Nirmatrelvir (Paxlovid) Mini-HTA for the treatment of COVID-19

Evidence Evaluation Center for Health Care Decisions - CEEDS

Global Institute of Clinical Excellence

Health and Innovation Chair

Contents

Title	Health Technology Assessment: Nirmatrelvir (Paxlovid) for the Treatment of COVID-1
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Executive Summary

COVID-19 antiviral treatments are still in the early stages of development, considering that the disease was first identified in late 2019.

COVID-19 nirmatrelvir is recommended for use in patients older than 12 years and weighing more than 40 kilograms with risk factors for moderate COVID-19 and who already have a positive COVID-19 test.

The risks of using nirmatrelvir appear to be lower than the potential benefits.

Methodology

We carried out a health technology assessment following the methodological manual for health technology assessment, Multicriteria Decision Analysis Matrix of the Global Institute of Clinical Excellence (IGEC).

The following are the steps used:

1. Identify the specific technology and use
2. Elaborate the PICOTS

3. Elaborate the CATWOE of the technology (Annex).

4. Establish the Search Equation (Annex)

5. Establish the incidence and prevalence of the problem to be solved by the technology. (Annex)

6. Establish the severity of the disease to be addressed by the technology (Appendix).

7. To establish the ethical evaluation of the use of the technology (Annex).

8. Establish the social evaluation of the use of the technology (Annex).

9. Establish the legal evaluation of the use of the technology (Annex).

10. Establish the environmental evaluation of the use of the technology (Annex).

11. Establish the impact of the technology on the quality of life of the patients (Annex).

12. Establish the Survival contributed by the technology to the patients. (Annex)

13. Establish the effect on caregiver/family well-being. (Annex)

Technology description.

Nirmatrelvir, also known as PF-07321332 and whose trade name is Paxlovid, is the analog of a veterinary drug GC376, which appeared in 2018 to treat a 100% lethal type peritonitis in cats caused by feline coronavirus (Pedersen et al., 2018).

Paxlovid consists of two 150 mg tablets of nirmatrelvir packaged together with a 100 mg tablet of ritonavir.

Nirmatrelvir aims to inhibit virus replication by targeting the 3C protease (3CLpro), also called major protease (Mpro) or C30 endopeptidase.

Proteases are usually a good therapeutic target; without them, it is not possible to process the polyprotein replicase (P0C6U8) in the case of coronaviruses, and if this protein is affected, the virus cannot replicate (Unitprot, 2021).

The formula of nirmatrelvir is $C_{23}H_{32}F_3N_5O_4$; its molar mass is 499.535 g-mol-1, and its melting point is 192.9 ^{0}C.

Pedersen et al. (2018) point out that "Protease inhibitors are also used in combination with HIV/AIDS reverse transcription inhibitors for lifelong therapy, and combinations of different protease inhibitors have been very effective in curing Hepatitis C Virus infection in people" this would be one of the reasons to use the combination nirmatrelvir with ritonavir . The other reason for use put forward by Pfizer is that ritonavir serves to decrease the metabolism of cytochrome complex enzymes, which helps to maintain higher concentrations of the drug nirmatrelvir; however, no published evidence was found on the superiority of using the two drugs alone or in combination.

There is also an intravenous version of nirmatrelvir called Lufotrelvir (PF 07304814), a prodrug whose phosphate group is cleaved in vivo to produce the active agent PF-00835231, for which positive in vitro results were published by Baig et al. (2021).

The recommended dose in adult patients is nirmatrelvir 300 mg (two 150 mg capsules) orally every 12 hours for five days, with or without food, and lopinavir 100 mg (1 100 mg capsule) orally every 12 hours, the three capsules taken concurrently every 12 hours. Treatment should be initiated within five days of symptom onset. (FDA, 2021).

According to FDA recommendations in the emergency authorization, it is noted that you should not take paxlovid if you are allergic to nirmatrelvir, ritonavir, or any of the ingredients of paxlovid or are taking any of the following medications: alfuzosin;

pethidine, piroxicam, propoxyphene; ranolazine; amiodarone, dronedarone, flecainide, propafenone, quinidine; colchicine; lurasidone, pimozide, clozapine; dihydroergotamine, ergotamine, methylergonovine; lovastatin, simvastatin; sildenafil (Revatio®) for pulmonary arterial hypertension (PAH); or triazolam, oral midazolam; apalutamide; carbamazepine, phenobarbital, phenytoin; rifampicin; St. John's wort (Hypericum perforatum).

According to the FDA analysis, the possible side effects of paxlovid are as follows: liver problems, loss of appetite, yellowing of the skin and whites of the eyes (jaundice), dark-colored urine, pale-colored stools, and itchy skin, pain in the stomach (abdominal) area. For patients who have untreated HIV infection, paxlovid may cause some HIV medicines to not work in the future. Other possible side effects include altered sense of taste; diarrhea; high blood pressure or muscle aches.

Paxlovid is not recommended in patients with severe renal impairment (eGFR <30 ml/min) (FDA, 2021).

PICOTS

Population: people older than 12 years with COVID-19 disease and weight over 40 kg.

Intervention: use nirmatrelvir (paxlovid) to treat COVID-|9.

Comparator: standard medical care, other pharmacological therapies, non-pharmacological medical management.

Outcomes: Safety, Effectiveness, and Quality of Life.

Timing: all outcomes up to a maximum of 1-year post-treatment initiation

Settings: outpatient management only.

Clinical Trials

In the clinical trials platform, there are 11 reported studies, only four of which appear completed, but for which we found no official results published at the time of the review. The report we have is the one made by Pfizer and the emergency evaluation made by the FDA.

Title	Status	Conditions	Interventions	Locations	URL
Renal Impairment Study of PF-07321332 Boosted With Ritonavir in Adult Participants With Renal Impairment and Healthy Participants With Normal Renal Function.	Completed	Renal Failure	Drug: PF-07321332/ritonavir	United States	https://ClinicalTrials.gov/show/NCT04909853
Food Effect Study to Evaluate the Effect of High-Fat Meal on the Relative Bioavailability of PF-07321332 Boosted With Ritonavir in Healthy Adult Participants	Recruiting	Healthy Participants	Drug: PF-07321332/ritonavir|Drug: Ritonavir	New Haven, Connecticut, United States	https://ClinicalTrials.gov/show/NCT05129475
Drug-Drug Interaction Study Assessing Effect of Carbamazepine on PF-07321332 Boosted With Ritonavir	Completed	Healthy Participants	Drug: PF-07321332/ritonavir|Drug: Carbamazepine|Drug: PF 07321332/ritonavir	Pfizer New Haven Clinical Research Unit, New Haven, Connecticut, United States	https://ClinicalTrials.gov/show/NCT04962230
PF-07321332/Ritonavir and Ritonavir on Dabigatran Study in Healthy Participants	Recruiting	Healthy Participants	Drug: Dabigatran|Drug: PF-07321332/ritonavir + Dabigatran|Drug: Ritonavir + Dabigatran	Research Centers of America (Hollywood), Hollywood, Florida, United States	https://ClinicalTrials.gov/show/NCT05064800
EPIC-HR: Study of Oral PF-07321332/Ritonavir Compared With Placebo in Nonhospitalized High-Risk Adults With COVID-19	Recruiting	COVID-19	Drug: PF-07321332|Drug: Ritonavir|Drug: Placebo	United States Argentina Brazil Colombia Czechia Hungary India Japan Korea, Malaysia Mexico Poland Puerto Rico Russian Federation South Africa Spain Taiwan Thailand Turkey Ukraine	https://ClinicalTrials.gov/show/NCT04960202
Drug-Drug Interaction Study Assessing Effect of Itraconazole on PF-07321332/Ritonavir in Healthy Participants	Completed	Healthy Participants	Drug: PF-07321332/ritonavir|Drug: Itraconazole	Brussels Clinical Research Unit, Brussels, Bruxelles-capitale, R√©gion DE, Belgium	https://ClinicalTrials.gov/show/NCT04962022

Title	Status	Conditions	Interventions	Locations	URL
Study to Estimate the Effects of Hepatic Impairment on the Pharmacokinetics (P.K.) of PF-07321332	Recruiting	Liver Failure	Drug: PF-07321332|Drug: Ritonavir	Orange County Research Center, Tustin, California, United States|Prism Research LLC dba Nucleus Network, Saint Paul, Minnesota, United States	https://ClinicalTrials.gov/show/NCT05005312
Drug-Drug Interaction Study to Estimate the Effect of PF-07321332/Ritonavir and Ritonavir on Midazolam in Healthy Participants	Recruiting	Healthy Participants	Drug: Midazolam|Drug: PF-07321332/ritonavir + Midazolam|Drug: Ritonavir + Midazolam	Brussels Clinical Research Unit, Brussels, Bruxelles-capitale, R√©gion DE, Belgium	https://ClinicalTrials.gov/show/NCT05032950
A Post-Exposure Prophylaxis Study of PF-07321332/Ritonavir in Adult Household Contacts of an Individual With Symptomatic COVID-19	Recruiting	COVID-19	Drug: PF-07321332|Drug: Placebo for PF-07321332|Drug: Placebo for Ritonavir|Drug: Ritonavir	USA Ukraine	https://ClinicalTrials.gov/show/NCT05047601
STUDY OF PF-07321332 IN HEALTHY PARTICIPANTS	Completed	Healthy Participants	Drug: PF-07321332 Dose 1|Drug: PF-07321332 Dose 2|Drug: PF-07321332 Dose 3|Drug: PF-07321332 Dose 4|Drug: PF-07321332 Dose 5|Drug: PF-07321332 Dose 4 or Placebo (Fed)	New Haven Clinical Research Unit, New Haven, Connecticut, United States|Brussels Clinical Research Unit, Brussels, Bruxelles-Capitale.	https://ClinicalTrials.gov/show/NCT04756531
Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients (EPIC-SR).	Recruiting	COVID-19	Drug: PF-07321332|Drug: Ritonavir|Drug: Placebo	USA Ukraine	https://ClinicalTrials.gov/show/NCT05011513

Fuente: información extraída de cada uno de los estudios.

Clinical Outcomes

The clinical outcome on which we focused this technology assessment was demonstrated effectiveness as a decrease in hospitalizations, mortality, and adverse events.

In the Pfizer study, the primary efficacy endpoint was the incidence of all-cause hospitalization (defined as ≥24 hours of acute care in a hospital or any similar facility) or death through day 29 in the modified intention-to-treat population.

Effectiveness of the use of technology

The estimated effectiveness of the study reported by Pfizer and the FDA's evaluation of the study was 89%.

In this paper, we divide the effectiveness evaluation into three parts:

a. In vitro models and animal models.

b. In silico models and

c. Results of clinical studies in humans.

a. Evidence from in vitro studies and animal models indicate that paxlovid works in inhibiting SARS-CoV-2 virus replication, and as Owen et al. (2021) conclude in their research, "PF-07321332 has demonstrated oral activity in a mouse-adapted model of SARS-CoV-2 and achieved oral plasma concentrations that exceeded in vitro antiviral cellular potency in Phase I clinical trial in healthy human participants.".

b. By in silico models, we refer to computational models, which establish matching trajectories between the molecular constituents of the virus and those of the drug. In the study published by Pavan et al. (2021) in which they used Supervised Molecular Dynamics (SuMD) to investigate the recognition process between PF-07321332, the first

orally available antiviral candidate Covid-19 reaching clinical phase I, and its biological target, the major protease of SARS-CoV-2 (Mpro), it was found that there is indeed an alteration of the coronavirus protease upon contact with the PF-07321332 molecule, concluding Pavan et al (2021) that " SuMD simulations suggest a possible role in the early stages of ligand recruitment to residues such as Leu141, Asp 142, Gln189 and Glu166 (....)".

c. The data from clinical studies were not found in indexed publications but in gray literature and publications of the pharmaceutical company Pfizer and can be summarized as follows: it does work in reducing hospitalizations and deaths by 89%, and it works similarly even with the omicron variant. Now the transcript of the results published by Pfizer on December 14, 2021: "The final data available from all high-risk patients enrolled in the EPIC-HR study (n= 2. 246) confirmed earlier interim analysis results showing that paxlovid™ (nirmatrelvir tablets [PF-07321332] and ritonavir tablets) reduced the risk of hospitalization or death by 89% (within three days of symptom onset) and 88% (within five days of symptom onset) compared to placebo; no deaths occurred compared to placebo in non-hospitalized high-risk adults with COVID-19. The above data have been shared with the U.S. Food and Drug Administration (FDA) as part of an ongoing Emergency Use Authorization (EUA) submission. Moreover, interim analyses from a second ongoing study in standard-risk adults (EPIC-SR) showed a 70% reduction in hospitalizations and no deaths in the treated population compared to placebo on the secondary endpoint; the new primary endpoint of sustained self-reported relief of all symptoms for four consecutive days was not met compared to placebo. In both EPIC-HR and EPIC-SR, an approximately 10-fold decrease in viral load was observed at day 5

compared to placebo, indicating strong activity against SARS-CoV-2 and representing the largest reduction in viral load reported to date for an oral COVID-19 antiviral agent. In addition, recent in vitro data confirm that nirmatrelvir is a potent inhibitor of the Omicron 3CL protease, which, combined with existing in vitro protease and other variants of concern (VoC) inhibition data, including Delta, indicates that paxlovid will maintain robust antiviral activity against current VoCs as well as other coronaviruses."

Finally, no data on clinical studies in pregnant women were found.

Quality of Life

There are no results of quality of life measurements in the study results available from Pfizer and those submitted to the FDA.

Given the above, it cannot be stated with sufficient certainty that nirmatrelvir has a positive impact on patients' quality of life with COVID-19.

Adverse Reactions

In the safety study in the outcomes evaluated by the FDA, the primary safety endpoint was the incidence of adverse events. Safety outcomes, including percentages of participants with adverse events, were evaluated in the safety population, which consisted of all participants who had been randomized and had received at least one dose of nirmatrelvir or placebo. The use of paxlovid is based on the diagnosis of SARS-CoV-2 infection in non-hospitalized adult subjects with a confirmed laboratory.

Subjects 18 years of age or older at high risk of developing severe COVID-19 disease received paxlovid (n=1.109) or placebo (n=1. 115). Adverse events (all grades regardless of causality) in the paxlovid group (≥1%) that occurred more frequently (≥5 subjects

difference) than in the placebo group were dysgeusia (6% and <1%, respectively), diarrhea (3% and 2%), hypertension (1% and <1%), and myalgia (1% and <1%) (FDA, 2021).

The following adverse reactions have been observed in clinical studies of paxlovid that supported FDA emergency use authorization. First, the rates of adverse reactions observed in these clinical studies cannot be directly compared to clinical studies of another drug and may not reflect the rates observed in clinical practice. Additional paxlovid-associated adverse events may become apparent with more widespread use (FDA, 2021).

Safety data from study C4671005 (EPIC-HR), a randomized, placebo-controlled Phase 2/3 trial. A total of 2,224 symptomatic adults received at least one dose of either.

Adverse events were those reported while subjects were taking the study medication and up to day 34 after initiating study treatment. paxlovid [300 mg nirmatrelvir (two 150 mg tablets) with 100 mg ritonavir] or matching placebo were to be taken twice daily for five days.

The proportion of subjects who discontinued treatment due to an adverse event was 2% in the paxlovid group and 4% in the placebo group (FDA, 2021).

In an embryo-fetal development study submitted for FDA emergency approval with nirmatrelvir, a reduction in fetal body weight was observed following oral administration of nirmatrelvir to pregnant rabbits at systemic exposures approximately ten times the clinical exposure at the licensed human dose of paxlovid. No other adverse developmental outcomes were observed in animal reproduction studies with nirmatrelvir

at systemic exposures greater than or equal to 3 times greater than the clinical exposure to the licensed human dose of paxlovid (FDA, 2021)....

No data are available on the presence of nirmatrelvir in human or animal milk, infant effects, or milk production. A transient decrease in body weight was observed in nursing offspring of rats administered nirmatrelvir (FDA, 2021).

Nirmatrelvir tested negative for mutagenic or clastogenic activity in a battery of in vitro and in vivo assays, including the Ames bacterial reverse mutation bacterial mutation assay using S. Typhimurium and E. coli, the in vitro micronucleus assay using human TK6 lymphoblastoid cells, and in vivo rat micronucleus assays (FDA, 2021).

In a fertility and early embryonic development study, nirmatrelvir was administered orally to male and female rats at doses of 60, 200, or 1,000 mg/kg/day once daily beginning 14 days before mating, throughout the mating phase, and continuing through the sixth week of gestation for females and up to a total of 32 doses for males. There were no effects on fertility, reproductive performance, or early embryonic development at doses up to 1,000 mg/kg/day, resulting in a systemic exposure approximately 4-fold higher than exposure with the licensed dose of paxlovid in humans (FDA, 2021).

Conclusions

a) Nirmatrelvir Treatment has FDA approval for use. The given approval for use does not imply support for its clinical effectiveness.

b) There are no serious methodological flaws in the existing studies that prevent inferring negative conclusions to the use of nirmatrelvir.

c) There is sufficient Evidence from in vitro and silico Evidence, and to a lesser extent from clinical studies, to consider Paxlovid as a part of managing patients with COVID-19.

d) If Paxlovid is used in patients with COVID-19, extended surveillance for adverse events and clinical response should be maintained in the short, medium, and long term.

e) The effectiveness criterion for using an antiviral drug in the context of broad vaccination (greater than 40%) should have a minimum cut-off point of 50%.

Cite as

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ANNEXES

PICOTS

What is the problem to be solved by the proposed technology?	COVID-19
What is the intervention (technology) to be evaluated?	Nirmatrelvir for the treatment of COVID-19
What are the comparators for the technology to be evaluated? If none, write None.	Standard medical care, other pharmacological therapies, non-pharmacological medical management.
What are the Outcomes you are evaluating or looking for? If you do not have them predetermined, write "No results specified."	Effectiveness, safety
Is there a time frame you are working on? If so, please indicate which one, otherwise enter "No predefined time frame".	No pre-set time frame
What is the target environment for the technology? ENTER all that apply.	Outpatient

CATWOE

What is the technology under analysis?	Nirmatrelvir for the treatment of COVID-19
Who are the direct beneficiaries of the technology?	Men and women over 18 years of age and those over 12 years weigh more than 40 kg.
And how does its use affect beneficiaries?	Decreases viral load, eliminate the virus at the end of treatment. Avoids hospitalizations by 89%.
Who will implement the technology?	Primary care and emergency physicians. While its use was tested in the first five days
What needs to be impacted for technology success?	The learning curve, technology acquisition, verification of delivery costs, safety of care, early diagnosis, patient follow-up. Active exclusion of patients at medium and high risk of pregnancy.

What is the purpose of the technology?	Decrease hospitalizations and deaths due to COVID-19.
What is the global vision of using or not using technology?	Controlling the pandemic.
What are the broader impacts of using or not the technology?	Cease virus transmission.
Who owns the technology being investigated?	Pfizer
What role will the owner of the investigated technology play in its implementation, evaluation, monitoring?	monitoring, encouragement of their use
What are the demands and constraints external to the System in which the technology will be deployed?	in ambulatory consultation. Service costs. Availability of reliable diagnostic tests; early access to medical service.

INCIDENCE, PREVALENCE, MORBIDITY, AND MORTALITY

What is the pathology that the technology will solve?	COVID-19
What is the technology being evaluated?	Nirmatrelvir for the treatment of COVID-19
What is the incidence of the health problem to be solved with the technology?	As of January 5, 2022, there are 5203374 confirmed cases in Colombia, of which 63608 are active.
What is the prevalence of the health problem to be solved with the technology?	Variable, today 63608 active cases
What is the mortality of the health problem to be solved with the technology?	Variable, today January 5, 2022 39 deaths
¿ What is the morbidity of the health problem to be solved with the technology?	Hospitalization and death.

SEARCH STRATEGY

- (("pf 07321332"[Supplementary Concept] OR "pf 07321332"[All Fields] OR "pf 07321332"[All Fields]) AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields])) AND ((y_10[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]))
- (("nirmatrelvir and ritonavir drug combination"[Supplementary Concept] OR "nirmatrelvir and ritonavir drug combination"[All Fields] OR "paxlovid"[All Fields]) AND ("sars cov 2"[MeSH Terms] OR "sars cov 2"[All Fields] OR "covid"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19"[All Fields])) AND ((y_10[Filter]) AND (booksdocs[Filter] OR clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter]))

QUALITY OF LIFE

What is the technology under evaluation?	Nirmatrelvir for treatment of COVID-19
Are QOL, O.S., PFS, W.B. C.G. being evaluated with comparators?	Not established in the literature

What is the impact of technology on patients' quality of life?	Not established, high risk of bias in existing data. Not reported
Which scale was used for the evaluation of patients' quality of life?	Undefined
What is the total Survival contributed by the technology to patients?	89%
What is the Survival Free of Disease Progression (SLPE) or Disease-Free Survival?	Non-evaluated
To what extent does technology improve caregiver well-being?	Non-evaluated

POLITICAL, ECONOMIC, SOCIAL, ENVIRONMENTAL, AND ETHICAL

What is the name of the technology to be evaluated?	Nirmatrelvir
Is the proposed technology change similar to something previously implemented or existing?	Yes
Is the current government ideologically opposed to the incorporation of this technology?	No
Does the current government have a price control strategy that may prevent access to technology?	No
Does the government have a regulatory initiative underway or planned in the short term (less than two years) for the technology or a broader category that includes it?	No
If you have answered yes to any of the above questions, please explain why	
Is the current macroeconomic context favorable to the introduction of new technology?	Yes
Explain in a paragraph your justification of the previous answer (remember to include as the following variables employment, price level, exchange rate, and interest rate)	.
Does the adoption of technologies imply a change in customs or ingrained beliefs?	No
Does the use of technology go against a belief or custom?	No
Is the use of technology acceptable to local elites?	Yes

Is the use of technology acceptable to non-elite groups?	Yes
Does the technology of interest replace an existing one?	No, it is complimentary.
If the above answer is yes, please indicate which one(s) it replaces	Supplements symptomatic management of COVID-19
Does the technology under evaluation complement an existing technology?	Yes
If the above answer is yes, please indicate which technology(ies) it complements.	Dexamethasone, oxygen.
How do you think this technology affects other existing technologies? Write your concept.	May decrease the use of other medications and use of the emergency department.
Does the use of technology imply a change in legislation?	No
Does the use of technology contravene a law or regulation?	No
Does the implementation of the technology require a regulatory change?	No
Does the implementation of technology violate the principle of patient autonomy?	No
Does the implementation of the technology violate the principle of patient benefit?	No
Does the implementation of the technology violate the principle of patient nonmaleficence?	No
Does the implementation of the technology	
harm any patients? No Does the implementation of the technology harm any individuals? (obligatorily individuals other than patients are judged).	No
Does the implementation of the technology violate the principle of patient justice?	No
Is the technology reusable?	No
whether the technology is reusable, how many times can it be reused after disinfection?	Zero
Estimate what materials make up the technology? you can choose more than one	Meds
Are there mechanisms in place in the organization to dispose of technology once it has completed its useful life?	Yes
Can the use of technology induce the violation of the value of Compassion?	No