Re: Paxlovid™ (PF-07321332 + ritonavir)

12/04/2022

Dear Colleagues,

The purpose of this correspondence is to update you on the imminent availability of the COVID-19 antiviral treatment Paxlovid™ (PF-07321332 + ritonavir) in Ireland and to highlight prescribing issues (particularly drug-drug interactions) associated with this medicine. It is indicated for the treatment of COVID-19 in adults who do not require supplemental oxygen and who are at increased risk for progression to severe COVID-19. Paxlovid™ is a combination of PF-07321332 (nirmatrelvir) tablets and ritonavir tablets.

The HSE COVID-19 Therapeutic Advisory Group (TAG) recommend the use of Paxlovid™ (PF-07321332 + ritonavir) for:

(a) unvaccinated adult patients at risk of progressing to severe COVID-19 infection not requiring supplemental oxygen (Tier 1 and Tier 2 as defined in Appendix 2 of the '**'HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19 v4.1'**) or

(b) immunocompromised adult patients at risk of progressing to severe COVID-19 infection not requiring supplemental oxygen who, despite vaccination, are unlikely to have generated protective immunity (Tier 1 as defined in Appendix 2 and 3 of the 'HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19' v4.1, see link above).

Patient should have COVID-19 confirmed with a positive PCR (or professionally administered, HSE-supplied antigen test) **within the last 5 days** and have symptom onset within the past 5 days to be considered for Paxlovid™ (PF-07321332 + ritonavir) treatment.

The recommended dosage is PF-07321332 (nirmatrelvir) 300 mg (two 150 mg tablets) with ritonavir 100 mg (one 100 mg tablet) all taken together orally every twelve hours (twice daily) for 5 days. In patients with moderate renal impairment (eGFR ≥ 30 to < 60 ml/min) the dose should be reduced to PF-07321332/ritonavir 150mg/100mg (one tablet of each) twice daily for 5 days.

The following are exclusion criteria for treatment with Paxlovid™ (PF-07321332 + ritonavir)

- Severe renal impairment (eGFR less than 30ml/min) and end stage renal disease on dialysis
- Severe liver disease e.g. Child Pugh Class C
- Co-administration of drugs that are highly dependent on cytochrome P450 3A4 (CYP3A4) for clearance and where elevated concentrations are associated with serious and/or life threatening adverse reactions
- Co-administration of drugs that are potent CYP3A4 inducers where significantly reduced Paxlovid™ (PF-07321332 + ritonavir) concentrations may be associated with potential for loss of virological response and possible resistance
- Signs and symptoms of severe COVID-19
- Any contraindications to Paxlovid™ (PF-07321332 + ritonavir) as listed in the Summary of Product Characteristics (SmPC).

The information contained in this letter is correct as of 12th April 2022. Please consult the Summary of Product Characteristics on each occasion prior to initiating treatment with Paxlovid®

In terms of drug interactions those resulting from inhibition of drug metabolism (as opposed to enzyme induction) may be considered more clinically relevant due to the rapid onset of adverse effects. Paxlovid™ (PF-07321332 + ritonavir) is a potent inhibitor of CYP3A (due to ritonavir) and may lead to an increase in plasma concentration of a wide range of commonly prescribed medications including, but not limited to, sedative/hypnotics (diazepam, alprazolam, zolpidem), antidepressants (sertraline, fluoxetine, paroxetine), antipsychotics (risperidone, quetiapine), analgesics (fentanyl, methadone), anti-infectives (azole antifungals, clarithromycin), anticoagulants (apixaban, rivaroxaban, dabigatran, warfarin), calcium antagonists (diltiazem, amlodipine), anti-arrhythmics (amiodarone, digoxin), statins, antihistamines, anti-cancer medicines and anti-HIV medicines. This is not an exhaustive list and more information is available in the SmPC and resources outlined below.

Due to the risk of drug-drug interactions a full review of patient medication history and interaction risk is required prior to initiating a prescription. Refer to SmPC and other suitable reference sources to review possible medicines that may interact with Paxlovid™ (PF-07321332 + ritonavir).

Summary of Product Characteristics (SmPC): Section 4.3, 4.4 and 4.5 contain detailed information on known interactions between Paxlovid™ (PF-07321332 + ritonavir) and other drugs. This can be accessed from the website of the European Medicines Agency:
https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid
University of Liverpool COVID-19 Drug Interaction Checker: This is a freely available and frequently updated resource, providing information on drug interactions and contraindications for Paxlovid™ (PF-07321332 + ritonavir): https://covid19-druginteractions.org/checker

The National Medicines Information Centre (NMIC) is available to assist prescribers with drug-drug interaction enquiries specific to the prescribing of Paxlovid™ (PF-07321332 + ritonavir) through their enquiry answering service. This service can be accessed via a secure email (e.g. Healthmail) at nmic@stjames.ie using the attached (Appendix A: National Medicines Information Centre (NMIC) template document for drug interaction review - Paxlovid™ (PF-07321332 + ritonavir)). Further copies of this template will be available on www.hse.ie/yourmedicines under the COVID-19 tab. The NMIC enquiry service is available Monday-Friday 9.00am - 5.00pm and a weekend service will be available for email enquiries specific to Paxlovid™ (PF-07321332 + ritonavir) from 10.00am – 1.00pm on Saturday and Sunday (and bank holidays) from April 11th 2022. This additional weekend service will be reviewed in line with service requirements in the coming weeks.

All adverse drug reactions that occur in patients taking Paxlovid™ (PF-07321332 + ritonavir) should be reported to the Health Products Regulatory Authority (HPRA): https://www.hpra.ie/homepage/about-us/report-an-issue/human-adverse-reaction-form

The HSE-Medicines Management Programme (MMP) will monitor the utilisation of Paxlovid™ (PF-07321332 + ritonavir) and other antivirals for the treatment of COVID-19 in the coming months.

With best wishes,

Michael Barry

Professor Michael Barry, **National Clinical Lead, Medicines Management Programme** www.hse.ie/yourmedicines

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Appendix A: National Medicines Information Centre (NMIC) template document for drug interaction review - Paxlovid™ (PF-07321332 + ritonavir)

For NMIC Use Only	
NMIC Reference Number	*Date Received*

Part 1: Patient Details	
Name of patient	
Date of birth	
Address	

Part 2: Prescriber Details	
Name of prescribing doctor	
Medical Council number	
Contact Details:	Practice address:
	Telephone:
	Email:

Part 3: Confirmations

Please refer to the **'HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19 v4.1'** for eligible patient groups suitable for treatment with Paxlovid™ (PF-07321332 + ritonavir)

All four confirmations are required for the NMIC to initiate a drug-drug interaction review

	Tick to confirm
I confirm that this patient meets the eligibility criteria set out by the HSE- Interim Guidance for the Pharmacological Management of Patients with COVID-19 (V4.1) for treatment with Paxlovid™ (PF-07321332 + ritonavir)	
I confirm that the attached medication list (or that listed on page 2) is complete to the best of my knowledge.	
I understand that the NMIC drug-drug interaction review will be based on the medication list that I have provided.	
I confirm that the patient is aware that their details are being submitted for the purpose of this review.	

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Medication list

It is imperative that a complete current patient medication record is available prior to initiating Paxlovid™ (PF-07321332 + ritonavir) this should include (but is not limited to) GP medication list, community pharmacy patient medication record, any medicines received from other sources (e.g. in-patient or out-patient hospital setting including intermittent treatments, pharmaceutical industry early-access schemes or clinical trials), patient-reported non-prescription medicine use (including any over-the-counter or herbal medicines) and illicit drug use.

Medication	Dose	Route	Duration

Please send this document via secure email (e.g. Healthmail) to nmic@stjames.ie

To enable timely medicine reconciliation, the HSE recommends that the patient's nominated community pharmacy is copied (via secure email, e.g. Healthmail) in correspondence to the NMIC for a drug interaction check for Paxlovid™ (PF-07321332 + ritonavir).

Patient nominated pharmacy:

If preferred, a copy of the medication list can be attached to the email along with the completed page 1 of this document.

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