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered	
	Paxlovid fact sheet	Alternatives
Gastrointestinal motility agents	Contraindication: cisapride (1)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal Use with caution: metoclopramide (1)
Anticoagulants	Contraindication: rivaroxaban (1), vorapaxar (1) Use with caution: warfarin (2), acenocumarol (2)	Use with caution: dabigatran (5), edoxaban (5) Likely safe use: heparin (6)
Antianginal	Contraindication: ranolazine (1)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal
Antiarrhythmics	Contraindication: amiodarone (1), bepridil (1)(4), dronedarone (1), encainide (4), flecainide (4), propafenone (4), quinidine (1)(4) Use with caution: digoxin (5)	Use with caution: disopyramide (4)
Calcium channel antagonists	Use with caution: amlodipine (1), diltiazem (1), nifedipine (1)	Use with caution: verapamil (1)
Endothelin antagonists	Contraindication: riociguat (1) Use with caution: bosentan (1)	Use with caution: ambrisentan (2)
HMG Co-A reductase inhibitors	Contraindication: simvastatin (1), lovastatin (1) Use with caution: atorvastatin (1), rosuvastatin (5)	Provisional discontinuation during the 5 days of treatment with Paxlovid should be considered, and treatment may be restarted within 24 hours of withdrawal Use without caution: pravastatin (6), fluvastatin (6), pitavastatin (2)
Lipid-modifying agents	Contraindication: Lomitapide (1)	It should be assessed whether provisional suspension can be carried out during the 5 days of treatment with Paxlovid, and it can be restarted within 24 hours of withdrawal, continuing with the previous dose
Phosphodiesterase type 5 inhibitors	Contraindication: avanafil (1), sildenafil (1) (in pulmonary arterial hypertension patients), vardenafil (1) Use with caution: sildenafil (1) (not to exceed 25 mg/day), tadalafil (1) (not to exceed 10 mg every 72 hours)	
Alfa1-adrenoreceptor antagonist	Contraindication: alfuzosin (1)	Use without caution: terazosin (6)
Hormonal contraceptives	Use with caution: ethinyl estradiol (2) (barrier methods of contraception should be considered)	
Steroids	Use with caution: inhaled, injectable or intranasal fluticasone propionate (1), budesonide (1) and triamcinolone (1) (a glucocorticoid dose reduction should be considered), dexamethasone (1), prednisolone (1) (monitor therapeutic and adverse effects)	Use with caution: prednisone (1), deflazacort (1), methylprednisone (1), betamethasone (1), beclomethasone (1)
Thyroid hormone replacement therapy	Use with caution: levothyroxine (2)	
Antibiotics	Contraindication: fusidic acid (1), rifampicin (3) Use with caution: rifabutin (1) (reduce dose to 150 mg 3 times per week), erythromycin (1) (monitor therapeutic and adverse effects), clarithromycin (1) (avoid doses higher than 1 g per day and consider a dose reduction of 50% and 75% in patients with ClCr 30-60 and < 30 ml/min, respectively).	Use with caution: azithromycin (5), ciprofloxacin (2), moxifloxacin (2), tigecycline (5). Use without caution: b-lactams (6), aminoglycosides (6), glycopeptides (6), polypeptides (6), lipopeptides (6), oxazolidinones (6), cotrimoxazole (6), doxycycline (6), levofloxacin (6)

Table 1	Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered (cont.)	
	Paxlovid fact sheet	Alternatives
Anti-tuberculous drugs	Use with caution: bedaquiline (1) (concomitant administration should be avoided. If the benefit outweighs the risk, concomitant administration of bedaquiline with ritonavir should be undertaken with caution. Monitor ECG and transaminases frequently), delamanid (1) (due to the risk of QTc interval prolongation associated with DM-6705, ECG monitoring is recommended)	Use with caution: rifabutin (1)(3). Use without caution: capreomycin (6), ethambutol (6), isoniazid (6), pyrazinamide (6)
Anti-malarial drugs	Use with caution: atovaquone (2)	Use without caution: cotrimoxazole (6)
Antifungal	Contraindication: voriconazole (1) Use with caution: ketoconazole (1) (a dose reduction should be considered), itraconazole (1) (monitor therapeutic and adverse effects)	Use with caution: posaconazole (5) (monitoring for adverse effects), isavuconazole (1) (monitoring for adverse effects) Use without caution: echinocandins (6), amphotericin B (6).
Antiretroviral	Use with caution: efavirenz (1)(2) (monitoring tolerability), maraviroc (1) (in adult patients with a creatinine clearance of <80 ml/min, the dose should be adjusted to 150 mg, once daily)	Use with caution: dolutegravir (2), ritonavir-boosted protease inhibitors (1) (monitoring for adverse effects) Use without caution: abacavir (6), emtricitabine (6), enfuvirtide (6), lamivudine (6), raltegravir (6), tenofovir (6), zidovudine (6)
Anti-hepatitis C virus agents	Contraindication: glecaprevir/ pibrentasvir (1)	Use with caution: ritonavir-boosted protease inhibitors (1) (monitoring for adverse effects), sofosbuvir (5), ledipasvir (5), velpatasvir (5) Use without caution: ribavirin (6)
Anticancer drugs	Contraindication: apalutamide (1)(3), dasatinib (1), nilotinib (1), vincristine (1), vinblastine (1), and neratinib (1) Use with caution: afatinib (5) (monitoring adverse reactions), abemaciclib (1) (adjust the dose to 100 mg twice a day), ceritinib (1) (5) (reduce the dose by 30%), venetoclax (1) (for patients who have completed the escalation phase and are receiving a constant daily dose, reduce the dose by at least 75%), encorafenib (1) (concomitant administration of encorafenib and ritonavir should be avoided. If the benefit is considered to outweigh the risk, patients should be closely monitored), fostamatinib (1) (concomitant administration of fostamatinib with ritonavir may increase exposure to the fostamatinib metabolite R406, leading to adverse events. Dose reduction may be necessary), ibrutinib (1) (reduce ibrutinib dose to 140 mg and monitor patient closely for toxicity)	Use with caution: acalabrutinib (1) (avoid or discontinue the drug on the fifth day of treatment with Paxlovid), alectinib (1), alitretinoin (1) (reduce the dose to 10 mg), alpelisib (2)(7), anagrelide (2), bendamustine (2), bexarotene (1), binimetinib (2), everolimus (1), bleomycin (8), bortezomib (1) (monitor adverse effects), brigatinib (1) (avoiding or reducing the dose by about 50 %, i.e. from 180 mg to 90 mg or from 90 mg to 60 mg), busulfan (1), cabozantinib (1), ceritinib (1) (reduce the dose of ceritinib by about one third, rounded to the nearest multiple of the 150 mg dose), cyclophosphamide (1) (monitoring effectiveness), dabrafenib (1)(2), dacarbazine (2), dacomitinib (1), docetaxel (1), trabectedin (avoid or reduce the dose), entrectinib (1) (avoid or reduce the dose), epirubicin (2), erlotinib (1), estramustine (8), etoposide (1), ibrutinib (1) (discontinue Paxlovid 5 days into treatment or reduce the dose to 140 mg/day), idelalisib (1) (monitoring for adverse effects), imatinib (1), idarubicin (2), ixazomib (8), lorlatinib (1) (reduce the dose), midostaurin (1), mitomycin (8), mitotane (3), mitoxantrone (5), nintedanib (5), olaparib (1) (reduce the dose to 100 mg every 12 h), paclitaxel (2), panobinostat (1) (reduce the dose), pegasparginase (8), ponatinib (1) (reduce the dose to 30 mg/day), rucaparib (1), ruxolitinib (1) (reduce the dose by 50%), selumetinib (2), sonidegib (1) (reduce the dose to 200 mg/48 h), talazoparib (1) (avoid or reduce the dose), thiotepa (1), tivozanib (7) (separate the administration of Paxlovid by at least 2 hours), trametinib (5), tretinoia (1) (reduce the dose), tucatinib (2), vemurafenib (3), zanubrutinib (1) (reduce the dose to 80 mg/day, all 5 days during the use of Paxlovid) Use without caution: aflibercept (6), azacytidine (6), capecitabine (6), carboplatin (6), carfilzomib (6), cisplatin (6), cytarabine (6), cladribine (6), clofarabine (6), chlorambucil (6), decitabine (6), eribulin (6), fludarabine (6), fluorouracil (6), gemcitabine (6), lenvatinib (6), melphalan (6), mercaptopurine (6), methotrexate (6), nelarabine (6), niraparib (6), osimertinib (6), oxaliplatin (6), padeliporfin (6), pemetrexed (6), pentostatin (6), raltitrexed (6), sorafenib (6), tegafur (6), thioguanine (6), arsenic trioxide (6), vandetanib (6), vismodegib (6)

Table 1	Drugs that are contraindicated or should be used with or without precautions when Paxlovid should be administered (cont.)	
	Paxlovid fact sheet	Alternatives
Immunosuppressants	Use with caution: cyclosporine (1), tacrolimus (1), everolimus (1) (close monitoring of therapeutic and adverse effects)	Use with caution: baricitinib (5), filgotinib (8), fingolimod (1), lenalidomide (2), leflunomide (1), mycophenolate (2), pomalidomide (2), siponimod (2), teriflunomide (2), tofacitinib (1), upadacitinib (1) Use without caution: apremilast (6), azathioprine (6), dimethyl fumarate (6), thalidomide (6)
Analgesics	Contraindication: piroxicam (1)	Use with caution: enzymes involved in NSAID metabolism can be induced (2)
Anti-gouts	Contraindication: colchicine (1)	
Opioids	Contraindication: pethidine (1), propoxyphene (1). Use with caution: fentanyl (1) (monitor therapeutic and adverse effects), methadone (2), morphine (2)(dose may need to be increased)	Use with caution: alfentanil (1), hydromorphone (2), oxycodone (1), tramadol (1), tapentadol (2) Use without caution: buprenorphine (6), remifentanyl (6)
Anticonvulsants	Contraindication: carbamazepine (3), phenobarbital (3), phenytoin (3) Use with caution: divalproex (2), lamotrigine (2) (close monitoring of plasma levels), phenytoin (2) (close monitoring of serum levels or therapeutic effects. May decrease serum ritonavir levels)	Use with caution: clonazepam (1), eslicarbazepine (2), stiripentol (1), ethosuximide (1), lacosamide (1), lamotrigine (2), oxcarbazepine (2), perampanel (1), rufinamide (3), topiramate (2), valproic acid (2) Use without caution: gabapentin (6), brivaracetam (6), levetiracetam (6), pregabalin (6), tiagabine (6), zonisamide (6)
Antidepressants	Use with caution: amitriptyline (4), fluoxetine (4), imipramine (4), nortriptyline (4), paroxetine (4), sertraline (4) (close monitoring of therapeutic effects), desipramine (1) (reduce the dose)	Use with caution: agomelatine (2), fluvoxamine (2), escitalopram (2), desvenlafaxine (2), duloxetine (2), maprotiline (4), mianserin (1), mirtazapine (1), moclobemide (4), reboxetine (1), trazodone (1), venlafaxine (1), vortioxetine (4)
Antipsychotics	Contraindication: clozapine (1), pimozide (1), lurasidone (1), quetiapine (1) Use with caution: haloperidol (4), risperidone (4), thioridazine (4) (monitoring therapeutic effects)	Use with caution: aripiprazole (1), asenapine (2), chlorpromazine (2), clotiapine (1), olanzapine (2), paliperidone (2), ziprasidone (2), zuclopenthixol (1) Use without caution: amisulpride (6), loxapine (6), sulpiride (6), tiapride (6)
Ergot derivatives	Contraindication: dihydroergotamine (1), ergonovine (1), ergotamine (1), methylergonovine (1)	
Sedative / hypnotics	Contraindication: lorazepam (1), diazepam (1), estazolam (1), flurazepam (1), oral midazolam (1), triazolam (1). Use with caution: midazolam (parenterally) (1), alprazolam (1) (precautions during the first days), buspirone (1), zolpidem (1) (monitoring hypersedation)	Use with caution: bromazepam (2), brotizolam (1), flunitrazepam (2), lorazepam (2), lormetazepam (2), zopiclone(1), hydroxyzine (1)
Smoke cessation	Use with caution: bupropion (2) (it is possible that the interaction is of no clinical significance)	
Antiasthmatic	Use with caution: theophylline (2)	Use with caution: montelukast (2), roflumilast (2)
β2-agonists	Contraindication: salmeterol (1)	Use with caution: indacaterol (1), formoterol (2), vilanterol (1) Use without caution: olodaterol (6), salbutamol (6), terbutaline (6)
Inhaled steroids	Use with caution: fluticasone propionate inhaled, injectable or intranasal (1), budesonide (1), triamcinolone (1)	Use with caution: beclomethasone (1), mometasone (1), ciclesonide (1)
Antihistamines	Contraindication: astemizole (1), terfenadine (1), fexofenadine (1) Use with caution: loratadine (1) (monitor therapeutic and adverse effects)	Use with caution: ebastine (1) Use without caution: cetirizine (6), levocetirizine (6), desloratadine (6)
Amphetamine derivatives	Use with caution: amphetamine (4) (monitoring of adverse effects)	
Herbal products	Contraindication: St. John's wort (<i>Hypericum perforatum</i>) (3)	

the treated patient may be receiving. These are global recommendations for which in many cases there is no direct confirmation of the existence and severity of the interaction other than the FS of each drug. Therefore, in no case is it a tool that replaces the responsibility of the prescribing physician.

Codes

1: Potential risk of increased substrate concentrations with risk of toxicity due to CYP3A4 inhibition. Avoid, reduce dose or monitor for adverse effects.

2: Potential risk of reduced substrate concentrations with risk of inefficacy due to Paxlovid induction. Monitor efficacy.

3: Potential risk of reduced Paxlovid concentrations with risk of reduced efficacy. Avoid.

4: Potential risk of increased substrate concentrations with risk of toxicity due to CYP2D6 inhibition. Reduce dose or monitor for adverse effects.

5: Potential risk of increased substrate concentrations due to inhibition of P-glycoprotein (P-GI) and/or breast cancer resistance protein (BCRP) produced by Paxlovid. Reduce dose or monitor for adverse effects.

6. In principle, the risk of interactions considering the profile of the drug and Paxlovid is probably very low. In any case, the combination of should be performed considering the general precautions of any combination.

7. Risk of increased Paxlovid concentrations due to increased absorption from reduced first pass in the gut. Precautions.

8. No information on the risk of interactions is available.

FUNDING

None to declare

CONFLICT OF INTEREST

The authors declare no conflicts of interest.