Feidhmeannacht na Seirbhíse Sláinte, Seirbhís Aisíocaíochta Cúraim Phríomhúil
Bealach amach 5 an M50, An Bóthar Thuaidh, Fionnghlas
Baile Átha Cliath 11, D11 XKF3
Guthán: (01) 864 7100 Facs: (01) 834 3589

Health Service Executive, Primary Care Reimbursement Service
Exit 5, M50, North Road, Finglas, Dublin 11, D11 XKF3
Tel: (01) 864 7100 Fax: (01) 834 3589

31st May 2022

Circular 014/22

Re: Paxlovid™ (PF-07321332 + ritonavir)

Dear Doctor,

Please find enclosed the information that was sent out from the Office of the Chief Clinical Officer on the 14th April 2022 in relation to Paxlovid™.

Information for patients and the public is available on the HSE website: https://www2.hse.ie/conditions/paxlovid/.

Yours faithfully,

Shaun Flanagan
Primary Care Eligibility & Reimbursement

Príomhoifigeach Cliniciúil
Oifig an Phríomhoifigigh Cliniciúil
Ospidéal Dr Steevens, Lána Steevens
Baile Átha Cliath 8 , D08 W2A8

Chief Clinical Officer
Office of the Chief Clinical Officer
Dr Steevens Hospital, Steevens Lane
Dublin 8, D08 W2A8

www.hse.ie
@hselive
t 01 635 2000
e cco@hse.ie

By Email Only

Date: 14th April 2022

Re: New Therapeutics Agents for COVID-19 – Paxlovid™ (PF-07321332 + Ritonavir)

Dear Colleagues

I expect you will be aware that we now have a number of new therapeutic agents available or becoming available for treatment of COVID-19. One such treatment – Sotrovimab – has already been rolled out, although it is now less helpful in the Irish context due to the prevalence of the BA.2 Omicron sub-variant.

As noted previously, the availability of new agents is a positive development for some patients but is associated with very significant communication, clinical and operational challenges for the healthcare system. I would like to outline the current situation and ask for your support in making the best use of the opportunities provided by a new agent, Paxlovid™.

Clinical Guidance

A multidisciplinary Therapeutics Advisory Group (TAG) has worked very rapidly to develop clinical guidance for the new agents currently available. Professor Colm Bergin and Dr Catherine Fleming, who are Clinical Leads for the Infectious Disease Programme, chair this group jointly.

As noted in my letter to general practice when Sotrovimab became available, developing clinical guidance is very challenging because of the pace at which research and real-world data are translating into practice. The available evidence is limited. In a number of cases, the studies included mainly non-vaccinated populations at a time when other variants of the SARS-CoV-2 virus were predominant. This means that the application of the limited available evidence to our population is not straightforward and subject to change as noted in the recent alert issue regarding Sotrovimab.

Current TAG clinical guidance refers to the use of currently available therapeutic agents including but not limited to Paxlovid™. This letter relates to use of Paxlovid™.

The HSE COVID-19 TAG recommend the use of Paxlovid™ for:

(a) ***unvaccinated adult patients*** at risk of progressing to severe COVID-19 infection (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**), *i.e. those over 65 or those under 65 with additional risk factors*

(b) ***immunocompromised adult patients*** at risk of progressing to severe COVID-19 infection who, despite vaccination, are unlikely to have 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).

Patients should have their COVID-19 diagnosis confirmed (PCR test, or professionally administered, HSE-supplied antigen test) **within the last 5 days** and also have symptom onset within the past 5 days to be considered for Paxlovid™ treatment.

The current treatment recommendation, including the pathway for general practice, is set out in the attached documentation for reference "Interim Guidance - Treatment for Covid-19 Infection with Paxlovid".

I have attached a letter from Professor Michael Barry (12th April 2022), National Clinical Lead, Medicines Management Programme, setting out support to be provided by the National Medicines Information Centre (NMIC). The purpose of Professor Barry's letter is to update on the imminent availability of the COVID-19 antiviral treatment Paxlovid™ and to highlight prescribing issues (particularly drug-drug interactions) associated with this medicine.

Importantly, a clinical advisory/ support service led by the NMIC will be available to general practice, including on Saturday and Sunday mornings. It is recognised that out-of-hours services will not necessarily have access to all current medications for patients. In this context, patients should have available for out-of-hours services an up-to-date medication list. Work is ongoing with advocacy and patient groups to support patients to communicate this requirement by compiling a list of their medications to support any prescribing discussions. This, combined with the support from the NMIC as outlined in the attached documents, should assist prescribers.

As noted in the attached letter, the NMIC service can be accessed via a secure email (e.g. *Healthmail*) at nmic@stjames.ie using the specific template (Appendix A of National Medicines Information Centre (NMIC) template document for drug interaction review - Paxlovid™). This template will also be available on the Medicines Management Programme section of the HSE website (www.hse.ie/yourmedicines) and on www.antibioticprescribing.ie. The NMIC enquiry service is available Monday-Friday 9.00am - 5.00pm, and a weekend service available for email enquiries specific to Paxlovid™ from 10.00am - 1.00pm on Saturdays and Sundays (and bank holidays). This additional weekend service will be reviewed in line with service requirements in the coming weeks.

The HSE is recommending that when GPs seek support from NMIC that they copy in the patient's pharmacy so that all involved can be provided with relevant information.

Paxlovid™ may also be prescribed by hospital clinicians. In the case of in-patients, it will be dispensed by the hospital pharmacy. In the case of community patients (including where the hospital clinicians have been contacted directly by those usually under their care), dispensing of Paxlovid will occur in the community pharmacy local to the patient to which the prescription will have been sent directly; GPs will not be required to transcribe hospital prescriptions.

Supply, Delivery and Logistics

A supply of Paxlovid™ has very recently arrived in the country, we can now commence roll out with Paxlovid™ available for use in the community from Tuesday 19th April 2022.

Once Paxlovid™ has been prescribed, it should be dispensed by the patient's usual pharmacy (to mitigate risk) for collection by a non-COVID-19 positive person or delivery from the pharmacy to the patient.

In the short term, the usual distribution pathway is that on receipt of a prescription, the community pharmacy will order directly from the wholesaler when stock is required. If the product is ordered by 4pm, it will be delivered before 5pm the next day. There will also be a weekend delivery service.

Pharmacies will be informed that they should only order stock to fulfil a *Healthmail* prescription from a GP or a Consultant for one of their patients. The pharmacist will also be asked to forward a copy of the prescription to Pharmacy.response@hse.ie, contemporaneously with their order for stock.

A key operational challenge that will remain throughout is the ability to reach any patient within the 5-day timeframe. Evidence has shown that efficacy reduces after 5 days, and as such the prescribing of, and access to, Paxlovid™ are time-sensitive events.

We have also updated patient information on hse.ie about therapeutics and about Paxlovid. https://www2.hse.ie/conditions/covid19/symptoms/treatments-for-covid-19/

Conclusion

It is an encouraging step to that we now have access to medication for those most at risk of severe COVID-19 and I thank you for your continuing support and we work together to roll this out for our patients in Ireland.

With Kind Regards

Dr Colm Henry Chief Clinical Officer

Interim Guidance - Treatment for Covid-19 Infection with Paxlovid

14 April 2022

1. Introduction and challenge ahead

The success of Covid -19 vaccination in Ireland has allowed for the lifting of restrictions and resumption of a more normal life, despite the advent of the more transmissible Omicron variant. The BA.2 Omicron sub-variant is now reported to account for nearly 95% of cases in Ireland. However, COVID-19 is still circulating widely and remains a challenge, particularly to those who are unvaccinated or who have significant immunosuppression. As such, there remains a need to remain vigilant and harness the availability of novel therapies to assist in the ongoing management of COVID-19 in our community. Therapies emerging to date display modest evidence to support efficacy claims in reducing mortality and hospitalisation rates in patients with COVID-19. Given the paucity of strong evidence, some clinicians may wish not to prescribe these novel therapies, and this is a valid clinical management strategy.

2. Description of Product / Indication / Targeted population (Tier 1/ Tier 2) supported by available evidence

Recently, the European Medicine Agency granted a conditional marketing authorisation for Pfizer's oral antiviral medicine Paxlovid™. Paxlovid™ is a co-packaged combination of drugs: nirmatrelvir (PF-07321332), a second-generation protease inhibitor, and ritonavir, a pharmacological enhancer, which when paired can be used to treat infection for those with COVID-19. More specifically, Paxlovid™ is directly aimed to treat those suffering from mild-to-moderate COVID-19 and those who are at high risk for progression to severe COVID-19, including hospitalisation or death.

There may be global logistical or supply constraints that make it impossible to offer the available therapy to all eligible patients who could potentially benefit, making patient triage and prioritisation necessary. Moreover, given recent data evidencing Sotrovimab's lack of efficacy against the BA.2 variant, Paxlovid™ supply will be further stressed.

The HSE COVID-19 Therapeutic Advisory Group (TAG) recommends 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

(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', see link above).

Patients should have symptom onset within the past 5 days and a confirmed diagnosis of COVID-19 (PCR or professionally administered, HSE-supplied antigen test) within the last 5 days to be considered for Paxlovid™ (PF-07321332 + ritonavir) treatment. Due to the nature of the product, Paxlovid™ (PF-07321332 + ritonavir) presents significant challenges for prescribers due to the drug-drug interaction

profile. A full review of the patient's medication history and interaction risk is required prior to initiating a prescription.

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

3. Eligibility and Setting for Prescribing

As Paxlovid™ is an oral medication, it is anticipated that most prescribing will happen in general practice. If the patient satisfies Tier 1 and Tier 2, as defined in Appendix 2 of HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19 and is confirmed as COVID positive where the prescriber is satisfied that the risk / benefit analysis indicates that Paxlovid™ should be prescribed, it will be dispensed by the patient's local pharmacy.

Appendix 6 of the HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19 also sets out a useful decision making aid for general practice to determine if Paxlovid™ (PF-07321332 + ritonavir) is a suitable treatment. (Please note that such materials are subject to amendment and checking with the primary source is advisable).

Prescribing by hospitals may occur where a patient, e.g. with a long-term condition, is prescribed Paxlovid™ by their hospital team – dispensing of Paxlovid™ to outpatients will occur in the community pharmacy local to the patient via electronic transfer of prescriptions; there will be no need for GPs to transcribe hospital prescriptions. Dispensing of Paxlovid™ by the hospital pharmacy will only occur for inpatients.

The following summary guidance and decision aid provides a useful summary of the information set out above and will help GPs in determining eligibility and suitability for treatment with Paxlovid™ (PF-07321332 + ritonavir).

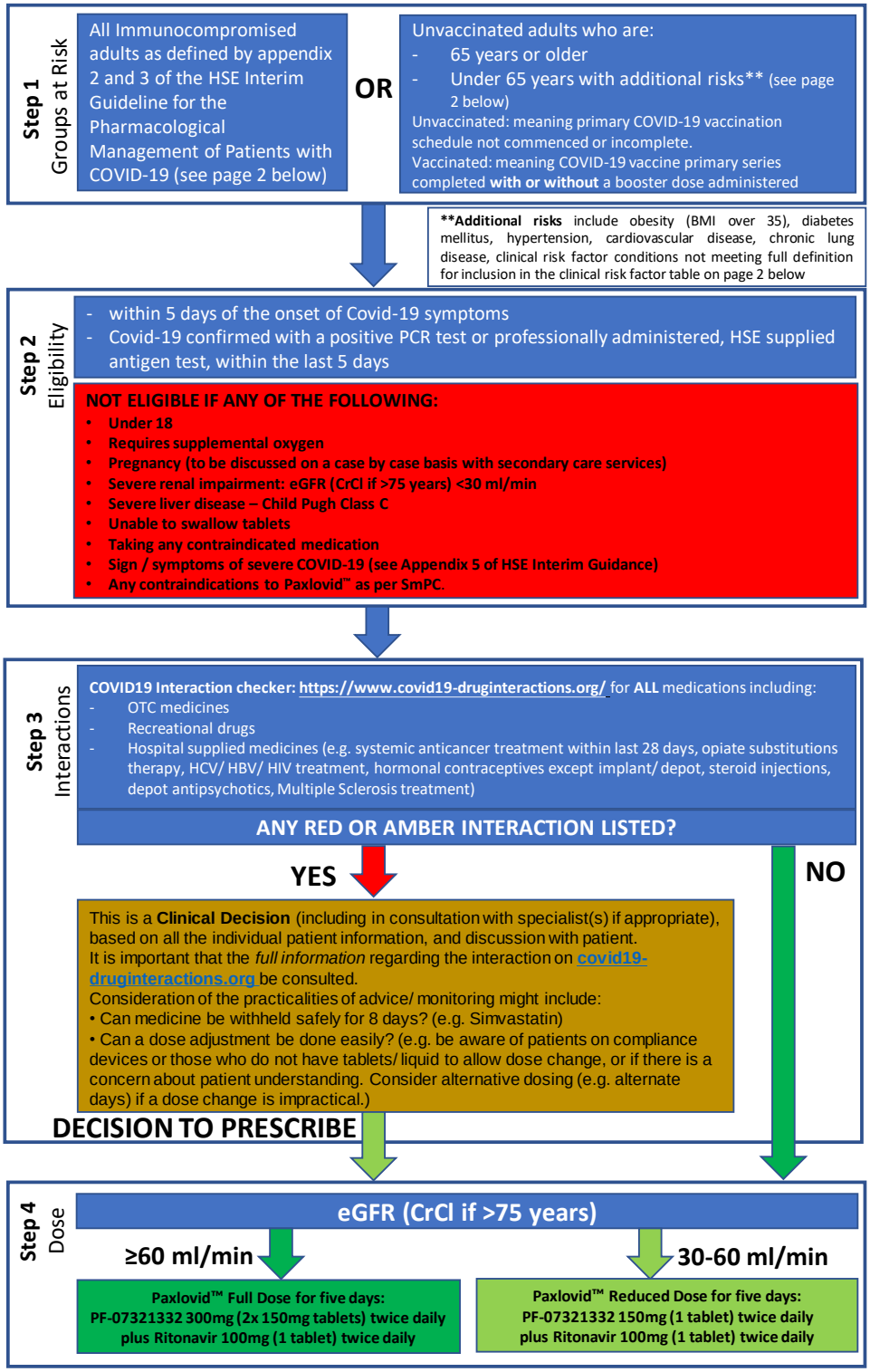
Interim Guidance - Treatment for Covid-19 Infection with Paxlovid

14 April 2022

Summary of HSE Interim Guidance for the Pharmacological Management of Patient with COVID-19 - Paxlovid™ (PF-07321332/ Ritonavir)

This document is intended for use by healthcare professionals with access to full information only. Correct at 12.4.2022.

Full guidance can be accessed here: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/guidance-documents.html. Refer to Paxlovid™ SmPC for details https://www.ema.europa.eu/documents/product-information/paxlovid-epar-product-information_en.pdf. Prescribing support is available, including the online resources listed, community pharmacies and an NMIC support team. Consider discussion with and/or referral to secondary care services. Treatment is time-critical, so timely use of local mechanisms for referral should be used especially if other intravenous treatments are to be considered if Paxlovid ™ is inappropriate in a high risk patient.



Links: https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/guidance-documents.html
https://www.ema.europa.eu/documents/product-information/paxlovid-epar-product-information_en.pdf.

Interim Guidance - Treatment for Covid-19 Infection with Paxlovid

14 April 2022

Immunocompromised adult patients not expected to mount an adequate immune response to COVID-19 vaccination or SARS-coV-2 infection due to their underlying conditions, regardless of vaccine status (see Clinical Risk Factors below) who may benefit from early treatments. (Adapted from appendix 2 of HSE Interim Guidance)

Click here for access to full HSE Interim Guidance the Pharmacological Management of Patients with COVID-19:
https://www.hse.ie/eng/about/who/acute-hospitals-division/drugs-management-programme/guidance-documents.html

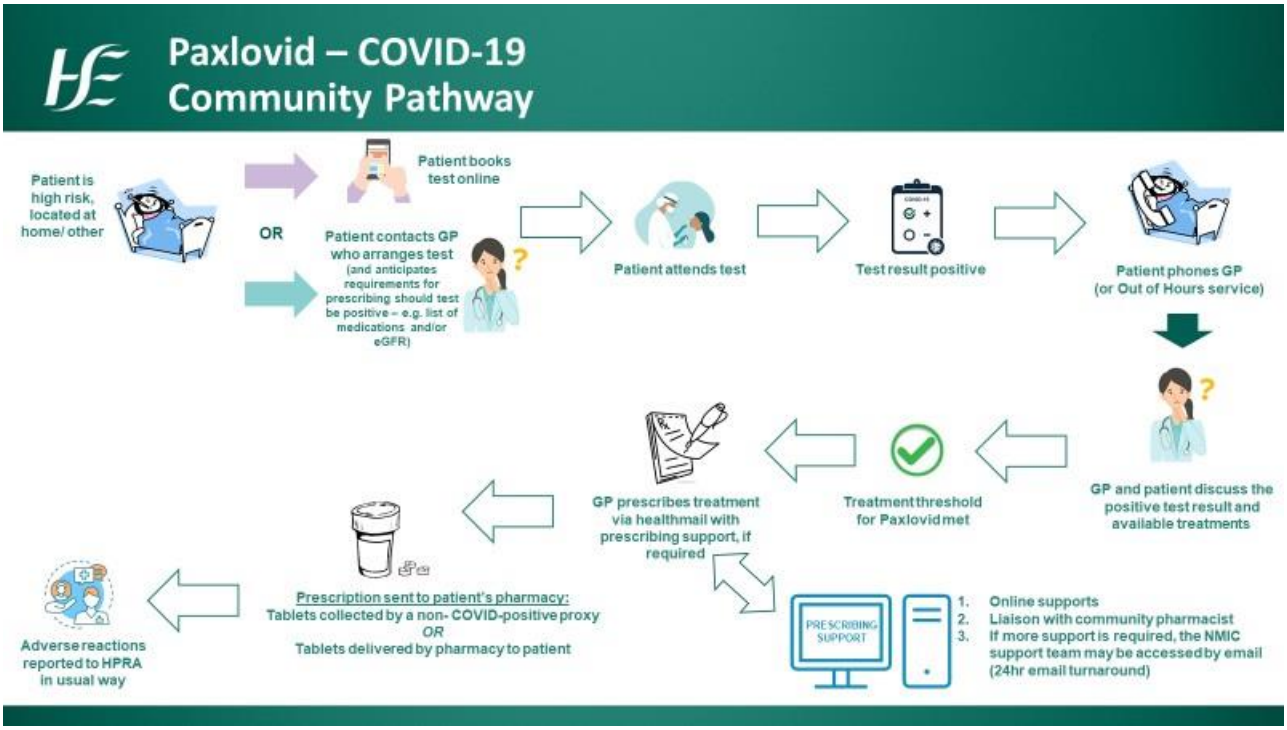
The clinical risk factors highlighted in red are those which would benefit most from treatment and Paxlovid ™ may be restricted to these in times of shortage.

Clinical Risk Factors of Immunocompromised Adults (Adapted from Appendix 3 of HSE Interim Guidance)	
PRIMARY IMMUNODEFICIENCY	
Diagnosis-based	CVID
	SCID / Combined Immunodeficiency
	Hypogammaglobulinaemia, associated with recurrent infections AND immunoglobulin replacement /prophylactic antibiotics
	Good's (thymoma + B cell deficiency)
	HyperIgM
	Autoimmune polyglandular syndromes
	IFN type 1 pathway defects / autoantibodies
SECONDARY IMMUNODEFICIENCY	
Solid organ transplant	Any solid organ transplant
	Lung
	Within 1 year of solid organ transplant
HIV	AIDS presentation or uncontrolled HIV infection
	Untreated (high viral load) with CD4<50
	CD4 <200
IMMUNE-MEDIATED INFLAMMATORY DISORDERS (IMID) (see further information in HSE Interim Guidance)	
Treatment-based	B- cell depleting Rx (e.g. rituximab) within 12 months; or where B cell reconstitution has not occurred
	Tacrolimus (systemic therapy - Excludes topical tacrolimus or other topical calcineurin inhibitors)
	Corticosteroids (Long term use of > 5mgs/day prednisolone, or intermittent high dose defined as adults receiving over 40mgs/day for more than 1 week or over 20mgs/day for two weeks within the previous 3 months)
	Cyclophosphamide (within last 6 months)
	Cyclosporin
	Mycophenolate Mofetil, Mycophenolic acid
	Biologic monotherapy with agents associated with significantly impaired vaccine response (See further information in HSE Interim Guidance) **NOTE: TNF alfa blockers alone do not warrant Paxlovid™ therapy**
	Biologic PLUS Azathioprine (thiopurine) or Biologic PLUS Methotrexate
	Abatacept
HAEMATOLOGY	
Diagnosis-based	HSCT < 12 months, OR where B cell reconstitution has not occurred
	GVHD active
	Chronic B cell lymphoproliferative disease
	Myeloma (NOT MGUS) (MGUS with impaired immune function, but not fulfilling myeloma definition)
	Myelodysplastic syndrome
Treatment-based	CART (Chimeric Receptor T-cell Therapy) within 2 years
	B-cell depletion therapies (anti-CD20, daratumumab) within 12 months OR where B cell reconstitution has not occurred
	T-cell depleting therapies (alemtuzumab, ATG) within 12 months
	Radiotherapy within 6 months
	Systemic anti-cancer therapy within 12 months (excluding tyrosine kinase inhibitors) for haem malignancy (NOT stable CML)
Non-malignant	Sickle cell disease
	Haem disorders receiving B-cell or T-cell depletion therapies within 12 months (anti-CD20, alemtuzumab, ATG)
ONCOLOGY	
Diagnosis-based	Active solid/metastatic cancer
Treatment-based	Radiotherapy within 6 months
	Chemotherapy within 3 months
RENAL	
Diagnosis-based	Renal transplant
	CKD 4 or 5 **NOTE: Paxlovid™ and Remdesivir both contraindicated in eGFR < 30**
Treatment-based	B cell depleting therapies within 12 months OR where B cell reconstitution has not occurred
LIVER	
Diagnosis-based	Cirrhosis (Childs C) **NOTE: Paxlovid™ contraindicated in Child Pugh C Liver cirrhosis**
	Liver transplant
Treatment-based	Any immunosuppression for liver disease (Excluding low dose corticosteroids)
NEUROLOGY	
Diagnosis-based	Huntington's
	MND on immune therapies
	MS on immune based therapies
	Myasthenia gravis on immune based therapies

At the time of first contact with Tier 1 and 2 patients (who may have a negative antigen test and require PCR), GPs will need to commence their assessment, recognising the time-sensitive 5-day window for treatment. Particularly important at this stage is an initial assessment of suitability for treatment, and the compilation of the patient's medication list (GP prescribed / Hospital administered/ Patient OTC) so that drug interactions can be considered at an early stage. The patient should be counselled on the risks and benefits of treatment before proceeding to prescribe (https://www.ema.europa.eu/en/medicines/human/EPAR/paxlovid - see relevant note below).[1]

The pathway from start to finish is set out overleaf.

[1] **Clinical Trial Information Note**
A main study (EPIC HR) recruited unvaccinated patients with COVID-19 and at least one underlying condition, putting them at risk of severe COVID-19. It looked at the effects of Paxlovid on rate of hospitalisation or death within 28 days of treatment compared with placebo. The analysis was done in patients who received Paxlovid within 5 days after COVID-19 symptoms began. In the 28 days following treatment, the rate of hospitalisation or death was 0.8% (8 out of 1,039) for patients who received Paxlovid, compared with 6.3% (66 out of 1,046) for those who received placebo. There were no deaths in the Paxlovid group and 12 deaths in the placebo group. The majority of patients in the study were infected with the Delta variant. Based on laboratory studies, Paxlovid is also expected to be active against Omicron and other variants. This means that eighteen (18) unvaccinated patients who are at high risk of severe illness from COVID-19 need to be treated to prevent one hospitalisation. The benefit of the treatment in vaccinated patients has not been established. Treatment needs to be commenced within 5 days of the onset of symptoms for the treatment to be effective. Most common side effects of Paxlovid include dysgeusia (altered or impaired sense of taste), diarrhoea, increased blood pressure, and myalgia (muscle aches).
It should be noted that given the period the study was conducted, the primary variant across both treatment arms was Delta (98.53%). Additionally, the population enrolled in Study C4671005 was limited to unvaccinated patients at high risk of progression to severe COVID-19. It is therefore difficult to extrapolate this data to the current Irish setting where 98% of the population is vaccinated and Omicron, BA2 is the circulating variant. For this reason, the likelihood is that the patients who will most likely benefit from this treatment are those who are unvaccinated or those who due to impairment of immune response are less likely to have responded to vaccination.



In the short term, the usual distribution pathway is that on receipt of a prescription, the community pharmacy will order directly from the wholesaler when they require stock. **If the product is ordered by 4pm, it will be delivered before 5pm the next day.**

N.B. First dose of Paxlovid™ must be taken within 5 days of symptom onset

Clinical Guidance and GP Support Services

A number of resources will be made available for GPs to use including:

- HSE Interim Guidance for the Pharmacological Management of Patients with COVID-19
- Medicines Management Programme section of the HSE website – www.hse.ie/yourmedicines
- The Paxlovid™ drug interaction checker (Free App available) – Liverpool COVID-19 Drug Interactions
- NMIC's clinical enquiry answering service – see email address below.
- National level webinars
- Paxlovid™ SmPC details https://www.ema.europa.eu/documents/product-information/paxlovid-epar-product-information_en.pdf.
- Resources will be available via www.antibioticprescribing.ie

Additionally, GPs may require a higher level of personal support on matters of clinical practice. The overall model of governance for the provision of this support is important.

The governance model provides for oversight by Professor Michael Barry, National Clinical Lead, Medicines Management Programme through the National Medicines Information Centre (NMIC). The NMIC have agreed under the auspices of Prof Barry to provide a prescriber support service building on their current model; this is an established, trusted and robust source for medicines information.

The National Medicines Information Centre (NMIC) will be 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.

To ensure an efficient turnaround, a template has been developed so that all relevant information can be provided to NMIC at 'first touch' contact. The template will be available on the Medicines Management Programme section of the HSE website as well as www.antibioticprescribing.ie.

It is recommended that the patient's community pharmacy is copied in correspondence to the NMIC to enable timely medicine reconciliation and ensure all involved in the patient's care get access to relevant information.

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.

It is recognised that out of hours service will not necessarily have access to all current medications for patients. In this context, patients should have available for the out of hours service an up-to-date medication list. Work is ongoing with advocacy and patient groups to communicate this requirement and to support patients to compile a list of their medications to support any prescribing discussions. This combined with the support from the NMIC as outlined in the attached documents should assist.

4. Delivery Model

Paxlovid™ will be dispensed by Community Pharmacies. On receipt of a prescription, the community pharmacy will order directly from the wholesaler. If the product is ordered by 4pm, it will be delivered before 5pm the next day. Pharmacies will not hold a stock of the medicine. This time needs to be considered in planning patient care to get first dose taken within 5 days of symptom onset.

Early and direct liaison by the prescriber with the pharmacist is advised. The prescription should be sent by *Healthmail* to the pharmacy of the patient's choice. It is preferable for safety and continuity of care that the medicine is dispensed by the pharmacy who dispenses the patient's usual medicines, but this

may not always be possible. Sunday delivery where a pharmacy is not normally open may present a challenge in some situations.

Until practice systems have been updated a prescription may need to be written manually (or in a word document) and scanned, including all patient and prescriber details and identifiers.
Prescription should be written as set out below:
"Paxlovid 300mg/ 100mg BD for 5 days"
("Paxlovid 150mg/ 100mg BD for 5 days (reduced renal dose)" where reduced renal dose is required).

5. Challenge around 5-day turnaround from symptoms to ingestion

A key operational challenge that will remain throughout is the ability to reach any patient within the 5-day timeframe. Evidence has shown that efficacy reduces after 5 days, and as such, the timeliness of prescribing and access to Paxlovid™ is a time-sensitive event. In such circumstances, there is the risk of wasting doses. As such, when considering if a patient is suitable for this product, it is vital that decisions are made in a timely manner ensuring a patient's best chance of mitigating harm to them.

6. Prescription Oversight

In order to further mitigate the risk of prescribing Paxlovid™, in using the patient's usual dispensing pharmacy, the final checks and balances can be conducted with the patient's medication record already available in the pharmacy who knows the patient and dispenses to them on a regular basis.

The HSE-Medicines Management Programme (MMP) will monitor the utilisation of Paxlovid™ (PF07321332 + ritonavir) and other antivirals for the treatment of COVID-19 in the coming months.

GPs should use the identification pathway as outlined above (Tier 1 / Tier 2) aligned to the clinical guidance already developed before considering prescribing and only then should carefully consider the risk / benefit to prescribe depending on the patient's current medication regimen.