HSE Prescribing Protocol for Paxlovid™ (nirmatrelvir/ritonavir) use in the Treatment of COVID-19

This document is intended for use by healthcare professionals only.

This guidance is specific to the management of patients with COVID-19 disease.

While the guidance is intended to strengthen clinical management of these patients it does not replace clinical judgement or specialist consultation.

INDICATION FOR USE: [1]

Refer to Summary of Product Characteristics (SmPC) of Paxlovid™ (nirmatrelvir/ritonavir) for full prescribing information

https://www.ema.europa.eu/en/documents/product-information/paxlovid-epar-product-information_en.pdf[1]

TREATMENT	INDICATION	ICD10	PROTOCOL CODE
Paxlovid™ (nirmatrelvir/ritonavir)	For the treatment of COVID-19 in adults patients (over 18) in **Tier 1/2/3** who: • Are less than or equal to 5 days of symptom onset • COVID-19 confirmed **within the last 5 days** • do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19	U07.1	COVID001

TREATMENT: [1]

Drug	Treatment
Paxlovid™ (nirmatrelvir/ritonavir)	300mg nirmatrelvir (two 150mg tablets) with 100mg ritonavir (one 100mg tablet) all taken **together** orally every 12 hours for 5 days.

Renal Dosing Table: A dose reduction is recommended in patients with moderate renal impairment

eGFR (mL/min)	Dose of nirmatrelvir	Dose of Ritonavir	Frequency	Duration
Greater than or equal to 60	300 mg	100 mg	12 hourly	5 days
30-60	150 mg	100 mg	12 hourly	5 days
Less than 30	Not recommended in SmPC *			

*There is limited evidence available for the use of low dose Paxlovid™ (nirmatrelvir/ritonavir) regimens in patients with eGFR less than 30mL/min or those on dialysis (i.e. advanced Chronic Kidney Disease) who are at high risk of progressing to severe COVID-19. This must be discussed with local infectious diseases and renal teams prior to prescribing[2,3,4,5].

ELIGIBILE PATIENTS:

- Patients meet all criteria outlined in the indication section

EXCLUSION CRITERIA:

- Patients who do not meet the eligibility criteria above

CONTRAINDICATIONS: [1]

- Severe renal impairment, (eGFR less than 30mL/min), including patients with End Stage Renal Disease under haemodialysis (*See note under Renal Dosing Table in Treatment section above)
- Severe liver disease- Child Pugh Class C
- Co-administration of medicinal products that are highly dependent on CYP3A for clearance and for which elevated concentrations are associated with serious and/or life threatening reactions.
- Co-administration of medicinal products that are potent CYP3A inducers where significantly reduced Paxlovid™ (nirmatrelvir/ritonavir) plasma concentrations may be associated with potential for loss of virologic response and possible resistance.
- Hypersensitivity to the active substance or to any other ingredients
- Any contraindications to Paxlovid™ (nirmatrelvir/ritonavir) as listed in the SmPC .

USE WITH CAUTION: [1]

- In patients with moderate renal impairment (eGFR less than or equal to 60mL/min), the dose of Paxlovid™ (nirmatrelvir/ritonavir) should be reduced to 150mg/100mg every 12 hours for 5 days.

Special attention for patients with moderate renal impairment

The daily blister contains two separated parts each containing two tablets of nirmatrelvir and one tablet of ritonavir corresponding to the daily administration at the standard dose. Therefore, patients with moderate renal impairment should be provided with only one tablet of nirmatrelvir with the tablet of ritonavir to be taken every 12 hours.

- Caution is advised in patients with pre-existing liver diseases, liver enzyme abnormalities or hepatitis, due to a risk of hepatotoxicity.
- Ritonavir is a CYP3A inhibitor (and PgP inhibitor). Nirmatrelvir is a substrate of CYP3A. Interactions with other medicinal products could lead to **clinically significant reactions, including potentially life-threatening or fatal reactions, loss of therapeutic effect of** Paxlovid™ (nirmatrelvir /ritonavir) **and possible development of viral resistance.**
- Carefully review concomitant medicines before and during treatment. Monitor the patient for adverse reactions associated with any concomitant medicine. Paxlovid™ (nirmatrelvir/ritonavir) should not be started immediately after discontinuation of certain contraindicated medicines, see SmPC for further information.
- The COVID-19 Drug Interactions tool developed by the University of Liverpool (https://www.covid19-druginteractions.org/) should be used to check for potential drug interactions. A mobile app of the Liverpool Covid-19 tool is also available. Further information on medicines contraindicated for concomitant use with Paxlovid™ (nirmatrelvir/ritonavir) and for potential significant interactions with other medicinal products are also available from SmPC [1,6].

- Ritonavir may reduce the efficacy of combined hormonal contraceptives. Patients using combined hormonal contraceptives should be advised to use an effective alternative contraceptive method or an additional barrier method of contraception during treatment with Paxlovid™ (nirmatrelvir ritonavir), and until one menstrual cycle after stopping treatment.

OTHER INFORMATION:

- Completion of the full 5-day treatment course is recommended even if the patient develops severe or critical COVID-19 after starting treatment[1].

Method of Administration:

Oral

DRUG INTERACTIONS:

Refer to SmPC

ATC CODE:

Antivirals for systemic use, protease inhibitors, J05AE30

REIMBURSEMENT CATEGORY:

- Hospital Reimbursement for hospital supplied courses.
- PCRS for community supplied courses.

REFERENCES:

1. Summary of Product Characteristics Paxlovid 150mg + 100mg film-coated tablets. Available from: https://www.medicines.ie/medicines/paxlovid-150-mg-100-mg-film-coated-tablets-35210/spc Accessed online: 04.10.2023
2. Hiremath S, McGuinty M, Argyropoulos C, Brimble KS, Brown PA, Chagla Z, Cooper R, Hoar S, Juurlink D, Treleaven D, Walsh M, Yeung A, Blake P. Prescribing Nirmatrelvir/Ritonavir for COVID-19 in Advanced CKD. Clin J Am Soc Nephrol. 2022 Aug;17(8):1247-1250. doi: 10.2215/CJN.05270522. Epub 2022 Jun 9. PMID: 35680135; PMCID: PMC9435977.
3. Hiremath S, Blake PG, Yeung A, McGuinty M, Thomas D, Ip J, Brown PA, Pandes M, Burke A, Sohail QZ, To K, Blackwell L, Oliver M, Jain AK, Chagla Z, Cooper R. Early Experience with Modified Dose Nirmatrelvir/Ritonavir in Dialysis Patients with Coronavirus Disease 2019. Clin J Am Soc Nephrol. 2023 Apr 1;18(4):485-490. doi: 10.2215/CJN.0000000000000107. Epub 2023 Mar 1. PMID: 36723285; PMCID: PMC10103226.
4. Renal Drug Database. Available from: https://renaldrugdatabase.com/monographs/paxlovid-nirmatrelvirritonavir. [Accessed on 08.11.2023]
5. Guidance for the use of nirmatrelvir/ritonavir in patients with advanced chronic kidney disease and patients on dialysis. www.covid19-druginteractions.org/prescribing_resources/paxlovid-renal-dosing. [Accessed on 08.11.2023]
6. Expert opinion from The COVID-19 Therapeutic Advisory Group in July 2022
7. Royal College of Physicians of Ireland. National Immunisation Advisory Committee (NIAC). NIAC Immunisation Guidelines Chapter 05a: COVID-19. [Accessed on 10.11.2023]

Appendix 1: Clinical Prioritisation Framework for the Use and Prescribing of Paxlovid™ (Nirmatrelvir/ritonavir)[6,7]

This guidance specifies which individuals might receive the greatest benefit from Paxlovid™. The treating physician will need to consider all co-morbidities and therapies to gauge for cumulative immune suppressing effect.

Tier	Risk Group
1	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 Appendix 2) Immunosuppressed adult patients taking rituximab within 12 months** and other B cell or T cell depleting therapies OR high dose steroids defined as adults receiving over 40mgs/day for more than 1 week or over 20mgs/day for two weeks within the last three months Unvaccinated adult patients at high risk or very high risk of severe disease (adults aged over 70 years or adults aged over 50 years with **additional risks**)***
2	Unvaccinated adult patients at risk of severe disease not included in Tier 1 (adults aged over 50 years or adults aged under 50 years with **additional risks**)***
3	Vaccinated adult patients at high risk of severe disease (adults aged over 70 years or adults aged over 50 years with **additional risks**)***
4	Vaccinated adult patients at risk of severe disease (adults aged over 50 years or adults aged under 50 with **additional risks**)***

*baseline or pre-treatment serology is not required

** Extended effect may occur and impact may be supported by consideration for serology testing

*** **Additional risks** include diabetes, overweight (BMI > 25 kg/m2), chronic lung disease (including asthma), chronic kidney disease, current smoker, immunosuppressive disease or immunosuppressive treatment, cardiovascular disease, hypertension, sickle cell disease, neurodevelopmental disorders, active cancer, medically-related technological dependence, or were 60 years of age and older regardless of comorbidities[1] and clinical risk factor conditions not meeting full definition for inclusion in Tier 1.

Appendix 2: Conditions or treatments associated with very high or high risk of severe COVID-19 disease[7]

May also include others, based on clinical judgement and a needs assessment.
Conditions in the shaded areas may be associated with a suboptimal response to vaccines.

Underlying Condition or Treatment	Very high risk	High risk
Cancer	Receiving or within 6 weeks of receiving systemic cytotoxic chemotherapy, targeted therapy, monoclonal antibodies or immunotherapies Receiving treatment or pending treatment for a haematological cancer Undergoing or within 6 weeks of surgery or radical radiotherapy for lung or head and neck cancer Advanced/ metastatic cancer	Haematological[2] – within 5 years of treatment
		Non haematological cancer within 1 year following immunomodulating treatment* All other cancers being treated (excluding hormonal treatment)
Chronic heart and vascular disease		e.g., heart failure, hypertensive cardiac disease
Chronic Kidney Disease	On dialysis, or eGFR less than 15ml/min	eGFR less than 30ml/min
Chronic Liver Disease		e.g., cirrhosis or fibrosis
Chronic neurological disease or condition	With evolving respiratory failure requiring non-invasive ventilation e.g., motor neurone disease, spinal muscular atrophy	Significantly compromised respiratory function and/or the ability to clear secretions e.g, Parkinson's disease, cerebral palsy
Chronic respiratory disease	Severe e.g., severe cystic fibrosis, severe COPD, severe pulmonary fibrosis	Other conditions e.g., stable cystic fibrosis, severe asthma (continuous or repeated use of systemic corticosteroids), moderate COPD
Diabetes	HbA1c 58mmol/mol or greater	All other diabetes (Type 1 and 2)
Inherited metabolic diseases	Disorders of intermediary metabolism at risk of acute decompensation e.g., Maple Syrup Urine Disease	Disorders of intermediary metabolism not fulfilling criteria for very high risk

Underlying Condition or Treatment	Very high risk	High risk
Immunocompromise due to disease or treatment	Severe e.g., **Transplantation:** • Listed for solid organ or haematopoietic stem cell transplant (HSCT) • Post solid organ transplant at any time • Post HSCT within 12 months **Genetic diseases:** • APECED[3] • Inborn errors in the interferon pathway • Some B and T cell deficiencies **Treatment e.g.,** Cyclophosphamide, Rituximab, Alemtuzumab, Cladribine or Ocrelizumab in the previous 6 months	Other e.g., High dose systemic steroids[4] HIV, not on treatment or CD4 count less than 200 /10^6L for adults
Intellectual disability	Down Syndrome	Intellectual disability excluding Down Syndrome
Obesity	BMI greater than 40kg/m^2	BMI greater than 35kg/m^2
Severe mental illness		e.g., schizophrenia, bipolar disorder, severe depression
Sickle cell disease	Sickle cell disease	

[7]NIAC Immunisation Guidelines, Chapter 05a COVID-19 updated 29.11.2023

[2] Including e.g., leukaemia, lymphomas, blood dyscrasias or other malignant neoplasms affecting the bone marrow or lymphatic systems

*See Appendix 3 below – Therapies which may alter vaccine response

[3]APECED - autoimmune polyendocrinopathy candidiasis ectodermal dystrophy

[4]The following doses of prednisolone (or equivalent dose of another glucocorticoid) are likely to be immunosuppressive:

- Adults ≥10kg: ≥40mg/day for more than 1 week, or ≥20mg/day for 2 weeks or longer

Appendix 3: Therapies which may alter vaccine response

The following therapies are likely to interfere with vaccine responses, and patients may be considered in Tier 1
• Systemic calcineurin inhibitors (e.g. tacrolimus; ciclosporin) • Potent anti-proliferative agents (e.g Cyclophosphamide; Mycophenolate) • Some MS therapies (e.g Fingolimod and other S1P receptor modulators) • Abatacept (Orencia®) • Alemtuzumab (Lemtrada®) • Belimumab (Benlysta®) • Blinatumomab (Blincyto®) • Brentuximab vedotin (Adcetris®) • Daratumumab (Darzalex®) • Gemtuzumab ozogamicin (Mylotarg®) • Inotuzumab ozogamicin (Besponsa®) • Mogamulizumab (Poteligeo®) • Obintuzumab (Gazyvaro®) • Ocrelizumab (Ocrevus®) • Polatuzumab vodotin (Polivy®) • Rituximab (Blitzima®, Mabthera®, Ritemvia®, Rixathon®, Riximyo®, Truxima®)
The following therapies may interfere with vaccine effectiveness, or have relatively little data available. Patients receiving these therapies may fall into Tier 1. MDT discussion is recommended, possibly supported by antibody measurement if feasible.
• Some MS therapies (Timing of dosing in relation to vaccination may be relevant) • Azathioprine and 6-mercaptopurine (dependent on dose and duration) • Corticosteroids (depends on dose and duration, and relationship to vaccine doses.) • JAK inhibitors (varies with agent and underlying condition) • Anakinra (Kineret®) • Canakinumab (Ilaris®) • Risankizumab (Skyrizi®) • Sacituzumab govitecan (Trodelvy®) • Satalizumab (Enspryng®) • Tocilizumab (RoActemra®) • Tralokinumab (Adralza®)

The following therapies do not ordinarily impair vaccine responses and patients do not automatically fall into Tier 1 unless there is clinical or laboratory evidence of immunodeficiency, and a poor antibody response to SARS-CoV-2 vaccines.

- Topical calcineurin inhibitors
- Methotrexate
- DiMethylFumerate
- TNF alpha inhibitors
- IL-1 and IL-6 inhibitors
- IL-17/IL-23 inhibitors
- Adalimumab (and all approved biosimilars)
- Alirocumab (Praluent®)
- Atezolizumab (Tecentriq®)
- Avelumab (Bavencio®)
- Benralizumab (Fasenra®)
- Bevacizumab (Avastin®, Alymsys®, Zirabev®, MVASI®)
- Brodalumab (Kyntheum®)
- Brolucizumab (Beovu®)
- Burosumab (Crysvita®)
- Cemiplimab (Libtavo®)
- Certolizumab (Cimzia®)
- Cetuximab (Erbitux®)
- Denosumab (Prolia®, Xgeva®)
- Dupilumab (Dupixent®)
- Durvalumab (Imfinzi®)
- Eculizumab (Soliris®)
- Emicizumab (Hemlibra®)
- Enfortumab vodotin (Padcev®)
- Etanercept (Benepali®, Enbrel®, Erelzi®, Lifmior®)
- Erenumab (Aimovig®)
- Evolocumab (Repatha®)
- Golimumab (Simponi®)
- Guselkumab (Termfya®)
- Infliximab (Flixabi®, Inflectra®, Remicade®, Remsima®, Zessly®)
- Ipilimumab (Yervoy®)
- Ixekizumab (Taltz®)
- Lanadelumab (Takhzyro®)
- Mepolizumab (Nucala®)
- Natalizumab (Tysabri®)
- Nivolumab (Opdivo®)
- Omalizumab (Xolair®)
- Panitumab (Vectibix®)
- Pembrolizumab (Keytruda®)
- Pertuzumab (Perjeta®)
- Pertuzumab / Trastuzumab (Phesgo®)
- Ramucirumab (Cyramza®)
- Ranibizumab (Lucentis®, Byooviz®)
- Reslizumab (Cinqaero®)
- Romosozumab (Evenity®)
- Secukinumab (Cosentyx®)
- Tildrakizumab (Ilumetri®)
- Trastuzumab (Herceptin®)
- Trastuzumab deruxtecan (Enhertu®)
- Trastuzumab emtansine (Kadcyla®)
- Ustekinumab (Stelara®)
- Vedolizumab (Entyvio®)

Expert opinion from The National Clinical Programme for Immunology Lead in July 2022